THE CHEMISTRY INSIDE SPICES & HERBS: RESEARCH AND DEVELOPMENT

Editors:
Pankaj Kumar Chaurasia
Shashi Lata Bharati

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The Chemistry inside Spices & Herbs: Research and Development

(Volume 1)

Edited by

Pankaj Kumar Chaurasia
P.G. Department of Chemistry, L.S. College, Muzaffarpur, Bihar, India
India

Shashi Lata Bharati
Department of Chemistry, NERIST, Nirjuli, Arunachal Pradesh, India
India

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FOREWORD

The book titled "The Chemistry inside Spices and Herbs: Research and Developments (Volume-1)" Edited by: Dr. Pankaj Kumar Chaurasia and Dr. Shashi Lata Bharati has an excellent collection of 10 chapters written by the experts of their subjects from countries like India, Iran, and Egypt. Each chapter of the book, attractively written by the experts, is full of research as well as academically momentous information. This book brilliantly deals with biologically valuable spices, herbs, their related chemistry, biochemistry, structure-activity relationships, biologically as well as pharmaceutically valuable active natural compounds, roles in the natural treatment of various human problems, treatment of neurobiological disorders, roles as antifungal and antibacterial agents, naturally-derived analgesics and anti-inflammatory agents, phenolic compounds, flavonoids, curcumin, turmeric, natural therapy, and so on.

In the present time of pandemic and other problems, when the whole world is searching for various types of immunity boosters to fight this virus, this volume may be helpful in this direction in order to provide in-depth information because there are different types of spices, herbs and their constituents discussed in the book which are radiantly useful in the treatment of various human problems and enhancements of immunity. In my view, after giving a thorough look at the contents, this book may be very advantageous for academicians, researchers and scientists working in the field of spices, herbs, their related chemistry, natural medicinal therapy, and so on. I am congratulating the editors of the book for producing such a useful, academically as well as a scientifically relevant book by compiling the comprehensive chapters contributed by the experts of various countries. I strongly recommend this volume for UG and PG students of life sciences, natural chemistry, biochemistry, natural medicinal studies and scientists working in aforesaid areas.

Prof. Gurdip Singh (Retd)
Chemistry Department D.D.U. Gorakhpur University,
Gorakhpur –273 009,
India

PREFACE

Plants are the boon of nature on the earth for us in many ways. They detoxify the environments and save the lives living on this earth. Out of several advantages of plants, their different parts and/or substances are known for their noteworthy medicinal values. Spices and herbs which are involved in our daily routine life are the treasure of good health. Spices, a routine part of the kitchen, as well as herbs of our garden, are full of medicinal virtues and benefits and can be significantly used for the treatment of various disorders and diseases of humans. Spices are actually fruits, seeds, barks, roots and other parts of the plants widely used for enhancing the taste, color and quality of the foods (https://en.wikipedia.org/wiki/Spice) and are the source of various valuable chemical constituents of pharmaceutical significances while herbs are leafy green or flowering parts of the various plants with savory or aromatic properties (https://en.wikipedia.org/wiki/Herb). They are the major source of Ayurveda and other traditional culture of treatments and also have a great potential in the modern time. Spices and culinary herbs and their various chemical constituents involved in the treatment of various problems, diseases and wounds have been beautifully covered in this book.

In the present time of the serious pandemic COVID 19 period, demands of pharmaceutically valuable spices and herbs have been surprisingly enhanced all over the world because they have a substantial and valuable position as nutraceutical which doubtlessly are due to their significant healthy, nutritious and immunity boosting properties. Actually, the main objective of the construction of this book was to collect the more significant valuable researches and information on spices and herbs, which are being widely used in our daily life either in the form of taste enhancing savory materials or quality improving materials or beautiful home decoration and so on. Collection of weighty researches on biologically active pharmaceutically interesting chemical compounds and their compositions and structure activity relationships of these compounds was the second most interesting objective of this book.

This book is full of scientific knowledge on spices, herbs, associated internal chemistry and wide biological performances. It includes biochemistry and biotechnology of spices and herbs, antimicrobial properties, analgesics and anti-inflammatory agents, cure of neurobiological disorders, phenolic compounds, flavonoids, structure activity relationship, biologically active compounds and isolation, and so on.

This volume consists of total ten chapters and each chapter has been written by the various learned experts of their field. Learned experts come from different countries like India, Iran and Egypt. This unique collection of chapters may be highly beneficial for the students of graduate and post graduate level studying in the field of life sciences, biotechnology and biochemistry, plant sciences and for researchers and scientists working research in the field of spices, herbs, compounds with biological activity, natural treatment and natural pharmacology. The book is full of updated knowledge, information and recent researches, and without any doubt, it will be very much fruitful for the readers.

Chapter 1, titled “Spices Biotechnology: Opportunities and challenges”, written by Hamid *et al*., provides an overview of various biotechnological solutions that increase the quality and productivity of spice plants.

Chapter 2, titled “Spices, the guards against the evil microbes: Antimicrobial properties of spices”, written by Jacob *et al.*, highlights the effect of various spices on various micro-organisms, the various metabolites in spices that lend this ability and also reviews.

Chapter 3, titled "Spices and Herbs in the Treatment of Neurobiological Disorders", written by Trivedi *et al.*, deals with the role of spices and herbs for the cure of neurobiological disorders. Based on the investigations on herbal plants and neurological substrates in disease conditions, herbal medicines can be effectively used in the treatment of various neurological disorders.

Chapter 4, titled "Spices and Herbs in Bacterial and Fungal Resistance", written by Trivedi *et al.*, describes the use of spices and herbs against bacteria and viruses. The use of spices and herbs presents a great potential alternative or supplementary medicine to reduce side effects, progressively increasing the resistance of pathogens induced by the use of allopathic drugs.

Chapter 5, titled "Naturally Isolated Compounds from Spices and Herbs and their Medicinal Uses", is written by Ramteke, A.M. This chapter includes a wide variety of isolated compounds such as phenolic compounds and flavanoids present in spices, which are now experimentally documented to possess antioxidant, anti-inflammatory, antimutagenic and anticarcinogenic activities. It also includes a list of spices compounds that are experimentally evidenced to control cardiovascular diseases, diabetes, cataract, cancer, *etc*.

Chapter 6, titled"Naturally-derived Analgesics and Anti-Inflammatory Agents",written by Fayez *et al.*,covers all the nutraceuticals and phytochemicals – derived from medicinal plants– which have been reported to possess analgesic and/or anti-inflammatory effects over the period between 2018 up to June 2020.

In Chapter 7, titled "Phenolic compounds and their Biological and Pharmaceutical activities", Kumar *et al.* have summarized information on the biological and pharmaceutical activities related to different classes of phenolic compounds.

Chapter 8, titled "Structure Activity Relationship of flavonoids: An update", written by Khare *et al.*, focuses on the majority of polyphenols present in the daily diet, which mainly exist as glycosides with different sugar units and acetylated sugars at different positions of the polyphenol skeletons.

Chapter 9, titled "Biologically active compounds and Structure-Activity Relationship" has been written by Ganatra, S.H. He has discussed all three methods in detail, along with examples. It also provides the practical procedure to use available computational tools. The final aim of this chapter is not only to provide the theoretical background of drug discovery using structure activity relationships, but also to provide practical methods.

Chapter 10, titled "Turmeric Supplementation and Its Valued Clinical Connections", demonstrates the renowned significance of turmeric in the treatment of various health issues and its role as a food supplement concisely.

Pankaj Kumar Chaurasia
PG Department of Chemistry, L.S. College,
Muzaffarpur, Bihar,
India

&

Shashi Lata Bharati
Department of Chemistry, NERIST,
Nirjuli, Arunachal Pradesh,
India

List of Contributors

Rasmieh Hamid	Cotton Research Institutes of Iran (CRII), Agricultural Researches, Education and Extension Organization, Gorgan, Iran
Feba Jacob	Centre for Plant Biotechnology and Molecular Biology, Kerala Agricultural University, Thrissur, India
Mehrnaz Entesari	Department of Agronomy & Plant Breeding, Faculty of Agriculture, University of Zanjan, Zanjan, Iran
Shri Hari Prasad	Centre for Plant Biotechnology and Molecular Biology, Kerala Agricultural University, Thrissur, India
Lavale Shivaji Ajinath	Centre for Plant Biotechnology and Molecular Biology, Kerala Agricultural University, Thrissur, India
Rashmi V. Trivedi	Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, India
Nitu L. Wankhede	Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, India
Mayur B. Kale	Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, India
Milind J. Umekar	Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, India
Archana M. Ramteke	Department of Chemistry, K. D. K. College of Engineering, Nagpur, India
Shaimaa Fayez	Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Cairo, Egypt
Mariam I. Gamal El-Din	Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Cairo, Egypt
Omayma A. Eldahshan	Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Cairo, Egypt Center for Drug Discovery Research and Development, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
Abdel Nasser B. Singab	Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Cairo, Egypt Center for Drug Discovery Research and Development, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
Ajay Kumar	CSIR-Central Institute of Medicinal & Aromatic Plants, Lucknow, India Department of Pharmacology, Government Pharmacy College, BRD Medical College campus, Gorakhpur, U.P, India
Feroz Khan	CSIR-Central Institute of Medicinal & Aromatic Plants, Lucknow, India
Dharmendra Saikia	CSIR-Central Institute of Medicinal & Aromatic Plants, Lucknow, India
Shruti Khare	Advance Institute of Biotech & Paramedical Sciences, Kanpur-209217, (U.P.), India
Rikeshwer Prasad Dewangan	Department of Pharmaceutical Chemistry, School of Pharmaceutical Education and Research, Jamia Hamdard (Deemed to be University), New Delhi, India
Sunil H. Ganatra	Department of Chemistry, Govt. Institute of Science, Nagpur, M.S, India

Pankaj Kumar Chaurasia	P.G. Department of Chemistry, L.S. College (A Constituent Unit of B.R.A. Bihar University), Muzaffarpur-842001, Bihar, India
Shashi Lata Bharati	Department of Chemistry, North Eastern Regional Institute of Science and Technology, Nirjuli (Itanagar), Arunachal Pradesh-791109, India
Sunil Kumar	Department of Chemistry, L.N.T. College (A Constituent Unit of B.R.A. Bihar University), Muzaffarpur-842002, Bihar, India
Ashutosh Mani	Department of Biotechnology, Motilal Nehru National Institute of Technology Allahabad, Prayagraj-211004, Uttar Pradesh, India

CHAPTER 1

Spices Biotechnology: Opportunities and Challenges

Rasmieh Hamid[1], Feba Jacob[2,*], Mehrnaz Entesari[3], Shri Hari Prasad[2] and **Shivaji Ajinath Lavale[2]**

[1] *Cotton Research Institute of Iran (CRII), Agricultural Research, Education and Extension Organization (AREEO), Gorgan, Iran*

[2] *Centre for Plant Biotechnology and Molecular Biology, Kerala Agricultural University, Thrissur, India*

[3] *Department of Agronomy & Plant Breeding, Faculty of Agriculture, University of Zanjan, Zanjan, Iran*

Abstract: Spices have been used since ancient times as a flavoring agent as well as an important medicinal resource. Biotechnology, using strategies such as cell, organ, and tissue culture, genetic engineering, and the application of nucleic acid markers can escalate the productivity and efficiency of spices. Cell, tissue, and plant organ culture have enabled the rapid and mass reproduction of many disease-free spice plants, which are uniform genetically and qualitatively. In recent years, cell and limb suspension (stem and hair roots) have been considered for producing secondary metabolites and for studying the biosynthesis pathway of metabolites. Plant genetic engineering has helped in the genetic identification and manipulation of enzymes of the biosynthetic pathway of secondary metabolites. Gene transformation has improved the production of secondary metabolites that have yield limitations. Molecular markers are powerful tools for accurately identifying important medicinal species, examining genetic diversity, classifying hereditary reserves, and determining their genetic map irrespective of their age, physiological, and environmental conditions. Next-generation sequencing (NGS) methods like restriction-site-associated DNA sequencing (RAD-seq) have revolutionized the study of genetic diversity, and the enzymes and genes implied in the secondary metabolites biosynthetic pathways can be studded by transcriptome profiling (RNA-seq). The ground-breaking genome editing techniques like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), sequence-specific nucleases of transcription activator-like effector nucleases (TALENs), and zinc-finger nucleases could help in customizing the plants according to the requirements. This article provides an overview of various biotechnology solutions that increase the quality and productivity of spice plants.

[*] **Corresponding author Feba Jacob:** Centre for Plant Biotechnology and Molecular Biology, Kerala Agricultural University, Thrissur, India; Tel: +91 8469400279; E-mail: Febajacob53@gmail.com

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

Keywords: Biotechnology, Genome editing, Molecular markers, NGS, Spices, Tissue culture.

INTRODUCTION

Spices are mainly the aromatic parts of plants that have been dried. The Food and Drug Administration (FDA) has defined spices as: "aromatic vegetable substances in whole, crushed, or ground form, the notable characteristic of which in food is preparation as opposed to nutrition." [1]. Flavors are regularly derived from the dried part of plant-like buds, barks (cinnamon), fruits/berries (cloves, black pepper, chili), blooms (cloves, saffron), seeds (cumin), or roots (ginger, turmeric) that contain unstable oils or fragrant scents and aromas [1, 2]. The majority of the well-known spices and herbs come from Asia, the Middle East, or Mediterranean countries and have been used since ancient times [3]. Spices and herbs have occupied, and still occupy, significant roles as seasoning specialists, food additives, and meds for quite a long time. Over the last few decades, the investigation into their medical advantages has expanded essentially; the same number of spices and flavors are considered to have properties that reduce the risk of chronic disease development. Specifically, a few of the potential wellbeing benefits of herbs and flavors include conferring security against cancer, chronic inflammation, cardiovascular illness, type 2 diabetes, neurodegenerative conditions and obesity [3 - 6]. Several herbs have been renowned for their anti-inflammatory, antioxidant, and anti-microbial properties [7, 8]. Additionally, the use of certain herbs and flavors will help in reducing the use of salt as the sole flavoring agent (*i.e*., lower sodium admissions), which has cardiovascular benefits [9]. Black pepper, turmeric, clove, vanilla, cardamom, nutmeg, ginger, cinnamon, tamarind, *etc*., constitute the major flavors, whereas fennel, fenugreek, coriander and cumin are imperative seed flavors. While anise, celery, lavender, oregano, saffron, sage and thyme are critical homegrown flavors. The transcriptomes of Piper player nigrum and Piper player colubrinum were analyzed to understand the host-pathogen activity in black pepper, with a focus on Phytophthora foot rot tolerance. The productivity of spices is poor, owing to the lack of high-yielding, pest and diseases resistant varieties, and also due to postharvest losses. Ordinary breeding programs were found to be time-devouring and lumbering in perpetual flavors, such as cardamom and black pepper. Dearth of sources of biotic and abiotic stress resistance within the evolved germplasm made the process even more arduous. Furthermore, crops like ginger and turmeric have no or very few seeds, rendering traditional breeding systems ineffective. Creating varieties with high yielding and disease resistance, under such circumstances, through biotechnology, is imperative for the improvement of spices. The use of biotechnological methods to achieve the above has increased dramatically in

recent years through marker-assisted breeding, development of novel varieties, and commercial propagation.

COMPARATIVE GENOMICS AND GENE TAGGING

Comparative genomics compares various genomic features like genes, regulatory sequences, DNA sequence, gene order and various genomic structural landmarks of several organisms. A crucial step in breeding is recognizing the loci of beneficial genes (high yield, quality, cost-efficiency, and pest and disease resistance). It may be a capable and swift strategy since it does not necessitate several generations of closely supervised parent strain breeding [9]. The detailed transcriptome of *Piper nigrum* and *Piper colubrinum* was conducted w.r.t host-pathogen interaction in black pepper with more focus to the Phytophthora foot rot tolerance [10]. The root transcriptome sequencing of black pepper [11] was done by the SOLiD platform and a detailed dataset of 10,338 UniGenes was found to be crucial for the molecular breeding of black pepper. The 4472 anticipated proteins appeared to have approximately 52% homology with the Arabidopsis proteome. The comparative proteome analysis of two roots revealed 615 differentially expressed proteins [12]. Hu, Hao [13] depicted the black pepper fruit transcriptome in conjunction with the piperine biosynthetic pathway and found 40,537 UniGenes included in piperine biosynthesis. The molecular mechanisms underlying foot rot susceptibility were understood by comparing the transcriptome of resistant (*Piper flaviflorum*) and susceptible (*P. nigrum* cv. Reyin-1) species. It was observed that the genes consolidated within the phenylpropanoid metabolism pathway were highly up-regulated in resistant species [10]. Karthika, Prasath [14], compared the ginger (*Zingiber officinale* Rosc.) and mango ginger (*Curcuma amada* Roxb.) transcriptomes in response to bacterial wilt infection and they observed that 105 genes were only expressed in C. *amada* (safe species) in reaction to contamination by *Ralstonia solanacearum*. These genes were linked to pathogen defence through hypersensitive, systemic acquired, and cell death responses mediated by salicylic acid (SA). Out of the 54 differentially expressed transcription factors, 32 showed upregulation in *C. amada*, which includes GATA, WRKY, zinc finger, MYB and leucine zipper protein domain transcription factors. The transcriptome of two samples of the elite ginger variety Suprabha obtained from two separate agro-climatic zones of Odisha was analyzed by Gaur, Das [15]. The novel transcripts coding for terpenoids related to anticancer and antimalarial in the transcriptome of *Curcuma longa* was reported by Annadurai, Neethiraj [16]. Comparative transcriptome (rhizome-specific) evaluation of *C. longa* and *Curcuma aromatica* associated with curcumin content provided information about the genetic basis and regulation of curcumin biogenesis [17]. Differential expression analysis identified two novel polyketide synthase genes (clpks1 and clpks2), which showed similarity to *Musa acuminata*

polyketide synthase type 2 (MaPKS2) and M. acuminata polyketide synthase type 4 (MaPKS4) that were found to be upregulated in *C. longa* [17]. Babu, Jose [18] analyzed the transcriptome assembly of the turmeric variety Suvarna (CL-Suv). The transcriptome from seeds, leaves, and flowers of Coriander (*Coriandrum sativum* L.) was sequenced and analyzed by Tulsani, Hamid [19], 8676 unigenes were assigned to 153 KEGG pathways in this study. Among them, 291 unigenes were related to terpenes biosynthesis. Paul, Mathew [20] explored the possibility of using comparative transcriptome analysis to point out the candidate genes responsible for the black pepper foot rot field tolerance. DD-RT PCR on cDNA fragments was used to compare transcriptome profiles, and the bands that were differentially expressed were sequenced. Sequence analysis showed the participation of signal proteins and defence enzymes like Aspartyl protease, beta-glucosidase enzyme, Cytochrome P450 signal protein, Nitrous oxide reductase family maturation protein, nucleoredoxin 1-1 enzyme, Phosphatase 2C-like domain-containing protein, Premnaspirodiene oxygenase, putative disease resistance protein RGA3 and Serine/Threonine Protein kinase WAG1 in field tolerance of black pepper to foot rot. Additional insights into the molecular function of tolerance were acquired by pathway analysis. Jiang, Liao [21], analyzed the transcriptome and phytohormone profiles of ginger (*Zingiber officinale* Rose) in reaction to postharvest dehydration stress. Transcriptome profiling found out a total of 1415, 2726, and 6641 genes were differentially expressed after 2 h, 12 h, and 24 h of water-loss stress treatment, respectively in comparison with that during zero h of ginger rhizomes. Moreover, 518 DEGs shared comparable expression patterns throughout twenty-four h of dehydration stress. These genes are specifically enriched in plant hormone signalling, carotenoid biosynthesis, starch and sugar metabolism, phenylalanine metabolism, fatty acid elongation, and phenylpropanoid biosynthesis.

Cloning and Genes Isolation

Genes involved in biotic and abiotic stresses and agronomically critical characters were distinguished in most spice crops [22]. Pathogenesis related candidate genes may also be distinguished using sequence data from libraries, extracted, and then integrated into promising varieties utilizing transgenic techniques. A family or genus, wild relatives of crops may have a set of genes for various biotic and abiotic resistance, agronomically important characteristics, *etc* [23]. Since hybridization based breeding programs to mobilize genes from wild relatives are challenging, the transgenic approach to join the genes is preferable.

Genetic Transformation

Diseases, a lack of resistant varieties, and post-harvest declines are the main

causes of lower spice yields [24]. Genetic transformation has great potential to overcome restrictions of conventional breeding methods and produce high yielding and disease resistant transgenic plants [25]. Plant transformation is considered as both a basic scientific method in plant biology and a practical tool for transgenic plant advancement [26].

Gene transformation is a powerful tool for increasing productivity. There are various methods for gene transformation; such as *Agrobacterium-tumefaciens* transformation, particle bombardment, and electroporation for gene transfer on herb and spice plants, but there are two fundamental classifications for gene delivery: biological and non-biological system [27].

NON- BIOLOGICAL GENE TRANSFORMATION SYSTEM

There are several non-biological systems, which are used for gene delivery *via* plant or protoplast. Non-biological systems like chemical treatment of isolated protoplasts by PEG, electroporation, lipofection, or fusion of protoplasts with liposomes, microinjection, and biolistic. In a direct gene transformation system; chemical solution including PEG, Polyethylene glycol (generally is used only PEG) is incubated with DNA fragment and protoplast. Protoplast is the most appropriate explant in this technique. Due to accessibility and simplicity, this protocol has been reported in numerous plants [28, 29]. There are some reports of using protoplast fusion mediated (PEG mediated) for production of abiotic or biotech disease tolerance or somatic hybridization in vanilla species [30], ginger [31], and coriander [32].

Lipofection mediated transformation involves liposomes (as artificial circular lipid with an aqueous interior for carrying DNA fragment), which can be stimulated *via* PEG to integrate into protoplasts [33]. A sudden electrical discharge for creating small pores in the plasma membrane is used in the electroporation system for the transformation of DNA to protoplast. Transformed protoplasm has the potential to regenerate transgenic plants. Electroporation is introduced as a reproducible system if a good quality protoplast is produced. In the microinjection method, DNA fragment is transferred mechanically to a specific target, which normally is the protoplast. The process is applied through a glass micro capillary-injection pipette. Using a micromanipulator is not practical for transformation in the plant due to the presence of the cell wall, however, it has been effectively used for the transformation of large animal and human cells [29, 34]. Although used rarely for gene transformation, biolistic gene transformation is an alternative non-biological method and has been referred to as an important and famous method for gene transformation to spices plants.

Biolistic Micro-Projectile Bombardment Gene Transformation

The micro projectile bombardment method (also mentioned as particle bombardment, particle gun method, particle acceleration, and biolistic) has been widely introduced as a routine, reliable, and physical gene delivery system [33]. In this method, DNA or RNA gene is coated on microinjection (which normally is tungsten or gold with the size of 1-4 m) then bombarded into callus explants. Micro-carrier size, explant target distance, and helium bombardment pressure and the constructs (circular or linear plasmid) used are factors affecting the efficiency of biolistic transformation. Among the various explants such as microspore, pollen, and shoot meristem reported as explants, embryogenic callus has a higher potential for uniform regeneration after the bombardment and has been considered as an optimum explant for biolistic gene transformation [35]. There are numerous reports of reproducible transformation protocol in capsicum [35], ginger [36], turmeric [37], cumin [38] *via* biolistic system. However, multi-copy integration, which causes transgenic silencing, has been reported as a major concern [39].

Biological System Agrobacterium-Mediated Gene Transformation

Agrobacterium tumefaciens mediated transformation is a natural mechanism for gene transformation in numerous plants. Even though, there are various approaches for gene transformation, the use of Agrobacterium is superior and more popular than other methods especially in dicotyledonous plants, due to more efficiency with lower cost, reproducibility, high capacity to transfer large inserts of DNA, and low copy number. This technology has been widely used for gene transformation (stable or transient) in many spices [40].

IN PLANTA GENE TRANSFORMATION

Another way to use agrobacterium in gene transformation is *in planta*, *i.e*. DNA transfer directly in the intact plants without using tissue culture methods [41]. This minimizes somaclonal variation and saves time significantly, decrease the costs and labour. The pollen tube pathway method is an in planta method that is effective only after pollination in plants. The DNA transformation process takes place by cutting the styles then using a syringe to transfer the DNA material down the pollen tube. This technique was successfully used in black pepper for improving *Phytophthora capsici* resistance [42]. Several genes have been transferred to spice plants *via* biological and non-biological methods for various purposes, which is discussed below (Fig. **1**).

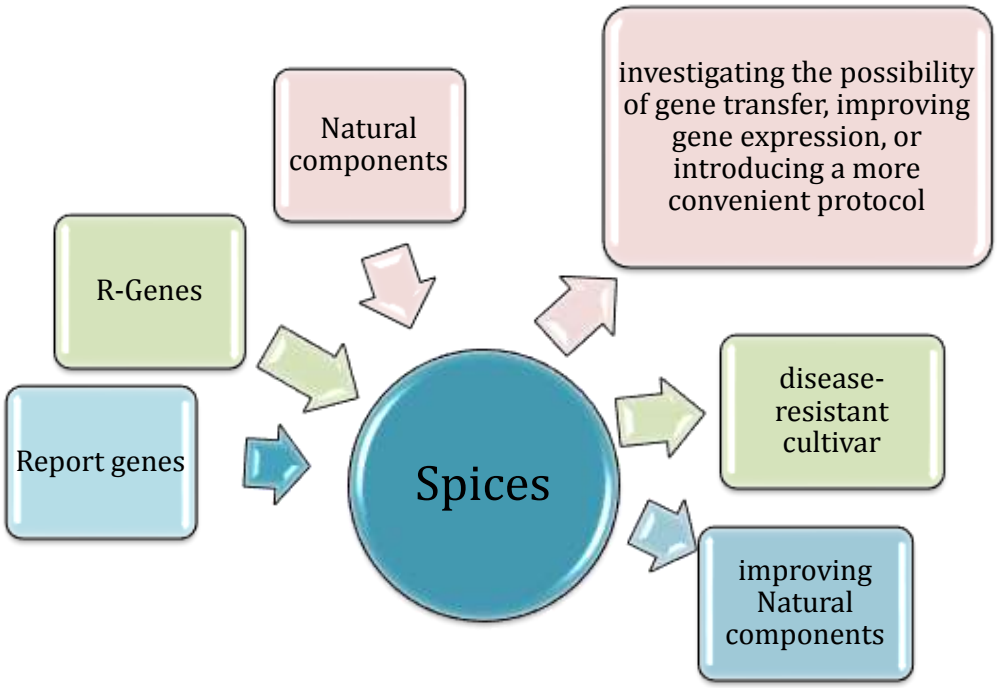

Fig. (1). Important purposes of gene transfer *via* biological and non-biological gene transformation systems and their results in spice plants.

Introducing a More Convenient Protocol

Varghese and Bhat [43], reported an efficient Agrobacterium-mediated gene transformation method in black pepper using somatic embryo explants for and GUS reporter gene. They succeeded in regenerating 9 plants per gram of embryo genic mass for the first time without using growth regulators and any genetic variation [43]. Sinojo *et al* 2014, also optimized somatic embryogenesis methods for Agrobacterium-mediated genetic transformation of a pathogenesis-related gene (PR5) in black pepper [44]. Compared with other solanaceous crops, pepper varieties (*Capsicum annuum*) are highly recalcitrant, so they have shown a very poor response toward transformation by Agrobacterium and regenerative capacity [45, 46]. In capsicum varieties, transformation frequency and shoot regeneration rate are highly genotype-dependent, also Agrobacterium-mediated transformation rate was low for cut-injured cotyledon and hypocotyl [47, 48].

A protocol for generation and gene transformation of two elite Indian cultivars of chili pepper (*Capsicum annuum* L.) was established through *Agrobacterium tumefactions*, strain LBA4404 containing pCAMB1A2301 plasmid for expression of GUS and NPT-II as reporter and marker genes respectively. Results of GUS

assay, PCR, Southern blotting as well as RT-PCR analyses confirmed transformation [49].

Due to the lack of seed set in ginger, there is a high limitation of diversity in its gene pool. Moreover, all breeding programs and vegetative reproduction *via* rhizomes lead to the spread of soil-borne diseases [50]. However, there are many successful reports of ginger (Zingiberaceae) transformation *via* Agrobacterium-mediated and biolistic methods. The opening report of gene transformation of ginger was reported *via* biolistic methods on embryogenic callus as an explant for GUS expression [51]. Successful transformation with the biolistic method through protoplast explant of ginger was published with high GUS gene expression [45]. In Agrobacterium-mediated methods, two strains of Agrobacterium LBA 4404 including p35SGUSInt and EHA 105 with binary vector pCAMBIA1301 containing GUS reporter were used. Gene transformation stability was confirmed by PCR [25]. High transformation efficiency in Agrobacterium transformation was reported in a new quick transient transformation protocol by using LBA4404 strain containing pGFPGUSPlus when the explants incubated with Agrobacterium for 2 days as the co-cultivation stage [26]. In comparison with ginger, there are a few reports of gene transformation in turmeric. He and Gange, (2013) reported two-development transformation systems (leaf-based transient expression and callus-based stable expression) *via* Agrobacterium transformation. Agrobacterium strain EHA105 consisting of plasmid pBISN1, optimized for both transient and stable transformation. Transgenic plants were confirmed by PCR, Southern blot as well as GUS essay analysis [52]. There is a report of using biolistic as an alternative transformation method for Capsicum species too [53, 54].

Natural Component Gene

There are several diseases, which reduce performance in spice and herb plants and cause annual losses around the world. In this section, some of these diseases, as well as the solution proposed by genetic engineering, are mentioned.

As some of the spice plants (such as Turmeric and Ginger) have underground rhizome, they are vulnerable to accumulate pathogens and are susceptible to soil-borne diseases. Pepper varieties (Capsicum) are susceptible to numerous pathogens counting bacteria, fungi, viruses, and nematodes. So some approaches are aiming at the production of red pepper transgenic with high resistance [55].

Appropriate conventional crop improvement methods in the field of disease resistance in plants are problematic and insufficient [37]. Genetic engineering methods by identifying candidate R-Genes (resistance-Genes), cloning, and transformation, are suggested as the novel solution to obtain disease-resistant cultivar [55]. Joshi *et al*., 2010 isolated five NBS-LRR resistance gene candidates,

via generated primers based on conserved domains of resistance genes. They suggested this NBS analogs can be a guideline for isolating more R-Gene in wild relatives turmeric for the genetic improvement of Curcuma [56]. In another report, by using molecular genetic methods, tree R-Gene was found out to be the most stable reference genes for developing Phytophthora- resistant black pepper [24, 42].

Furthermore, there are many available reports for validation, cloning, or expression of the genes related to defense mechanisms against various diseases in spices. Primary genes, expressed in black pepper *via* Agrobacterium-mediated transformation, were NPT II gene (neomycin phosphotransferase) and GUS gene in 1994 and 1998 respectively. There are some reports of the transformation of CP genes (as the genes resistance to CMvirus and ToMvirus) through Agrobacterium-mediated transformation to chili pepper [46, 57]. Gene of BC1 (linked with chili leaf curl Joydebpur virus) was induced in hypocotyl explants of six deferent cultivars of red pepper, by a methodical Agrobacterium-mediated transformation protocol. Transgenic lines were validated by PCR and Southern blotting analysis [58].

The primary efficient biolistic gene transfer method in turmeric was reported for the transformation of plasmid pAHC25 that included by the bar (Glufosinate) as an herbicide gene and GUS reporter. The stability of transformation was confirmed by the results of the GUS assay and PCR analysis [59].

Plant Tissue Culture

Plant tissue culture involving *in vitro* direct or indirect regeneration from various explants is a fundamental approach to take advantage of biotechnological applications in plants [60]. Progress in plant tissue culture has led to the development of other biotechnological methods. In the case of spice plants *in vitro* method has generally been used for overcoming the poor germination seed problem and improving mass propagation, producing disease-free plants and germplasm conservation.

Mass Propagation

The most crucial factors for plant mass propagation efficiency are genotypes, growth regulators, the culture medium, and the physical factors. The different parts of a plant such as leaves, terminal buds [61], bulblet [62], rhizomes [63, 64], stem and root fragments [65], have been studied as explants for spice micro-propagation. In addition, depending on the genotype, different compounds of growth regulators affect productivity [66, 67]. Numerous *in vitro* techniques led to established several efficient protocols for large-scale *in vitro* propagation in

various spices. Using different dosages of cytokinins such as BA or 2ip, were reported for improving shoot regeneration in black pepper [68], ginger [65], garlic [62], turmeric [69]. An efficient protocol for micro-propagation of large cardamom was established by culturing rhizome buds as explant in MS medium containing 1 mg each of BA and IBA (tissue-cardamom3). *In vitro*, culture methods have been able to improve reproduction in garlic also in MS medium containing 2ip and NAA for proliferation step [62]. In Myrtle micro-propagation, modified WPM medium supplied with BA and IBA was reported as an optimum culture medium in comparison with MS and applying different concentrations of IBA or NAA were used for rooting step in another report [70]. A high rate of *in vitro* propagation of curcuma (almost 18 shoots) was reported by using thidiazurone as a growth regulator in MS medium [71].

Somatic Embryogenesis

Effective and developmental production of somatic embryos is a prerequisite for commercial crop production. Somatic embryogenesis is the process by which somatic embryos develop from a group of somatic cells or tissues. These embryos are similar to zygote embryos (embryos from sexual fertilization) and can be transformed into seedlings in a suitable culture medium. Plant reproduction using somatic embryogenesis from a single cell has been demonstrated in many spices and herbs. Therefore, in this case, according to the different potential in different cells for the production of natural compounds, plants with superior characteristics can be produced compared to the primary plant. Most of the reports confirmed that decreasing the concentration of growth regulators in culture medium improves somatic embryogenesis. 2,4-D is referred to as an important auxin for callus induction and somatic embryogenesis. A blend of 2,4-D and with a cytokinin, same as BA on MS medium, has a progressive effect on somatic embryogenesis and callus induction in spices. In ginger, a high number of somatic embryos, 87.7% and 93.3%, were formed by indirect and direct culturing in MS liquid medium using a combination of 2,4-D and BA *via* leaf sheath explants, respectively [72, 73]. Guo and Zhang reported the somatic embryogenesis of four ginger cultivars by cell suspension culture in liquid MSN medium containing 2,4-D and Kinetin [74]. The first report for direct somatic embryogenesis of turmeric with 91.1% efficiency was reported *via* using solid MS medium containing 2,4-D in dark condition and liquid MS medium with BA [48]. High-frequency black pepper plantlet regeneration *via* somatic embryogenesis was reported in several protocols [75, 76]. Application of endophytic fungi in somatic embryogenesis culture for promoting growth and hardening of *in vitro* cultured plants was established in Black pepper [70]. The highest somatic embryogenesis frequency (100%) was reported in *Panax notoginseng* in liquid MS medium contusing 2,4-D *via* Bioreactor cultures [77].

In-vitro Culture by Bioreactors

Automation of the micropropagation process can play a major role in overcoming the limitations of conventional laborious methods. Bioreactors are widely used for producing microbial, animal, or plant metabolism. Although applying bioreactors has been largely intended for cell suspension or hairy roots of spices and herb plants, the optimization of bioreactors for embryogenesis and tissue or organ culture has been reported in the number of studied spices [78]. The temporary Immersion (TI) system is a famous kind of bioreactor for tissue and organ culture. AKA *et al*., 2019, reported the optimized protocol for Myrtle micropropagation and rooting by TIB. The efficiency of Myrtle plantlet in all growth factors (Number of roots, plantlet and root length, root fresh and dry weight) in TIS was better when compared to the conventional method [79]. TI system was used for the mass improvement of the propagation of Vanilla also [80]. Three kinds of bioreactor systems were compared for micropropagation of *Vanilla planifolia*, TI, and RITA systems were introduced as a suitable system for commercial mass propagation and reduction of cost and labour in this spice respectively [77]. The same experiment was carried out for improving shoot and bulblet generation in garlic. However shoot propagated performance was significantly upper in the CI system, the BI system was introduced as an optimal system for bulblet formation in garlic [81].

In vitro Conservation and Cryopreservation

It is important to slow down the growth of spice shoots for the maintenance of their germplasm. *In vitro* conservation is one of the reliable methods for the maintenance of different vegetatively produced plant germplasm [82]. Increasing the concentration of sucrose in rhizome formation medium, using different concentrations of macroelements including EDTA and iron in MS medium and various kinds and amount of gelling agents are *in vitro* approaches reported for extending conservation period in spices [83]. In a successful report of *in vitro* turmeric conservation, low-cost medium (up to 73% cost reduction) including commercial sugar and bacteriological agar as a carbon source and gelling agent were used respectively. *In vitro*, conserved turmeric after 12 months does not have any significant variation in their RAPD profile when compared to the mother plants [84]. Primary *in vitro* conserved cardamom plantlets were achieved using ½ MS medium without growth regulators and decreasing osmotic potential in the culture medium. In a subsequent study, the efficiency of carbendazim as a fungicide on the conservation of Curcuma and ginger shoot explants was reported. The genetic stability of conserved plants was confirmed by the RAPD profile after 3 years [85]. There are several successful reports for *in vitro* clonal micropropagation and conservation in ginger and turmeric [86 - 88] also.

One of the important approaches to micropropagation is cryopreservation [89]. Cryopreservation refers to the storage and degradation of germplasm usually in liquid nitrogen at -196°C. During this time, all cell division and metabolism operations are stopped, and germplasm can be maintained safely without any genetic changes. *In vitro* maintenance of some spices germplasm such as wasabi [89 - 91], garlic [92 - 94], piper [95, 96], ginger [96, 97], *via* cryopreservation is increasingly applied. The cryopreservation technology for black pepper, cardamom, turmeric, and their germplasms using methods like vitrification, encapsulation, and encapsulation-vitrification methods is available [98 - 101]. Cryopreservation of Coriander (*Coriandrum sativum* L.) somatic embryos using air desiccation and sucrose preculture was reported by Popova, Kim [102]. González-Benito and Iriondo [103], also used LN 2 for Celery Cryopreservation.

Secondary Metabolites Production

Secondary metabolites are complex chemical organic matter that plants produce during their lifetime; however, they do not have any important role in their growth and vital activities, mainly produce against biotic and abiotic stresses or attracting pollinating insects. Mass production of these natural components on a large scale through chemical methods is mainly “difficult or impossible”. Appling tissue culture methods like cell suspension cultivation, organ culture, and polyploidy induction are suitable solutions for the rapid and mass secondary metabolites production in plants.

There are available reports for enhancing natural components in spices by micropropagation. The significance of various MS salt concentrations, as well as sucrose were evaluated on four major volatile constituents of *Chenopodium ambrosioides* L. *in vitro* condition. The results showed that all four natural compounds have changed under the influence of changing culture medium [104]. Another successful protocol for *in vitro* culture of *Spilanthes acmella* MURR *via* shoot tip explants was given recently [105, 106].

In most plant species, the induction of polyploidy by increasing cell size has created the ability to produce stronger vegetative organs. Growth organs are the source of a variety of commercially valuable secondary metabolites. Therefore, it is possible to induce polyploidy which can play an imperative role in improving the quantity and quality of these valuable compounds [107]. A significant rise in the production of secondary metabolism has been observed in comparison with numerous polyploidy plants with their diploid counterparts, such as Astragalus [108], Artemisia [109], Jujube [110], Lemon balm [111]. Colchicine is the most important chemical agent in chromosomal doubling, which is widely used in spice and herb plants. Colchicine inhibits the formation and polymerization of

microtubules through binding to a microtubule protein, called tubulin; hence chromosomes enter the cell together at the metaphase stage, making it an active polyploid inductor [112]. In various experiments, the range of 0.01 up to 0.5% has been reported as an optimal concentration for colchicine [108].

Agrobacterium rhizogenes soil born Gram-negative bacterium is a principal agent for Hairy root disease. The infection by the bacteria culminated in production of hairy roots near the site of bacterial entry. Hairy root induction has been tried on various spices plants, hence resulted in an upturn in the production capacity of metabolites by them. Rapid growth, short duplication duration, and having more efficiency for the production of the various natural component of hairy root make them a permanent source for the secondary metabolites production. Many available reports for the usage of hairy root culture for secondary metabolites production such as; Sotolon from *Trigonella foenum* in airlift bioreactor [113], Sarpagin alkaloids from *Rauvolfia serpentine* [114, 115], α-phellandrene and apiole (as an essential oil from) in dill [116].

Protoplast Culture

Protoplast is a plant cell in which the cellulose wall has been removed. In other words, protoplasm has only a thin plasma membrane that surrounds the cell. Plasma has many applications in direct and indirect DNA transformation through electroporation and PEG mediated transformation as well as in the transient system. Protoplast culture has been reported successful in spices. Effective protocol in protoplast culture from cell suspension and leaf tissue of turmeric, cardamom, black pepper, and ginger, from the root of fennel, from mesophyll of fenugreek, from the shoot of garlic, have been elucidated [117].

Molecular Markers

Germplasm diversity is essential for a successful breeding program. Variation is significant for the increase in the genetic base since it raises the chances of discovering dynamically exceptional genes for which the alleles from the two parents are different (that is, the genetic distance) [118]. DNA markers are a powerful tool for distinguishing spice species effectively, as they are independent of age, physiological and environmental conditions. The profile obtained from the DNA fingerprint of a spice plant is the same. Also, the physical shape of the sample is not important for its evaluation and in addition to fresh tissue; it can be extracted from the dry tissue of the DNA. For species or varieties of medicinal plants that are morphologically and phytochemically similar, DNA markers are very important, as they can be used to accurately differentiate. Several kinds of nucleic acid-based markers, like RFLP, RAPD, AFLP, SNP, and SSR are used to study the genetic structure of organisms (Table **1**). In last years, many studies

have been performed to find out the relationship between DNA markers and quantitative and qualitative variations of active drug compounds among species and near relatives of spice plants (Table **2**). In order to study geographical origins and investigation of interrelationships of Indian cardamom, the molecular level profiling of 11 species including 5 major tribes, *viz.*, Amomum, Alpinia, Aframomum, Elettaria, and, Hedychium as well as 96 collections of cardamom germplasm using RFLP, ISSR and RAPD markers was performed by Babu, Divakaran [119]. Tamayo 2007 performed the molecular profiling of chosen cardamom genotypes in Columbia using AFLP molecular markers. The genetic diversity among the various species was appraised using various strategies (Table 2), in addition to conventional molecular markers. Next-generation sequencing (NGS) based genotyping approaches are being used of late in whole-genome sequencing and re-sequencing research programs. An enormous number of single-nucleotide polymorphisms (SNPs) identified from multiple specimens by sequencing can be used to investigate within-species polymorphism, establish haplotype maps, and conduct genome-wide association studies (GWAS). NGS has made the tedious screening of plant germplasm feasible and cost-effective [120]. Using SNP markers has been pretty powerful due to its abundance in plants, cost-effectiveness, the flexible technique, little error rate and high speed of detection [121]. GBS (genotyping by sequencing) is a modern method that uses second-generation sequencing methods to classify and represent SNPs in a smaller scale genome-wide [122]. Using restriction enzymes in GBS reduces repetitive regions and thus the genome complexity, resulting in the most rapid bioinformatics analysis for large genomes [123, 124]. Therefore, this technique, is a rapid, genome-wide, high-throughput, and cost-effective method for SNP finding [125].

Table 1. Most usable molecular markers.

Category	Marker name	Features
Hybridization based	RFLP	-Co-dominant -Unlimited number of loci generated Conveyable across population and species -A large quantity of DNA needed, frequently results in less levels of polymorphism
PCR based	AFLP	-Dominant -Small DNA quantities required -High levels of polymorphism generated -Dominant Complicated methodology
	RAPD	-Dominant -Fast Results -Requires less DNA quantities -High genomic abundance -Low repeatability within and across laboratories

(Table 1) cont.....

Category	Marker name	Features
PCR based	SSR	Co-dominant -Highly polymorphic -Technically simple -Species-specific
	ISSR	-Dominant -Highly polymorphic -Species-specific
	STS/EST	-Co-dominant/Dominant -Highly reliable -Small DNA quantities required -Prior sequence information required
	SNP	-Co-dominant Suitable for high throughput technology -Very high development costs, Sequence information required
	SCARS/CAPS	-Co-dominant -Small DNA quantities required, Highly reliable -Sequence information required

Table 2. Application of different molecular markers in spices.

Molecular markers	Spice: aim and goal of the research	References
RAPD	Black pepper: Evolution of genetic variability and identification of important cultivars, varieties and related species; evolving mapping population for preparation of the genetic map	[135 - 138]
RAPD	Turmeric: Developing molecular genetic fingerprints; assessing genetic diversity	[82, 139, 140, 140]
	Coriander: investigation and assessment of genetic diversity	[141, 142]
	Cardamom: Associated with katte resistance	[143, 144]
	Basil: Assessing genetic variability	[145, 146, 147].
	Fenugreek: Assessing genetic diversity	[148, 149, 150]
	Lavender: Assessing genetic diversity	[151, 152]
	Ginger: Assessing genetic diversity	[153]
AFLP	Black pepper: study of genetic variation and identification of vital cultivars and varieties	[154]
	Fenugreek: Assessing genetic diversity	[155, 156]
SSR/ISSR/EST SSR	black pepper: Developing new EST-SSR markers in black pepper, Evolution of genetic diversity, exploration of important varieties	[157, 51, 158]
	Turmeric: Developing molecular genetic markers; studying genetic diversity	[159, 160]

(Table 2) cont.....

Molecular markers	Spice: aim and goal of the research	References
	Coriander: Developing molecular genetic fingerprints; genetic variation investigation	[19, 161]
	Cumin: genetic diversity examination, introducing vital varieties	[162, 163]
	Large Cardamom: Analyzing genetic diversity	[164]
	Garlic: Assessment of genetic variability	[165, 166, 167]
SNP/SCAR	Garlic: Characterization of bolting behavior in garlic	[168]
	Black pepper: *Phytophthora* resistance responsible gene identification	[169]
	Saffron: Assessing genetic variability	[170]

This technique could aid in genotyping genomes without prior knowledge also it is useful for plant genetic diversity investigation in genome-wide spectrum [126]. Recently, GBS has been utilised in exploring the genetic heterogeneity of many crop species, such as capsicum, barley, maize, sorghum, soybean, tomato, and wheat [127 - 134]. Employing molecular markers, transcriptome and genome sequencing, qRT-PCR approaches can aid classical methods of breeding through the clonal selection and improving elite genotypes.

DNA BARCODING TECHNOLOGY

DNA barcoding is a new molecular recognition tool in which short genomic DNA fragments are used as and identifier marker in different species. Paul Hebert in 2003, firstly suggested this technique, wherein a comprehensive barcode is habituated by DNA screening; a DNA barcode database and recognition platform are settled, and the DNA data are analysed and compared by bioinformatics analysis to identify species [171, 172]. The use of DNA barcoding has helped overcome the limitations of conventional morphology-based identification methods that bank on long-term skills. In due course, instinctive identification might be possible. Barcoding DNA is a step forward and an effective alternate to classic biological characterisation methods [173, 174]. Chen *et al*. studied the variabilities of nuclear gene sequences as well as plastid genomes, of herbal plants and their closely related species and generated a medicinal plant DNA barcode investigation system [175, 176]. Afterwards, Wang *et al*. showed that the ITS2 sequences can be successfully utilized to identify various types of components of soybean pods, which can serve as a new technique for certifying clinical drug safety [177, 178]. M. Zhang, *et al*., used the ITS2 and psbA-trnH sequences for developing a DNA barcoding technique for the verification and uncovering of adulterants in powdered spices. The ITS2 and psbA-trnH sequences effectively distinguished sixteen types of spices and their usual adulterants. A significant

degree of adulteration was observed in the adulteration detection test of 91 commercially available powdered spices. Congeneric plant, vegetal admixture, or cheaper crop-based products were the commonly detected adulterants [179]. The DNA barcoding method is thus a powerful tool for the regulation of the spice market.

CRISPR–Cas9 System for Engineering Resistance to Viruses Infecting Spices

Modern preventive methods are used to manage viral diseases. The control of viral vectors, the development of virus-free plants using different methods, and quarantine regulation are the preventive measures used. Nonetheless, these controls have limitations as the virus vectors develop resistance to pesticides [180]. The recent methods consist of pathogen-derived resistance, RNA interference-mediated resistance, and ribozyme-mediated resistance. Since the last few years, clustered, regularly interspaced, short palindromic repeats (CRISPR)–Cas 9 tools have been used for targeted silencing of viral pathogens in plants. With this technology, it is possible to simultaneously target multiple viruses at various sites and the results are quite favourable. CRISPR is widely distributed in bacterial and archaeal genomes and provides defence against invading viruses and plasmids [181]. The CRISPR locus has short repeats of prokaryotic DNA interspersed with short segments of 'spacer DNA' from the bacterial virus or plasmids they were previously exposed to. CRISPR spacers identify and cleave these exogenous genetic elements like RNA interference in eukaryotic organisms. This interference technique has massive potential and applications like altering the germline of humans, animals, other organisms, and plants [182]. The Cas9 protein and guide RNAs are delivered into the cell so that the genome can be specifically cut at any desired location. Thus CRISPR-Cas system can be efficiently used to develop resistance to DNA and RNA plant viruses through editing or introducing novel traits, precisely at the loci of interest, into plants [183]. It can also be used for manipulating the host genome itself to insert viral immunity. To date, there are only a few reports of using this technology in spices genome editing, Costa *et al* used CRISPR-Cas9 based strategy to engineer *Saccharomyces cerevisiae* for producing curcumin from ferulic acid [184]. Thus, this method has great potential to overcome viral and bacterial diseases in spices.

CONCLUSION AND FUTURE PERSPECTIVES

The availability of nutritious food to nourish the ever-growing population is crucial. Conventional breeding is inadequate to improve the growth and yield of these forgotten plants. Biotechnology based breeding methods (BBBMs) are the solution for high throughput improvement of spice plants in a rapid ways.

Biotechnology can be a key device to accomplish maintainable farming and agriculture-based industry, by the progress of food creation in terms of amount, quality, and wellbeing and at the same time protecting the earth. There has been noteworthy advancement in the field of biotechnology for molecular characterization, micropropagation, and protection, and genetic resources management, management of infections, diseases and pests. Distinguishing markers connected to significant agronomic characters will help in MAS to cut short reproducing time. The utilization of recombinant DNA innovation for biotic and abiotic stress tolerance needs a lot of research before they can be adequately used. Although projects have been started in numerous research facilities for *in vitro* optimal metabolite creation, these methods are to be refined and scaled up for conceivable mechanical creation of the items. Due to their business potential, strengthening, and using biotechnology in spices will be significant in the coming decade. Microbial mediation through T. *harzianum*, T. *viride*, P. *florescens,* and AM fungi has been discovered powerful in disease repression and plant growth promotion. Induced systemic resistance (ISR) as mirrored in defence response seems to be one among the modes of action in disease suppression in ginger and black pepper. The farming community is currently using this microbial biocontrol technology to effectively treat disease in spice crops. The powerful methodology of NGS-based polymer barcoding, which solely targets short regions of genomic polymer and does not need full genome-scale information, will facilitate breeders in quicker identification and classification of untamed populations of these plants. Plant tissue culture could be a core part of BBBMs, which helps in the conservation and micropropagation of spice plants. In in vitro condition, induction and bioreactors are the two alternative tissue culture-derived methods that have led to prominent improvement of spices plants. Agrobacterium-mediated transformation (*A. tumefaciens* and *A. rhizogenes*) is another technique that has led to the wide-ranging improvement of spices by overexpressing the key genes which respond to an organic phenomenon or abiotic stress and special substance pathway. Genome editing approaches (TALLENs, ZFNs, CRISPR/Cas9) are other alternative ways to improve spices plants. Among all genome editing methods, CRISPR/Cas9 has emerged as a promising approach to induce targeted mutation within spice plant genomes, ultimately purposefully altering their organic chemistry profile. Thus, biotechnology-based techniques are definitely the way forward for the overall development of spice plants.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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LIST OF ABBREVIATIONS

NGS	Next-generation sequencing techniques
RAD-seq	Restriction-site-Associated DNA sequencing
TALENs	Transcription Activator-Like Effector Nucleases
FDA	Food and Drug Administration association
KEGG	Kyoto Encyclopedia of Genes and Genomes
DEGs	Differentially Expressed Genes
PEG	Polyethylene glycol
RAPD	Random amplification of polymorphic DNA
MS medium	Murashige and Skoog medium
BBBMs	Biotechnology based breeding methods
RFLP	Restriction fragment length polymorphism
SSRs	Simple-sequence repeats
AFLP	Amplified Fragment Length Polymorphism
SNP	Single nucleotide polymorphisms
SCAR	Species-specific sequence-characterized amplified region
EST-SSRs	Expressed sequence tag-derived simple sequence repeat markers
GWAS	Genome-wide association studies
CAPS	Cleaved Amplified Polymorphic Sequences
CRISPR	Short palindromic repeats
ISR	Induced systemic resistance

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CHAPTER 2

Spices, the Guards Against the Evil Microbes: Antimicrobial Properties of Spices

Feba Jacob[1], Rasmieh Hamid[2,*], Lavale Shivaji Ajinath[1], Shri Hari Prasad[1] and **Mehrnaz Entesari[3]**

[1] *Centre for Plant Biotechnology and Molecular Biology, Kerala Agricultural University, Thrissur, India*

[2] *Cotton Research Institute of Iran (CRII), Agricultural Research Education And Extention Organization (AREEO), Gorgan, Iran*

[3] *Department of Agronomy & Plant Breeding, Faculty of Agriculture, University of Zanjan, Zanjan, Iran*

Abstract: Since time immemorable, spices have been known to combat the onslaught of various microbes like bacteria, fungi and viruses, responsible for various diseases. These microbes also led to food spoilage, which in turn reduced its shelf life. Spices can be used as food preservatives instead of chemical preservatives that are harmful to our health. Studies have proven that the spices commonly used in the kitchen like pepper, clove, ginger, coriander, garlic, cinnamon, *etc*., are highly potent anti-microbial agents. Moreover, they are also eminent anti-inflammatory and carminative agents. The essential oils in spices are also used for protection against various pathogens in plants. These properties are due to the various chemical compounds like eugenol, gingerol, flavonoids, terpenes, anthocyanins, phenylpropanoids and various organosulphur compounds among others present in spices. Hence, spices can be exploited for food preservation and in the pharmaceutical industries. They can also be used as biopesticides, insecticidal agents, antioxidants and natural colorants. This chapter highlights the effect of various spices on various micro-organisms, the various metabolites in spices that lend this ability, and also reviews the various works undertaken to understand the antimicrobial activity of spices.

Keywords: Spices, Anti-microbial, Metabolites, Food preservatives.

INTRODUCTION

The use of spices and herbs dates back to the prehistoric period when the hunter-gatherers wrapped the meat they hunted in leaves and found that this added the flavor and fragrance to meat. They also added some plant products and saw that

[*] **Corresponding author Rasmieh Hamid:** Cotton Research Institute of Iran (CRII), Agricultural Research Education And Extention Organization (AREEO), Shahid Beheshti Aven. Zip Code: 49166-85915, Gorgan, Iran; Tel: +98-1--32236402/+989161001203; Fax: +98-17-32227781; E-mail: rasihamid@gmail.com

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

spices improved its texture, aroma and also improved its shelf-life [1]. These plant products have been used ever since and have found a prominent position in history, religious and cultural practices. Many explorers carried out sea expeditions for this precious commodity, many lands were taken over and many treaties were signed for this precious commodity. Spices were among the most precious trade items during the medieval and ancient eras.

India is known as the "Land of spices". From the saffron of Kashmir to the pepper from Kerala, India is blessed in terms of the abundance of all types of spices due to favorable edaphic and climatic conditions. The health benefits of using spices in our everyday life have been elucidated in Ayurveda, which developed in India and is among the earliest systems of medicine in the universe. According to Ayurveda, using spices and herbs in a small amount in our diet keeps our body healthy. Over the years, humans have realized the essence of spices and understood their multiple uses as medicine, natural colorants, preservative, antioxidants, nutraceuticals, flavoring agents, immunity boosters and anti-microbial agents. Spices are also widely used in cosmetics, like essential oils and perfumes. In this chapter, we will focus on the anti-microbial activity of spices, their use in food preservation and as a medicine.

ANTIMICROBIAL ACTIVITY OF SPICES

Diseases caused by harmful pathogenic micro-organisms and food poisoning brought about by consuming food spoiled due to the activity of microbes are a great threat to human health all over the world. Essential oils extracted from spices by steam or water distillation of plant parts contain many active antimicrobial compounds. These compounds are found to be quite active against many bacteria, fungi, viruses and even many antibiotic-resistant microbes [2]. Regulatory agencies such as the European Union standards, the US Food and Drug Act, Codex Alimentarius, and Food Safety and Standards Authority of India have recognised spices, herbs, and their constituents as generally recognized as safe (GRAS) [3]. Hence spices have immense prospective to be developed as new and safe antimicrobial agents. Let us have a look at the main antimicrobial activities of the spices we generally use, their biochemical properties and their mode of action.

Anti-bacterial Activity of Spices

Bacteria are small microscopic organisms found everywhere, even inside the human body. Most bacteria are harmless, but the few that are pathogenic to humans cause fatal diseases. Many spices or their active metabolites can either kill or inhibit (reduce the rate of their growth) these pathogenic bacteria. The active ingredients present in the plant-derived spices and extracts have received

growing attention, not only for their active antibacterial activity but also due to the fact that developing resistance to them is relatively challenging. The spices possess antibacterial activity due to their innate ability to degrade the bacterial cell wall and cause cell lysis [4]. They can also cause loss of electrolytes, ATP, proteins, and DNA materials, through leakage caused by the damaged cell membranes [5]. The antibacterial activity of major spices is listed in Table **1**.

Table 1. List of spices with their anti-bacterial effects.

S. No.	Spices/Herbs	Active Component	Antibacterial Effect On	References
1	Garlic	Allicin	*Escherichia. coli*, *Salmonella species*, *Citrobacter*, *Enterobacter*, *Pseudomon*, *Klebsiella, Streptococcus*, *Bacillus anthrax*	[6]
2	Ginger	Gingerol, Zerumbone, Zingerone	*Porphyromonas gingivalis*, *P. endodontalis, Prevotella intermedia*	[7]
			Pseudmonas aeruginosa, *Salmonella choleraesuis*, *Bacillus subtilis*	[8]
			Bacillus cereus, *Staphlococcus aureus*, *E. coli*, *Yersinia enterocolitica*	[9]
3	Tumeric	Curcuminoid, Turmerone, Curlone	*E. coli, S. aureus, Salmonella typhi*	[10, 11]
			B. cereus, Bacillus coagulans, B. subtilis, S. aureus. E. coli and P. aeruginosa	[12]
4	Thyme	Thymol	*B. subtilis, Salmonella enteritidis, P. aeruginosa*	[13]
5	Clove	Eugenol	*P.aeruginosa*, *S. aureus*, *S. choleraesuis*, *Klebsiella pneumoniae*	[13]
6	Cinnamon	Cinnamaldehyde, eugenol, cinnamic acid, cinnamate	*P.aeruginosa, S. aureus, E. coli, Bacillus megaterium, K. pneumonia, Enterobacter cloaca, Corynebacterium xerosis, Streptococcus faecalis, S. typhi, Pseudomonas fluorescens, Bacillus licheniformis, Y. enterocolitica, Proteus spp.*	[14]
7	Cardamom	1, 8-cineole, α□terpinyl acetate, linalool	*E. coli, P. aeruginosa, S. aureus, Bacillus pumilus*	[15]
8	Pepper	Piperine, terpenes, phenols	*S. typhimurium, Bacillus, E. coli, S. aureus*	[16]
9	Cumin	Cuminaldehyde, cymene, terpenoids	*E. coli, S. aureus, S. faecalis, P. aeruginosa, K. pneumoniae, B. megaterium, Brevibacillus brevis, Enterococcus faecalis, Pseudomonas pyocyaneus*	[17]
10	Basil	Linalool, estragole, eugenol, 1,8-cineole	*S. aureus, E. coli, B. subtilis, Pasteurella multocida*	[18]

(Table 1) cont.....

11	Oregano	Carvacrol and thymol	*Staphylococcus gallinarum, Salmonella enteritidis, Salmonella typhimurium, S. aureus, B. subtilis, E. coli, P. aeruginosa*	[18]
12	Fenugreek	Galactomannan 4-OH isoleucine, steroidal saponin	*E. coli, P. putida, S. typhimurium, S. aureus*	[19]
13	Rosemary	p-cymene, linalool, gamma-terpinene, thymol, beta-pinene, alpha-pinene and eucalyptol	*Leuconostoc mesenteroides, Lactobacillus delbruekii, S. cerevisiae, E. coli, S. typhimurium, S. enteritidis, Shigella sonei, Listeria monocytogenes*	[20]

Antifungal Activity of Spices

Fungi are ubiquitous microorganisms. Some of them, beneficial as food or as the basis for effective medicines, while other few are less desirable, such as food-mold or spores that bring about diseases in humans like skin infections, allergies and other diseases. The active component of several spices is known to completely or partially inhibit mycelial growth, penetrate the cell wall of various fungi and damage the organelle membranes [21], hinder the normal synthesis of DNA and proteins, and prevent cell wall formation and aflatoxin production, *etc*. A few examples of the antifungal activities of spices are listed in Table **2**.

Table 2. List of spices with their anti-fungal activity.

S. No.	Spices/Herbs	Active Component	Antifungal Effect On	References
1	Garlic	Allicin	*Candida albicans*	[18, 22]
2	Ginger	Gingerol and shagelol	*Aspergilus niger, Fusarium oxysporum*	[23, 24]
3	Turmeric	Curcuminoid, turmerone, curdione, curcumol	*C. albicans, Fusarium graminearum, Paracoccidioides brasiliensis, Aspergillus fumigatus, Aspergillus flavus, Aspergillus clavatus*	[25, 26]
4	Thyme	Carvacrol and γ-terpinene	*C. albicans, F. graminearum, Saccharomyces cerevisae*	[27, 28]
5	Clove	Eugenol	*C. albicans*	[29]
6	Cinnamon	Cinnamaldehyde and eugenol	*C. albicans, Aspergillus niger*	[30, 31]
7	Cardamom	1,8-cineole, α-terpineol, terpinen-4-ol, spathulenol	*A. flavus, C. albicans, S. cerevisiae*	[32, 33]
8	Pepper	Piperine	*F. graminearum*	[34]
9	Cumin	Cuminaldehyde	*C. albicans, A. niger, S. cerevisiae*	[35]

(Table 2) cont.....

10	Basil	Estragol	*A. niger, A. flavus, Fusarium proliferatum*, *Fusarium subglutinans*, *F. oxysporum*	[18, 22]
11	Oregano	Carvacrol and thymol	*C. albicans, A. niger, F. oxysporum, A. niger*	[36, 37]
12	Fenugreek	Galactomannan 4-OH isoleucine, steroidal saponin, cumarin	*Microsporum gypseum, F. oxysporum, Trichoderma viridae*	[38, 39]
13	Rosemary	Rosmarinic acid	*C. albicans*	[40]

Antiviral Activity of Spices

The outbreak of different human pathogenic viruses has brought research on viral diseases and its cure to the forefront. Many researchers are also looking at spices as probable anti-viral agents. These spices can effectually avert viral infections by acting as entry inhibitors, replication inhibitors, protease inhibitors, an integrase inhibitor, Tat protein inhibitor and can also inhibit gene expression. Thus the active chemicals in various spices prevent the virus from establishing itself in the host and thus prevents infection. Molecular docking experiments have shown that many Indian spices have potent activity against the SARS-CoV-2 virus. The antiviral activity of a few spices is mentioned in Table **3**.

Table 3. List of spices with their anti-viral activity.

S. No.	Spices/Herbs	Active Component	Antiviral Effect On	Family	References
1	Garlic	Allicin	HPV	*Papilomaviridae*	[41]
			Influenza A and B	*Orthomyxoviridae*	[42]
			HIV	*Retroviridae*	[43]
			HSV-1	*Herpesviridae*	[44]
			Rhinovirus	*Picornaviridae*	[45]
2	Ginger	Gingerol and shagelol	Influenza	*Orthomyxoviridae*	[46]
			RSV	*Pneumoviridae*	[47]
			FCV	*Caliciviridae*	[48]

(Table 3) cont.....

3	Turmeric	Curcuminoid, turmerone, curdione, curcumol	CHIKV	*Togaviridae*	[49]
			DENV	*Flaviviridae*	[50]
			HBV	*Hepadnaviridae*	[51]
			HCV	*Flaviviridae*	[52]
			HIV	*Retroviridae*	[53]
			HPV	*Papilomaviridae*	[54]
			HSV	*Herpesviridae*	[55]
			IAV	*Orthomyxoviridae*	[56]
			JEV	*Flaviviridae*	[57]
			MNV	*Caliciviridae*	[58]
			RSV	*Pneumoviridae*	[56]
			RVFV	*Phenuiviridae*	[59]
			ZIKV	*Flaviviridae*	[60]
			H5N1	*Orthomyxoviridae*	[61, 62]
5	Clove	Eugenol	FCV	*Caliciviridae*	[48]
			HSV1	*Herpesviridae*	[63]
6	Cinnamon	Cinnamaldehyde and eugenol	HSV1	*Herpesviridae*	[64]
			H1N1	*Orthomyxoviridae*	[64]
7	Cardamom	1,8-cineole, α-terpineol, terpinen-4-ol, spathulenol	HSV1, HSV2, HSV6,	*Herpesviridae*	[65]
			HBV	*Hepadnaviridae*	[65]
			HCV	*Flaviviridae*	[65]
8	Pepper	Piperine	CVB3	*Picornaviridae*	[66]
9	Cumin	Cuminaldehyde	HSV1	*Herpesviridae*	[67]
11	Oregano	Carvacrol and thymol	MNV	*Caliciviridae*	[68]
			HSV-1	*Herpesviridae*	[68]
			RSV	*Pneumoviridae*	[69, 70]
12	Sage	safficinolide and sageone	HIV-1	*Retroviridae*	[71]
			HSV-1	*Herpesviridae*	[72]
13	Rosemary	Oleanolic acid	HSV1	*Herpesviridae*	[73]
			H1N1	*Orthomyxoviridae*	
			HIV	*Retroviridae*	[74]
14	Basil	Estragol, apigenin and ursolic acid	Herpes viruses	*Herpesviridae*	[75]
			HBV	Hepadnaviridae	[76]
			Enterovirus	Picornaviridae	

Apart from the wide range of action against Gram-positive and Gram-negative bacteria, yeasts and fungal pathogens, spices also have a broad spectrum of activity against molds. As mold spoilage is a big concern for both cheese manufacturers and marketers, causing the development of off-flavor and production of toxins the spices like black pepper along with mesquite smoke and hickory smoke oil used as flavouring can also aid in controlling the molds. According to Bachmann [77], when large quantities of spices like cinnamon, cloves, and allspice are used, the growth of molds is retarded, thus acting as a preservative. The mold growth is inversely dependent on the amount of spice used and the inhibition of mold is due to the diffusion and volatilization of the spice. The essential oil derived from bush-basil possess anti-Fungal activity against molds like *Penicillium islandicum* [78], *Alternaria sp*., *Mucor* [79] *Aspergillus flavus, Botrytis cinereal* cinereal *and Aspergillus niger* [80]. Coriander EO showed antifungal activity against *M. racemosus, A. alternata* and *P chrysogenum* [82]. Alves-Silva, dos Santos [81] reported an antagonistic effect for mold inhibition when cinnamaldehyde was combined with essential oil of clove, also additive effect on mold inhibition was obtained when different eugenol and peppermint combination was used in tomato fruit.

ESSENTIAL OILS EXTRACTION FROM SPICES

Essential oil is the essence of the plant. It consists of concentrated hydrophobic liquid which consists of volatile chemical compounds from plants [83]. An essential oil may comprise of several hundreds of chemical compounds and this is what gives it, its distinctive fragrance and flavour. Essential oils from spices are being widely utilized and are a rich source of several bioactive compounds with quite a lot of antioxidative and antimicrobial properties [84] as mentioned earlier. Instead of being synthetically manufactured in laboratories, essential oils are extracted from plant materials through removal methods that are specific for plant parts containing the oils. Commonly, essential oils are extracted by the process of hydrodistillation, steam distillation and solvent extraction. Other processes include supercritical fluid extraction, absolute oil extraction, solvent extraction, resin tapping, *sfumatura*, wax embedding, and cold pressing, pulsed electric fields, microwave, ultrasound, ohmic-heating and microwave (MW) extraction techniques [85]. Essential oils have been widely used in cosmetics, perfumes, soaps and other products, to add-on fragrances to incense and household cleaning products and also as a food and drink flavouring agent. They may also be fractioned and sold as individual natural components.

USE OF SPICES IN PHARMACEUTICAL INDUSTRY

Spices are used widely for drug development. Ancient medical systems like Ayurveda and Unani have exploited the innumerable health benefits and healing properties of spices effectively. Turmeric is a well-known example of a spice used for wound healing, skin allergies and other infections [86]. Garlic and ginger have been found effective against antibiotic-resistant bacteria such as *B. subtilis, E. coli, K. pneumoniae, P. aeruginosa, Shigella, S. aureus,* and *S.typhi* [87]. Many spices such as mint, clove, camphor, and ginger have been used against microbes that harm oral health. The gingerol in ginger is quite effective against *Porphyromonas gingivalis*, *P. endodontalis, Prevotella intermedia* [7]. Even deadly diseases like HIV can be controlled by methanolic extracts of rosemary, cinnamon, sage [88]. Thus understanding the specific antimicrobial activity of the spices can help developing new drugs. Molecular docking approaches are being used with active compounds of spices as lead molecules for drug discovery. Extensive research is being carried out for discovering a drug against Covid-19 from Indian spices [89].

SPICES AS FOOD PRESERVATIVES

Have you ever wondered why the food in the tropical regions has more spices than those in the comparatively colder regions? It is because spices delay the process of spoiling due to microbes. Due to higher temperature and humidity in the tropical regions, the contamination of food by microbes was faster and hence they started adding more spices for food preservation. Moreover, it enhanced the taste.

Spoilage of food is an irreversible modification of food, making it unfit for human consumption or a compromise in its quality. It can be due to physical (oxygen, temperature, light) and/or biological (enzymatic activity and microbial growth) factors. Inspite of the advanced technologies available within the assembly chain (for instance, freezing, pasteurization, drying, preservatives), it appears impossible to do away with the risk of food spoiling [90].

One of the primary causes of food spoiling is lipid oxidation. Hence, food industries consider the application of antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) of the utmost importance so as to prevent spoilage [91]. But the use of these chemicals may not be safe and so the consumers are increasingly demanding the use of natural compounds. The antioxidant capacity of the spices can be attributed to the presence of phenolic compounds, and they do so by chelating transition metals, scavenging free radicals, quenching singlet oxygen, and enhancing the activities

of antioxidant enzymes [92]. Many surveys have discovered the utility of spices against food spoilage [92 - 95].

The antimicrobial activity of spices is exerted in two different ways: by preventing the growth of microorganisms that cause food spoilage (food preservation), and/or by inhibiting/regulating the development of these pathogens (food safety) [96]. Some of the natural antimicrobials reported for meat products include lactoferrin, bacteriocins, essential oils, lysozyme species, and a variety of plant extracts. Spices, for instance, cinnamon, clove, cumin and oregano, were found to be effective against the gram-positive and gram-negative bacteria inoculated on meat [31, 97, 98].

Pros & Cons of Using Spices as Preservatives

The antioxidant and antimicrobial activity of spices has a crucial role in preserving the food. But, for ensuring the effectiveness of spices as preservatives, we need to study several aspects. As reviewed, various spices have different flavours and varying levels of aroma but they are commonly categorised as being strong and so they may interfere with the original flavour of the food, if used in more measures to achieve good antioxidant or antimicrobial activities. Essential oils extracted from spices maybe good substitutes for meat preservation. But when used in meat, the high levels of fat and protein can protect the bacteria from the action of essential oils, as essential oils easily dissolve in the fatty phase of the food, thus reducing their availability to act against the microorganisms [99].

Encapsulated rosemary essential oil has a higher antimicrobial effect against L. *monocytogenes* in pork liver sausage than standard rosemary essential oil and this is associated with the interacttion of essential oils with the fatty phase of meat [100]. Thus, using higher concentration of spices may ensure better antioxidant and antimicrobial activity but the strong flavour of spices may affect its commercial value due to the alteration in the flavour of meat. Essential oils also need the additional extraction process from spices which can make it more expensive eventhough it may not have a better antimicrobial activity. Therefore, using whole spices might be a better alternative for food preservation as they are cheaper, less complex, and have equivalent antimicrobial activity. Another fact is that the efficacy of the spice formulation against microorganisms fluctuates depending on the food or media, the same formulation can be effective for one type of meat but not for another.

SPICES IN PACKAGING MATERIAL

Active Packaging (AP) is a high-tech concept for food packaging that combines the advances in packaging, material sciences and food technology, for food

preservation. In antimicrobial packaging, antimicrobial agents can be infused into the packaging material, smeared over the surface of packaging film or an antimicrobial compound sachet can be added into the package [101]. Sachets and pads being the most successful applications of active food packaging. Active antimicrobial packaging gives a headspace to reduce, retard, or even inhibit the growth of spoilage and pathogenic microorganisms by interacting with packaged food. The transfer of active compounds to food may be achieved through the direct contact between food and the packaging material or through gas-phase diffusion from the inner packaging layer to the food surface [102].

The addition of EOs to a wax coating for antimicrobial active packaging of strawberry preservation was studied. The release of antimicrobial agents from the coating to prevent contamination by microorganisms was evaluated [103, 104]. In another study, carvacrol was added to chitosan-based films for active packaging, and its antimicrobial efficiency against microorganisms that cause food spoilage was demonstrated by using a headspace chromatographic technique. The shelf-life of a complex bakery product was increased by more than three times using cinnamon-based active material with minimal changes in the packaging and no extra manipulation steps [105].

Prevention of Toxin Production

Certain filamentous fungi produce mycotoxins as secondary metabolites, which may contaminate agricultural commodities. They are toxic to humans and animals, cause a substantial drop in crop yield and thus economic losses. Food contaminated with mycotoxins, particularly with aflatoxins, can lead to fatal acute illness and are even related to increased cancer risk [106]. Many countries have imposed strict limits in the aflatoxin concentration due to its high risk to human health. The US Food and Drug Administration (USFDA) has established 20 ppb as the minimum level of aflatoxin acceptable, in all foods other than milk. The European Union has put a ban on the import of peanuts having >2 ppb of AFB1 content and >4 ppb of total aflatoxins in nuts prepared for human consumption. For the export of tree nuts to the European market, the level of aflatoxin should be <3 ppb [107].

Plant extracts or essential oils can be utilized as promising alternatives to the toxic fungicides, currently used for controlling post-harvest fungal deterioration. The extracts of certain plants, toxic to fungi, can impede the biosynthesis of aflatoxin B1 and thus control fungal growth and mycotoxin production. Extracts of garlic and onion can efficiently check growth and aflatoxin production. The effect of turmeric leaf oil on fungal growth and aflatoxin production was determined [107]. Essential oils from aromatic plants like coriander, ginger, pepper, rosemary,

cinnamon, and thyme were found effective against *A. flavus* IMI 242684 on PDA [108]. P. *betle* chloroform fraction substantially reduced the aflatoxin B1 production. This fraction caused a decrease of 91% in mycelial growth and completely inhibited toxin biosynthesis by A. *flavus* at 500 μg/ml [106].

Edible Films

Edible films are thin films prepared from edible material that acts as a barrier to external elements (factors such as oils, gases, moisture, and vapors) thus protecting the product, improving its quality and extending its shelf life. Edible films can control the transfer of moisture, oxygen, carbon dioxide, flavor, and aroma between food components or the atmosphere and the food [109]. Recently, more research has been conducted on biodegradable films, which are made from plant and animal edible protein sources like cottonseed, soy, wheat gluten, corn zein and peanut protein, albumin, casein, collagen, gelatin, and whey proteins. The addition of essential oils to coatings and edible films inhibits the growth of pathogenic and spoilage bacteria. It boosts the sensory properties of foods like meat and meat products. The essential oils of garlic, cinnamon, lemongrass and oregano are widely used for applications on food wrappings [110]. Using apple films comprising 0.5% carvacrol or cinnamaldehyde- the active ingredients of oregano and cinnamon oils, respectively for wrapping pieces of chicken, inhibited the growth rate of *E. coli* O157:H7, *Salmonella enterica*, and *L. monocytogenes* [36].

CONCLUSION

Spices are valuable resources. Many spices used daily have been shown to have antimicrobial activity and medicinal value. They have been used extensively in pharmaceutical industries and also for food preservation. The active chemical components obtained by different extraction methods are quite effective against various bacteria, fungi, viruses and many other pathogenic microbes. They are safe to use and can also eliminate antibiotic-resistant bacteria. Medicinal systems like Ayurveda and Unani have been using spices, and they are found to be successful in treating many diseases. They are also widely used in food preservation. However, there is a need for much more extensive research to escalate the stability of the active compounds, proper target delivery, drug development, *etc*., to reap the complete benefits of spices. Moreover, the multiple possibilities of using various spices individually and also in different combinations against the different pathogens have to be explored.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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CHAPTER 3

Spices and Herbs in the Treatment of Neurobiological Disorders

Rashmi V. Trivedi[1,*], Nitu L. Wankhede[1], Mayur B. Kale and **Milind J. Umekar[1]**

[1] *Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee- 441002, India*

Abstract: Spices and herbs have been used for centuries for treating and preventing many ailments. They have been popularised over the commercial and new drugs due to their purported therapeutic efficacy with lesser side effects, easy availability, and cost-efficiency. Herbal extracts contain mixtures of phytochemicals, mainly secondary metabolites, which include fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, terpenes, and many others. Phytochemicals play a vital role in maintaining chemical balance in the brain and, therefore, can be targeted to treat neural disorders. In recent years, many herbs and spices have gained attention in the treatment of neurological disorders. Although the precise mechanisms of action of herbal medicines have not yet been defined, some of them have been shown to exert anti-inflammatory and antioxidant activities. Several herbs and spices have also shown neuroprotective activity, and their extracts have been found to be effective in learning and memory improvement, depression, anxiety, pain, Alzheimer's disease and other neurodegenerative conditions. Based on the investigations on herbal plants and neurological substrates in disease conditions, herbal medicines can be effectively used in the treatment of various neurological disorders.

Keywords: Antioxidant, Depression, Herbs, Neurodegeneration, Reactive oxygen species, Spices.

INTRODUCTION

For centuries, spices and herbs have been used as food adjuncts for various purposes such as seasoning, flavouring, colouring, and sometimes as a preservative. Aside from food ingredients, they have also been used as nutritional supplements as they play a crucial role as supplementary, complementary, and synergistic components [1]. The ancient Indian system of medicine used a large number of herbs and spices, alone or in combination, for treating and/or preven-

* **Corresponding author Rashmi V. Trivedi:** Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee- 441002 India; E-mail: rashmitrivedimishra@gmail.com

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

ting many ailments. They contain a number of biologically active constituents that are responsible for their biological effects. The heterogeneous collection of compounds present in spices and herbs inarguably contributes to their therapeutic usage. Natural products obtained from them in pure form or as extracts have been considered to possess medicinal value and have been used in the indigenous systems of medicine [2].

Dietary herbs and spices have been proven to be beneficial for human health through a number of actions, such as antioxidative, chemopreventive, antimutagenic, anti-inflammatory, antibacterial, and immunomodulatory on gastrointestinal, cardiovascular, respiratory, metabolic, reproductive, neural, and other systems of body [1]. Their extracts had been used for a long to cure various disorders, such as cough, bronchitis, laryngitis, tonsillitis, spasmodic, gastric-intestinal complaints, carminative, and as diuretic agents. Also, the topical preparations of these extracts were used in the treatment of wounds and disorders of the oral cavity. Herbs and spices exert protective effects in various chronic conditions, including diabetes, cancer, and cardiovascular disease, but the exact mechanisms underlying their action are, however, not very clear.

Today, a growing number of people worldwide have brain disease or disorder such as Alzheimer's disease, Parkinson's disease, depression, schizophrenia, and addiction, which affects the quality of daily life through abnormal behaviors, thoughts, emotions, and social communication. Despite exhaustive research, the aetiologies of these ailments remain poorly understood. Although multiple factors are responsible for the development of neurological diseases, dysregulation in the inflammatory mediators, oxidative imbalance, excitotoxicity, and loss of protective mechanism are key components in the pathogenesis of various neurological conditions such as neuropsychiatric and/or neurodegenerative disorders [3 - 7]. Therefore, for targeted treatment, the agents should be pharmacologically safe, cost-effective, and immediately available with minimal side effects. But one of the major disadvantages of the current treatments for neurological disease with synthetic drugs is that they are associated with multiple side effects.

Extensive research on herbs and spices has taken place, which could provide a new alternative therapeutic approach for diseases of the central nervous system [8]. Generally, herbal extracts contain a number of bioactive phytochemicals that have a wide range of actions, including antioxidant, anti-inflammatory, and neuroprotective, thus use of herbal medicines or natural products was found to be the most commonly used alternative treatment because they can easily cross the blood-brain barrier, exert multiple synergistic effects due to a number of constituents and show less toxicity [9].

Recently, herbs and spices have received attention in their useful physiological functions. More research is required on the usefulness of herbs and spices in disorders related to the brain. The present chapter deals with the involvement of different constituents of herbs and spices in the treatment of neurological disorder and their possible mechanism.

BIOACTIVE PHYTOCHEMICALS IN HERBS AND SPICES:

The biological activities of herbs and spices have been related to the presence of different phytochemicals. The herbal extract contains mixtures of phytochemicals, which are mainly secondary metabolites including fatty acids, polyphenols (phenolic acids, anthocyanins, proanthocyanidins, flavonols, and tannins), isoprenoids (sesquiterpenes, diterpenes, triterpenes, steroids, and saponins), alkaloids, glycosides, and so forth. These phytochemicals are currently used in the pharmaceutical industry for various purposes as they can regulate a variety of enzymes as well as cell receptors [10].

Polyphenols

Polyphenols are a group of plant secondary metabolites that contain phenols, anthocyanins, proanthocyanidins, flavonols, and tannins and are characterized by the presence of phenolic hydroxyl group which is directly linked to the aromatic ring. There has been a growing interest in the beneficial effects of active polyphenols derived from spices and herbs endowed with potent antioxidative and anti-inflammatory activity [11]. Polyphenols have the property to reduce free radical species, which contributes to their neuroprotective effects. Apart from the antioxidant action, this category of compounds can also alter several signaling pathways by acting on a variety of molecular targets [12]. Also, the polyphenolic substance has the potential to inhibit lipid peroxidation, neutralize Reactive Oxygen Species (ROS) and NO-based free radicals (nitric oxide and peroxynitrite) [13, 14].

Flavonoids form the most important group of polyphenols. Numerous studies show that flavanols have beneficial effects on neuronal health. Most common flavonoids include flavones (*e.g*. apigenin, luteolin,), flavanones (*e.g*. hesperetin,), catechins [*e.g*. epicatechin, epigallocatechin-3-gallate (EGCG)], and anthocyanins. They are found in various spices and herbs like oregano, thyme, parsley, coriander, celery, dill weed, onions, spinach, and rosemary [15]. Catechin, epicatechin, and epicatechin gallate found in cumin and cinnamon have been shown to reduce neuroinflammation, protect the brain against injuries produced by neurotoxins and also attenuate the apoptotic mediators of neurons [16, 17]. In addition, they also delay the onset of neurodegenerative disorders *via* iron chelation, radical scavengers, and modulation of prosurvival genes [16]. Chinese medicinal herb

Epimedium revicornum Maxim contains Icariin, a major constituent of flavonoids, is found to improve memory in rats after common carotid artery occlusion [18]. Quercetin has been found in rosemary, oregano, sage, bay, and thyme and is shown to protect against calcium dysregulation during an ischemic injury in neuronal cell death and brain damage. It is also found to be beneficial in attenuating protein oxidation and apoptosis in the hippocampus [19 - 21].

Phenols and flavonoids have antioxidant properties, which may be attributed to their molecular weight, presence of conjugated aromatic rings, and hydroxyl groups, which have the potential to scavenge the free radicals involved in oxidative processes through hydrogenation and complexation with oxidizing species and thus resist oxidative stress [22].

Table **1** enlists herbs and spices including thyme, oregano, rosemary, curry leaves, sage, nutmeg, mace, clove, allspice, ginger, and turmeric which contain antioxidant properties [23]. Anthocyanins have been found to act against oxidative stress, lipid peroxidation and exhibit neuroprotective action in improving cognitive brain function [24].

Table 1. Major phenolic compounds found in herbs and spices.

Common Name	Family	Scientific Name	Total Phenolic Content (g of gae/ 100 g of Dried wt. or Fresh wt.)	Phenolic Compounds
Oregano	Labiatae	*Origanum vulgare L.*	10.17 ± 0.010[a]	Phenolic acids (caffeic acid, p-coumaric acid, rosmarinic acid, caffeoyl derivatives), volatile compounds (carvacrol), flavonoids
Rosemary	Labiatae	*Rosmarinus officinalis L.*	5.07 ± 0.036[a]	Phenolic acids (caffeic acid, rosmarinic acid, caffeoyl derivatives), phenolic diterpenes (carnosic acid, carnosol, epirosmanol), volatile compounds (carvacrol), flavonoids
Sage	Labiatae	*Salvia officinalis L.*	5.32 ± 0.006[a]	Phenolic acids (rosmarinic acid), phenolic diterpenes (carnosic acid), volatile compounds, flavonoids

(Table 1) cont.....

Common Name	Family	Scientific Name	Total Phenolic Content (g of gae/ 100 g of Dried wt. or Fresh wt.)	Phenolic Compounds
Thyme	Labiatae	*Thymus vulgaris L.*	4.52 ± 0.006[a]	Phenolic acids (gallic acid, caffeic acid, rosmarinic acid), volatile compounds (thymol), phenolic diterpenes, flavonoids
Cinnamon	Lauraceae	*Cinnamomum cassia Presl*	6.34 ± 0.021[a]	Phenolic acids, phenolic volatile oils (2-hydroxycinnamaldehyde, cinnamyl aldehyde derivatives), flavan-3-ols
Nutmeg	Myristicaceae	*Myristica fragrans Houtt.*	1.61 ± 0.001[a]	Phenolic volatile oils, phenolic acid (caffeic acid), flavanols (catechin)
Clove	Myrtaceae	*Eugenia caryophylata Thunb.*	14.38 ± 0.006[a]	Phenolic acids (gallic acid), flavonol glucosides, phenolic volatile oils (eugenol, acetyl eugenol), tannins
Black and white Pepper	Piperaceae	*Piper nigrum L.*	0.30 ± 0.002[a] 0.78 ± 0.004[a]	Volatile oils, phenolic amides
Dill	Umbelliferae	*Anethum graveolens L.*	0.98 ± 0.009[a]	Phenolic acids (protocatechuic acid), flavonoids (catechin), volatile oils
Caraway	Umbelliferae	*Carum carvi L.*	0.61 ± 0.017[a]	Volatile oils, phenolic acids, flavonoids (kaempferol), coumarins
Coriander	Umbelliferae	*Coriandrum sativum L.*	0.88 ± 0.007[a]	Phenolic acids (caffeic acid), flavonoids, volatile oils
Cumin	Umbelliferae	*Cuminum cyminum L.*	0.23 ± 0.005[a]	Volatile oils, phenolic acids, flavonoids (kaempferol), coumarins
Parsley	Umbelliferae	*Petroselinum crispum L.*	0.97 ± 0.002[a]	Phenolic acids (caffeic acid), flavonoids, volatile oils
Ginger	Zingiberaceae	*Zingiber officinale Rosc.*	0.63 ± 0.009[a]	Phenolic volatile oils (gingerol, shogaol), phenolic acids
Cardamom	Zingiberaceae	*Elettaria cardamomum* Maton.	0.46 ± 0.009[a]	Phenolic acids (caffeic acid), volatile oils

a-Total phenolic content expressed as g of gallic acid (GAE)/100 g of dry weight (DW)(17), b- Total phenolic content expressed as g of gallic acid (GAE)/100 g of fresh weight (FW) [25].

Terpenoids

Terpenoids, also known as isoprenoids, consist of a very large group of two or more branched 5 carbon units synthesized from precursor mevalonic acid. Depending upon the number of isoprene units, they are subdivided into different classes: monoterpenes, sesquiterpenes, diterpenes, triterpenes, and steroids [26]. Herbs and spices mainly contain monoterpenes and diterpenes. These compounds are lipophilic, thus can cross the blood-brain barrier.

The representative molecules among these are monoterpenes formed from the coupling of two isoprene units (C10). These compounds are responsible for the antioxidant and anti-inflammatory, anxiolytic, and anticonvulsant activity of herbs and spices. The presence of phenolic monoterpenes in thyme, thymol, and oregano are identified as the dominant compounds for antioxidant activity [27]. Also, the presence of thymol in oregano showed anti-inflammatory effects by decreasing the levels of proinflammatory cytokines like TNF-α, IL-1b, and IL-6, as well as increasing the production of the anti-inflammatory cytokine IL-10 [27]. Many of the monoterpenes possess its Anti- Cholinesterase activity due to the presence of a hydrocarbon skeleton. The 1,8-cineole and a-pinene, cyclic monoterpenes present in S. lavandulaefolia oil inhibit the striatum and the hippocampus Cholinesterase (ChE) [27].

The Sesquiterpene class of terpenes consists of three isoprene units (C15). Recent reports show that sesquiterpenes also had beneficial effects on neurological conditions. *Ginkgo biloba* contains sesquiterpene, bilobalide is extensively used as an anticonvulsant and cognitive enhancement. Valerian root and rhizome contain sesquiterpenes, valerenic acid, which has beneficial effects in a number of neurological disorders such as epilepsy, insomnia, dizziness, and anxiety. Atractylenolide, isolated from *Atractylodes macrocephala*, is used to treat sleep disorders, as these sesquiterpenes enhance the action of GABA [28].

Diterpenes are formed from the coupling of four isoprene units (C20) and are responsible for the antioxidant activity of many herbs. Carnosic acid, carnosol and rosmarinic acid are antioxidant diterpenes present in aromatic herbs [29]. Ginkgolide in *Ginkgo biloba* leaf and Zerumin isolated from *Curcuma kwangsiensis* rhizomes have GABAA modulatory action [30]. Terpenoids responsible for the biological activities in herbs and spices are shown in Table **2** [29, 30].

Table 2. Terpenoids in herbs and spices that are responsible for the biological activities of herbs and spices [29, 30].

Isoprene Class	Terpenoids	Plant Source	Mechanism	Action
Monoterpenes	Borneol	Rosemary type B	Modulation of GABA receptors	Anticonvulsant
	Carvacrol	Caraway, spearmint, and dill	GABAA Modulation Anti-inflammatory Antioxidant	Anxiety Anticonvulsant Anti-inflammatory
	Epinepetalactone	Nepeta sibthorpii	Agonists on the BZD binding site on GABAA receptors, increasing chloride conductance.	Anticonvulsant
	Isopulegol	Zanthoxylum schinifolium	Activate the GABAA–BZD site	Anxiety Depressant Anticonvulsant
	Menthol	Peppermint and thyme	Suppresses excitability *via* increasing GABAA receptor-mediated inhibition of hippocampal neurons The modulator of the GABAA receptor	Anticonvulsant
	Thujone	Oregano, sage	Inhibition of the GABAergic system	Convulsion Memory enhancement
	Thymol	Oregano	Positive allosteric modulator of GABAA receptor Antioxidant	Anticonvulsant
	Cineole	Coriander, lavender, rosemary, sage, and thyme	Opioid system Interact with excitatory amino acid	Anticonvulsant
	A-pinene	Caraway, coriander, fennel, juniper berry, rosemary, And thyme	Anti-ache activity	Dementia Alzheimer's disease
Sesquiterpene	Valerenic acid	Valerian (Valeriana officinalis)	an allosteric modulator of GABAA receptors	Anxiolytic Sleep disorder
	Bilobalide	Ginkgo biloba	GABA antagonist	Convulsant Cognition enhancement
	Atractylenolides	Atractylodes macrocephala	potentiate GABA-induced chloride currents	Anticonvulsant

(Table 2) cont.....

Isoprene Class	Terpenoids	Plant Source	Mechanism	Action
Diterpenes	Ginkgolides	Ginkgo biloba	GABA antagonist	Not defined
	Zerumin A	Curcuma kwangsiensis	positive GABAA receptor modululator	Not defined
	Rosmanol	Rosemary, sage	Anti-inflammatory-Inhibits the activation of NF-kB and STAT3	Inflammation

Alkaloids

Alkaloids are naturally occurring nitrogen-containing compounds, usually divided into different classes based on their sources and chemical structures [31, 32]. They are mainly found in certain families of flowering plants such as Solanaceae (nightshades), Papaveraceae (poppies family), Ranunculaceae (buttercups), and Amaryllidaceae (amaryllis) [33]. Alkaloid-containing extracts have been used for the treatment of a variety of ailments.

Capsaicin is the primary capsaicinoid alkaloid found in chili and peppers, which exhibits antioxidant and anti-inflammatory properties. It also ameliorates synaptic damage and tau hyperphosphorylation in stressed mice [34]. Tobacco pyridine alkaloid nicotine belonging to the Solanaceae family found in *Nicotiana tobacum* has been extensively investigated as it enhances cholinergic function [35 - 37].

Berberine is an isoquinoline alkaloid isolated from Chinese herb and several plants, including *Hydrastis canadensis* (Goldenseal), *Berberis vulgaris* (barberry), *Coptis chinensis* (copies or golden thread), and *Berberis aristata* (tree turmeric). It has multiple pharmacological effects like anti-inflammatory, antioxidant, anxiolytic, antidepressant, and anti-amnesic and also has potential for the treatment of drug addiction [36]. It also improves memory by enhancing neurogenesis and inhibiting apoptosis in the hippocampal dentate gyrus [38].

Also, Piperine alkaloid, the main chemical constituents of long pepper (*Piper longum*) and black pepper (*Piper nigrum*), have demonstrated the beneficial effects of piperine which include anti-inflammatory effects, analgesic effect, anticonvulsant, antidepressant effect, cognitive enhancing effect, cytoprotective effect, and antioxidant activity. Piperine also significantly attenuates the memory impairment, the elevation in AChE activity, and neurodegeneration [39]. In combination with curcumin, piperine inhibits the action of Monoamine Oxidase (MAO) enzymes, thus increasing serotonin and dopamine levels which is found to be beneficial for the treatment of depression [40].

Harmine is an indole β-carboline, characterized by indole structure and a pyridine ring, found in *Peganum harmala* belonging to Nitrariaceae family. It has a wide spectrum of activities, including antioxidant, antimicrobial, anti-inflammatory, and neuroprotective activity through various targets AChE, MAO-A, MAO-B, and tyrosine phosphorylation regulated kinase (DYRK1A) inhibition [36]. Harmine is also found to reduce tau protein phosphorylation and thus can be beneficial in the treatment of Alzheimer's Disease (AD) [41].

Some of the alkaloids also produce toxic effects. Pyrrolizidine alkaloids and their N-oxides (PANO) are predominantly present as contaminants in herbal food supplements, as well as in spices. Culinary herbs like oregano and cumin also contain high amounts of PA/PANO [42]. Commonly used alkaloids in herbs and spices for neurological treatment are shown in Table **3**.

Table 3. Commonly used alkaloids in herbs and spices for neurological treatment.

Class of Alkaloid	Plant Source	Alkaloid	Mechanism	Disease	References
Isoquinoline alkaloids	*Hydrastis Canadensis*, *Coptis Chinensis*, *Berberis Aquifolium*, *Berberis vulgaris*, *Berberis aristata*	Berberine	Anti-oxidant, MAO inhibitor, anti-amyloid	AD, PD, HD, and Epilepsy	[32, 38]
	Papaver somniferum (opium Poppy)	Morphine	Neuroprotective against oxidative stress	AD	[43, 44]
	Hippeastrum vittatum	Montanine	Enhance GABAnergic Neurotransmission	Epilepsy	[45]
Piperidine alkaloids	Black pepper (*Piper nigrum*) and Long pepper (*Piper longum*)	Piperine	MAO inhibitor	AD, PD, Epilepsy	[39, 40]
Pyridine alkaloids	*Nicotiana tobacum*	Nicotine	Nicotinic agonist, anti-amyloid	AD, PD	[35 - 37]
Indole β-carboline	*Peganum harmala*	Harmine	COMT inhibitor, Tyrosinephosphorylation regulated kinase (DYRK1A) inhibition, MAO inhibitor	AD	[32, 41]

(Table 3) cont.....

Class of Alkaloid	Plant Source	Alkaloid	Mechanism	Disease	References
Capsaicinoid alkaloid	*Capsicum annuum* (red pepper)	Capsaicin	Anti-amyloid	AD	[34]

REGULATORY MECHANISM UNDERLYING TREATMENT

Today neurological diseases represent a severe health problem, as the prevalence of neurological conditions, including neurodegenerative and psychiatric disorders, are steadily increasing. The functional methods of treatment should target the major causes underlying the diseases. The major etiological targets for these disorders are oxidative stress, neuroinflammation, and dysregulation in the neurotransmitter system. Though synthetic medicine can show beneficial effects by targeting the etiological factors, one of the major disadvantages of the current treatments for neurological disease with synthetic drugs is that they are associated with multiple side effects.

Possible Mechanism of Herbs and Spices in Neurological Disorders

Herbs and spices have been recognized to have advantageous effects on the body. In recent years, these have garnered special attention in the treatment of neurological degeneration, for their broad spectrum of molecular and cellular actions. Although the precise mechanisms of action of many phytochemicals in herbs and spices are yet to be defined, some of them have been shown to exert anti-inflammatory and antioxidant effects. Also, herbs and spices have neuroprotective activity and their extracts have been found to be effective in learning and memory improvement, antidepressant, anxiolytic, antipain, Alzheimer's, and other neurodegenerative conditions. The possible mechanism of spices and herbs in neurological disorders is shown in Fig. (**1**).

Antioxidant

Among the theories proposed to explain the mechanisms of pathogenesis at the molecular level, oxidative stress or imbalance is the key component in brain-related diseases. Oxidative stress can be defined as an imbalance in the cell oxidation/reduction (redox) status that results in the production of partially reduced oxygen intermediates termed as reactive oxygen species (ROS), which are more reactive than molecular oxygen in their ground state. Numerous pieces of evidence suggest that reactive oxygen species (ROS) play an important role in neurological and psychiatric disorders [46, 47].

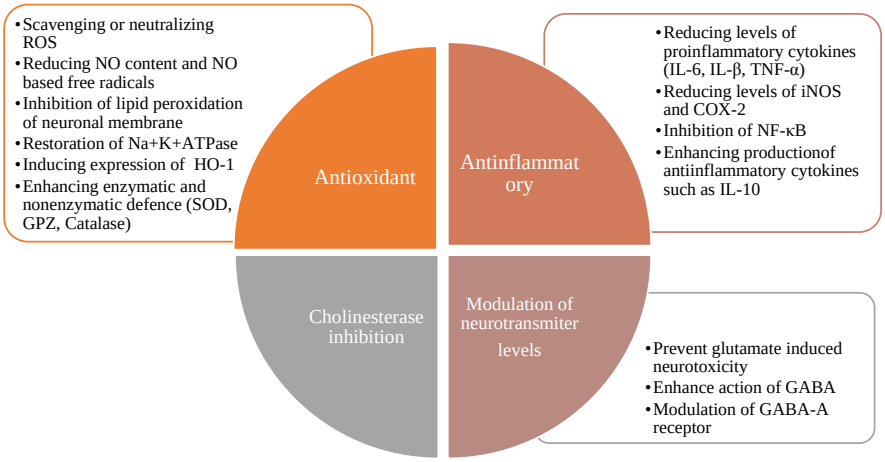

Fig. (1). Possible mechanism of spices and herbs in neurological disorders.

Although the brain weighs less than 2% of the body, it consumes approximately 20% of the oxygen, thus due to its high oxygen demand, the brain is most susceptible to oxidative damage [48]. Aerobic organisms produce ROS following the use of molecular oxygen during oxidative phosphorylation in mitochondria. However, the excessive production of ROS can pose serious neurological damage to biological targets such as DNA, lipids, and proteins, thereby altering cellular responses and pathways. In addition to this, a high amount of polyunsaturated fatty acids (PUFAs) are present in neuronal membranes, which makes the brain tissues more susceptible to lipid peroxidation; resulting in the production of cytotoxic aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) [49]. Natural antioxidantdefence comprises of Superoxide Dismutase (SODs), catalase, and Glutathione (GSH), which can quench free radicals, and thus counteract the imbalance in the redox homeostasis and keep the ROS levels under the threshold thereby preventing oxidative damage [50].

Therefore, treatment with the appropriate antioxidant agent can show beneficial effects. Unfortunately, with the risks and unwanted side effects associated with drug therapies, natural alternatives are potential solutions to alleviate the condition. The phytochemical constituents in herbs and spices, mainly responsible for the antioxidant activity, are polyphenols. In several studies, herbs and spices including clove, ginger, cinnamon, turmeric, black pepper, cumin, oregano, sage, peppermint, thyme, rosemary, dill, parsley, basil, cinnamon, and saffron, were reported to have the greatest antioxidant capacity [29, 51 - 53].

All of these compounds appear to act on different molecular targets, affecting several signaling pathways. The major mechanisms by which these herbs and spices show antioxidant properties are: scavenging ROS to protect neurons from oxidative damage through hydrogenation and complexation with oxidizing species and thus resist oxidative stress [22, 54]; neutralizing ROS and NO-based free radicals [13, 14]; inhibiting lipid peroxidation of neuronal membranes (54); enhancing enzymatic and nonenzymatic antioxidant defence such as, SOD, Glutathione Peroxidase (GPx), Catalase (CAT), in the brain [55]; inducing HO-1 expression thereby increasing resistance to oxidative injury [56]; reducing nitric oxide content and restoration of Na^+-K^+ ATPase [57].

Anti-inflammatory

Neuroinflammation is a prominent pathological feature of neurological disorder, characterized by activated microglia and infiltrating T-lymphocytes at sites of neuronal injury [58]. Injury to the neurons stimulates the microglia, a member of the innate immune system, which further activates other glia such as astrocytes to coordinate a collective response to neuronal injury. In response to alterations induced in the innate immune system, T-lymphocytes, members of the adaptive immune system, infiltrate the CNS at sites of neuronal injury. Thus, active participation of inflammation in neurological disease pathogenesis, as well as its contribution to neurodegenerative pathology and tissue destruction is evident [59, 60].

Like the macrophages, microglia can cause a transition from protective anti-inflammatory to a cytotoxic proinflammatory state, thus offering a potential pathway for neurodegeneration [61]. Thus, in response to injury, proinflammatory response mediated by microglia secretes potent ROS such as superoxide radicals and nitric oxide, proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, and IL-1β and also reduces the release of neurotrophic factor. Other inflammatory mediators include the chemokine macrophage inflammatory protein-1α (MIP-1α), interferon-γ (IFN- γ), and compounds such as lipopolysaccharide (LPS) [61].

While the mechanisms behind the health benefits from spices and herbs are becoming clearer over time, the vast majority of spices and herbs are found to act *via* its anti-inflammatory effect. The most frequently identified spices that possess anti-inflammatory effects are thyme, oregano, rosemary, sage, basil, mint, turmeric, dill, parsley, cinnamon, clove, nutmeg, lemongrass, ginger, chili pepper, fenugreek, and pepper [29].

The reported mechanism behind the anti-inflammatory effects of herbs and spices in the presence of compounds such as curcumin, gingerol, and capsaicin, which appear to operate by inhibiting one or more of the pro-inflammatory mediators responsible for neurotoxicity [62].

A diet rich in herbs and spices may contribute to the reduction of inflammatory mediators. Several herbs and spices also exhibited anti-inflammatory activity by increasing anti-inflammatory IL-10 production [63]. Quercetin (found in basil, cumin, and fennel), ursolic acid (found in basil and rosemary), gingerol (found in ginger), capsaicin, and curcumin, are found to inhibit the NF–κB pathway [64]. Curcumin is also reported to significantly decrease the levels of proinflammatory cytokine IL-1β of oxidized proteins of Aβ peptide and it also inhibits microglia activation [65, 66]. The highest anti-inflammatory activity has been detected in chili pepper, which enhances the IL-10, IL-6 levels and reduces TNF-a secretion, iNOS expression. The chili pepper compound, capsaicin also modulates NF-jB- and IL-8 pathways [67, 68]. Black pepper also strongly inhibits IL-6 production and the expression of iNOS. Nutmeg extract was reported to be the most potent inhibitor of TNF-a, IL-6, and IL-10 production and COX-2 expression. According to the literature, macelignan, a constituent of nutmeg is found to show anti-inflammatory activity in the hippocampus and primary microglial cells [69].

Cholinesterase Inhibition

In the central nervous system, acetylcholine (Ach) is involved in various physiological functions such as learning, memory, and mood. But once released in the synaptic cleft, it is cleaved by the enzyme acetylcholinesterase (AChE) thereby terminating the synaptic activity (Soreq and Seidman 2001). Inhibitors of AChE have become an important strategy to treat cognitive impairment, orientation, comprehension, learning, thinking, and judgment in AD and PD [70].

The cholinergic hypothesis is the basis for the development of treatment approaches designed to facilitate the survival of the cholinergic system. For this purpose, cholinesterase inhibition (ChEI) has proven to be a preferable therapy, as it amplifies the action of ACh. Several ChEI's have been approved by the Food and Drug Administration (FDA) for the symptomatic treatment of AD. However, these drugs have limitations due to unfavorable side effects. Hence, more studies must be conducted to look for better alternatives for ChEIs from natural sources [71].

The phytochemicals present in herbs and spices such as terpenoids, flavonoids, and steroidal alkaloids have been reported to possess potent ChE inhibitory activity. In in-vitro and in-vivo studies of *Ferula asafoetida* have been reported to have ChE inhibiting activity on the snail nervous system [72]. Two of the main

rosemary constituents, rosmarinic and carnosic acids, were found to exhibit promising AChE inhibitory activity for preventing AD [70]. Berberine has also demonstrated acetylcholinesterase-inhibiting property [72].

Modulation of Amino Acid Neurotransmitter System (GABA)

The brain neurotransmitter system plays an important role in neurological disorders. The principal inhibitory neurotransmitter is gamma-aminobutyric acid (GABA), while the principle excitatory neurotransmitter is glutamate [72]. Coordination between these two neurotransmitters ensures adequate synaptic excitation/inhibition and neural oscillation. Thus dysregulation in the neurotransmitter system has been implicated in a number of neurological and psychiatric diseases including epilepsy and schizophrenia [72]. Several different categories of drugs modulate GABAergic synapses and are used for the treatment of anxiety and sleep disorders, epilepsy, alcohol withdrawal, and induction and maintenance of anesthesia [73]. Also, glutamate dysfunction has been correlated with neurological disorders, such as Alzheimer's disease, schizophrenia, pain disorders, drug addiction [73].

Recent studies have reported that phytoconstituents in herbs and spices act on the neurotransmitter system, indicating theirrole in positive correlation or the treatment of neurological disorders. Gambogic acid present in Kokum spice is found to prevent glutamate-induced neuronal cell death and neurite outgrowth in PC12 cells [74]. Atractylenolide, isolated from *Atractylodes macrocephala*, herb is used to treat sleep disorders, as this sesquiterpene enhance the action of GABA (28). The essential oil of thyme has been suggested to have a neuroprotective effect against toxicity *via* facilitating GABA action and modulates the GABAA receptor [75 - 77]. Flavonoids present in garlic extract are found to have a protective effect on primary neurons from glutamate toxicity and oxidative injuries [74].

SPICES AND HERBS USED IN MAJOR NEUROLOGICAL DISORDERS

Alzheimer's Disease (AD)

Amongst a variety of neurodegenerative diseases, Alzheimer's disease is the most devastating disorder which typically appears after age 60 and is linked to a specific genetic defect. Clinically AD is characterized by progressive and irreversible memory deficits. Memory impairment is the hallmark of disease at the early stage and is followed by a later stage that involves motor and sensory dysfunction. The diagnosis of the disease is based on the presence of one or more cognitive deficits including the impaired ability for motor activities, language impairment, failure to recognize or identify objects, and impairment in executive

functioning [78]. Over the decade, researchers have tried to discover the pathophysiology and risk factors responsible for AD and possible mechanisms leading to the formation of plaques and tangles in the brain. The primary mechanism underlying the neurodegeneration in AD is attributed to the production and accumulation of β-amyloid (Aβ) peptides in the specific region inthe brain [79]. In addition, other etiological cause for disease progression includes oxidative stress manifested by lipid peroxidation, ROS formation, protein oxidation, nitrotyrosine, and DNA/RNA oxidation [80, 81]. The major risk factor for AD is aging, which leads to loss of free radical scavenging ability by the endogenous defence system [29]. Hence, these contribute to a disturbance in the normal balance between free radical generation and free radical scavenging [78].

Current conventional treatment approved by FDA includes acetylcholinesterase inhibitors (AChEIs) (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate (NMDA) receptor antagonist (memantine) [78]. Complex pathophysiological mechanisms of AD provide insight for a potential new therapeutic compound. In recent years, the therapeutic potentials of alternative herbal drugs have become popular in the treatment of many ailments. It has been also implicated for symptomatic treatment of AD based on the mechanisms of action and therapeutic targets of herbal drugs. The therapeutic strategies for the treatment of AD using herbs and spices include anti-amyloid action, β- and γ-secretase inhibition, inhibition of Tau hyperphosphorylation, antioxidant and antiapoptotic effect, anti-inflammatory effect, anticholinesterase activity, *etc*. The possible mechanism of herbs and spices in Alzheimer's disease is shown in Fig. (**2**).

Researchers have also evaluated several constituents in herbs and spices for their anti-amyloidogenic activities, including ellagic acid, garlic acid, ginger, mulberry leaf extract [39]. Recent research has also reported that curcumin improves memory and synaptic functions in animal models of AD [82]. Further, it reduces the levels of oxidized proteins and IL1B in brains [66]. It inhibits peroxidase and binds to redox-active metals, iron, and copper, and suppresses inflammatory damage by preventing metal induction of nuclear transcription factor-κB (NFκB) [83 - 85]. Extract of Ginkgo biloba has been widely used in memory impairment *via* multiple cellular and molecular neuroprotective mechanisms; which includes attenuation of apoptosis, the inhibition of membrane lipid peroxidation, anti-inflammatory effects, and the direct inhibition of Aβ aggregation [39]. The phenolic and flavonoid contents in *Atriplex laciniata* possess significant antioxidant and anticholinesterase effects, which are effective in the treatment of AD and other neurological disorders [86]. Garlic extract, Rosmarinic acid in sage reduces amyloid-beta induced apoptosis in PC12 cells [87, 88]. Turmeric, ginger, cinnamon, and curcumin extracts have been found to successfully block amyloid-

beta aggregation and thus, are effective in the treatment of AD [89, 90]. Ursolic acid in basil and linalool in coriander is found to treat AD by inhibiting acetylcholinesterase activity [91].

Piperine present in Black pepper improves memory impairment and neurodegeneration in AD [39]. A list of commonly used herbs and spices in the treatment of AD is shown in Table **4** [91, 92].

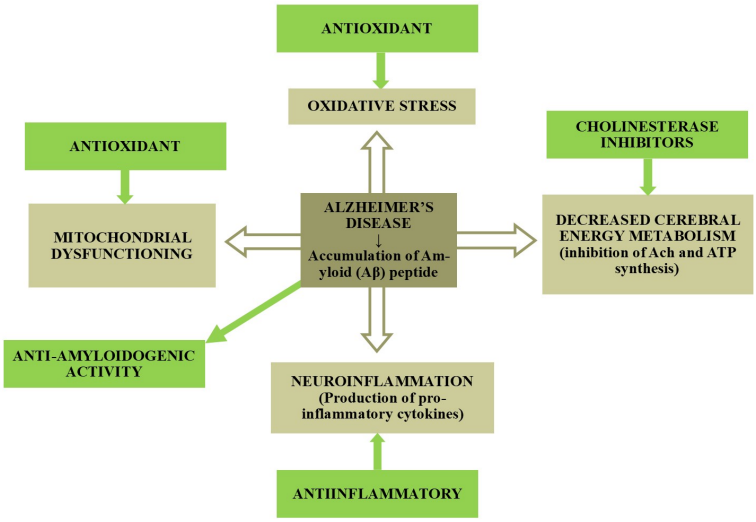

Fig. (2). Possible mechanism of herbs and spices in Alzheimer's disease.

Table 4. List of commonly used herbs and spices in treatment of AD [91, 92].

Herbal Drug	Biological Source	Family	Possible Mechanism	References
Ginkgo	*Ginkgo biloba*	Ginkgoaceae	Antioxidant, Free radical scavengers for free radicals, inhibits lipid peroxidation	[93]
Sage	*Salvia officinalis*	Lamiaceae	Antioxidant and Acetylcholinesterase-inhibitory effect	[94]
Rosemarry	*Rosmarinus officinalis*	Lamiaceae	Antioxidant, inhibitors of lipid peroxidation	[95]
Turmeric	*Curcuma longa*	Zingiberaceae	Inhibition of NFκB and amyloid-beta aggregation	[96]

(Table 4) cont.....

Herbal Drug	Biological Source	Family	Possible Mechanism	References
Ginseng	*Panax ginseng*	Araliaceae	inhibition of amyloid-beta aggregation and enhancement of the removal of Aβ from the neurons, interruption of tau hyperphosphorylation	[97]
Ginger	*Zingiber officinale*	Zingiberaceae	inhibition of amyloid-beta aggregation	[98]
Basil	*Ocimum basilicum*	Lamiaceae	Inhibited acetylcholinesterase	[99]
Coriander	*Coriandrum sativum*	Apiaceae	Inhibited acetylcholinesterase *in vitro*	[100]
Sage	*Salvia officinalis*	Lamiaceae	Protected PC12 cells from Abeta-induced neurotoxicity	[101]

Parkinson's Disease (PD)

Parkinson's disease is the second most common neurodegenerative disease that can impair quality of life. It is a chronic and progressive movement disorder characterized by muscular rigidity, tremor, and bradykinesia [3]. The etiology of PD is not clear, but studies have implicated that oxidative stress from exogenous stressors or endogenous neurotoxins can cause dysfunction in the dopaminergic system. The disease is triggered by the reduction of dopaminergic neurons in the substantia nigra pars compacta, along with the presence of Lewy bodies within dopaminergic neuronal populations [102]. Apart from dopaminergic dysfunctioning, chronic neuroinflammation is considered a pathological hallmark of PD. Chronic release of pro-inflammatory cytokines by activated astrocytes and microglia leads to the expression of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, and interferon-γ, which leads to the worsening of neuronal degeneration in the SNpc [102].

Most of the current treatment approaches in PD are aimed to replenish the striatal dopamine levels to provide symptomatic relief during the early stage but do not effectively tackle tremor, postural instability, and cognitive deficits. These drugs do not exhibit neuroprotective effects in PD. Thus, novel therapies involving natural antioxidants and plant products with neuroprotective properties are currently being explored as adjunct therapy.

Curcumin is a polyphenol component of *Curcuma longa* that exhibits antioxidant and anti-inflammatory properties. It is also reported to cross the blood-brain barrier and shows neuroprotective effect in neurological disorders. Moreover, studies in different experimental models of PD suggested the clinical application

of curcumin in PD [103]. It also reduces synuclein toxicity, intracellular ROS, and apoptosis in neuroblastoma cells in PD [104].

Zingerone in ginger and eugenol in clove have been reported to prevent 6-OHDA induced dopamine depression in the striatum and increased superoxide scavenging activity in mouse brain [105, 106]. Growing studies indicated that various herbs such as green tea polyphenols (catechins), ginseng (ginsenoside), ginkgo biloba, *etc*. attenuate degeneration of dopamine neurons caused by the neurotoxins 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) and have suggested to promote neuronal survival, and facilitate functional recovery of brain injures through neuroprotective effects such as the antioxidants, dopamine transporter inhibitors, monoamine oxidase inhibitor, free radical scavengers, chelators of harmful metal ions, modulating cell survival genes, signaling and anti-apoptosis activity [107]. Studies also reported a protective effect of ginseng against PD by promoting neuronal cell survival and reducing the neurotoxicity induced by neurotoxin toxins [108]. Commonly used spices and herbs are shown in Table **5**.

Table 5. List of commonly used Spices and Herbs in PD.

Herbal Drug	Biological Source	Family	Possible Mechanism	References
Ginkgo	*Ginkgo biloba*	Ginkgoaceae	protects apoptosis of PC12 cells by increasing bcl-2 activation, maintaining mitochondrial membrane potential and decreasing caspase-3 activation through the mitochondria-dependent pathway, blockade of lipid peroxidation, reduction of oxidative stress, and prevents neurodegeneration of the nigrostriatal pathway	[93]
Ginseng	*Panax ginseng and Panax notoginseng*	Araliaceae	Antioxidant effect on hydrogen peroxide (H2O2)-induced oxidative stress to PC12 cells, the release of cytochrome c and activation of caspase-3, elevated Bax/Bcl-2 ratio, decreases the increase of iron influx	[97]
Baicalein	Scutellaria baicalensis	Labiatae	Inhibits the accumulation of ROS, deficiency of ATP, dissipation of mitochondrial membrane potential, and activation of caspase-3/7	[109]
Curcumin	Curcuma longa	Zingiberaceae	Decrease intracellular ROS generation and inhibit caspase-3 activation, inhibits MPTP-induced hyperphosphorylation of c-Jun N-terminal kinase (JNK), prevents the degeneration of nigrostriatal neurons by inhibiting the dysfunction of mitochondria, neuroprotection	[66]

Herbal Drug	Biological Source	Family	Possible Mechanism	References
Gastrodin	Gastrodia elata	Orchidaceae	Reduces the proportion of apoptotic cells, ROS, and Bax/Bcl-2 ratio	[110]
Tenuigenin	Polygala tenuifolia	Polygalaceae	Prevents the abnormal shrinking of dendrites and promotes the survival of mesencephalic dopaminergic neurons, downregulate caspase-3 activity, neuroprotective effects *via* its antioxidant and antiapoptotic profile	[111]

Epilepsy

Epilepsy is a group of heterogeneous disorders characterized by the propensity to experience spontaneous recurrent seizures. The condition can be genetic or acquired, and the underlying mechanisms of disease initiation, propagation, and comorbid conditions are incompletely understood. Reports suggested that metabolic changes, including the production of reactive species, are known to result from prolonged seizures and may further contribute to epilepsy development [112].

Bilobalide in *Ginkgo biloba* is extensively used as an anticonvulsant and cognitive enhancement. Valerenic acid present in Valerian root and rhizome has beneficial effects in a number of neurological disorders such as epilepsy, insomnia, dizziness, and anxiety. Ginkgolide and Zerumin isolated from *Curcuma kwangsiensis* rhizomes have GABAA modulatory action [30]. Black pepper extract has been found to prolong anticonvulsant activity against audiogenic seizures in different animal models [113]. Eugenol in clove suppresses epileptiform field potentials in neocortical and hippocampal tissues [114]. Anethole in tarragon exhibited dose-dependent antiseizure activity in maximal electroshock and pentylenetetrazole models of experimental seizures [112]. Horseradish and Celery seed reduces seizure phenotype attributed to the presence of kaempferol and apigenin [115].

Curcumin is reported to have a beneficial effect in ameliorating seizures, oxidative stress, and cognitive impairment in pentylene-tetrazole-treated animals [116].

Depression

Major depression is a commonly occurring multifactorial disorder classified under life-threatening neuropsychiatric conditions. Several mechanisms for the pathophysiology of depression are known. Traditionally, decreased monoamine function in the specific region of the brain is considered to be the primary cause of depression [117]. The imbalance between neuroprogressive and neuroprotective

factors is observed in major depression. Other factors include proinflammatory cytokines and lipid peroxidation. Also, Mitochondrion dysfunctioning plays a significant role in the pathophysiology of depression *via* actions of free radicals, nonradical molecules, and reactive oxygen and nitrogen species [118]. Stress and inflammatory processes are known to contribute to the development of depression. Several studies also suggested that stress leads to the activation of microglia, which increases the production of inflammatory mediators such as IL-1β, IL-6, and TNF-α [3]. Further studies have shown that major depressive disorders are associated with the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to elevated levels of glucocorticoids and impaired glucocorticoid receptor-mediated negative feedback on the function of the HPA axis [117]. Recent reports also suggest that neurotrophic factors play a critical role in the pathogenesis of depression. Analysis revealed that depression is associated with lower levels of BDNF [118].

The secondary metabolites present in herbs and spices, such as polyphenols, flavonoids, and alkaloids possess antidepressant activity through a different mechanism. Alkaloids present in *Areca catechu* (Arecaidine, Arecoline, Guvacine) and *Withania somnifera* (Withanolides and withanols) show mood-stabilizing action through inhibition of MAO-A. Curcumin, Hyperforin, and Rutin also possess inhibitory action against MAO-A. Flavonoid present in herb *Apocynum venetum* is found to modulate the central monoaminergic system and thus can be effective in the treatment of depression. Several herbs also act against oxidative stress and thus can be potential molecules against depression, such as bacoside-A in *Bacopa monniera* and warifteine in *Cissampelos sympodialis* [119].

Although several spices are found to be effective in the treatment of depression, saffron has been one of the first to be tested as a treatment of mild depression in clinical trials [64]. Garlic extract also possesses anti-depression properties *via* inhibition of monoamine oxidases and thereby increasing levels of monoamine neurotransmitters such as norepinephrine, dopamine, and serotonin, and also by decreasing GABA levels [120]. Chronic treatment of piperine significantly ameliorates behavioral deficits of CUMS-treated animals, associated with significantly increased BDNF protein expression in the hippocampus and frontal cortex [121]. Curcumin also alle*via*tes symptoms of depression by enhancing neurogenesis in the hippocampus and frontal cortex of the brain [122]. Traditionally Ginkgo biloba has been prescribed in the treatment of depression [123]. Eugenol in Cloves also acts as an antidepressant by inducing the expression of metallothionein-III in the hippocampus. Eugenol also induces upregulation of BDNF in the hippocampus of mice [124].

Schizophrenia

Schizophrenia is a neuropsychiatric condition characterized by positive symptoms such as the presence of abnormal feelings or behaviors, including hallucinations, delusions, and negative symptoms such as lack of interest and indifference in daily life. Two major hypotheses that explain the etiology of schizophrenia include dopamine dysfunction and glutamatergic hypofunction. More recently, increased cytokine levels, including pro-inflammatory cytokines IL-6, IL-1β, TNF-α, have been found to be associated with schizophrenia [3]. Apart from neuroinflammation, oxidative stress has been suggested to contribute to the pathophysiology of the disease. Experimental findings demonstrated that oxidative stress is responsible for behavioral and molecular anomalies associated with schizophrenia [125].

Quercetin rutoside, an antioxidant glycoside present in several herbs and spices, can quench the superoxide production without interfering with the electron transfer activity of the reductase. It is also reported that higher concentrations of quercetin in red onions may be beneficial in neuropsychiatric conditions [126]. The anthraquinone derivative emodin suppressed the acoustic startle response and abolished prepulse inhibition associated with psychiatric conditions. The application of emodin also attenuated the phosphorylation of ErbB1, ErbB2, and EGF receptor signaling and ameliorated behavioral deficits [125].

CONCLUSION

Herbs and spices are gifts of nature to mankind, as they are inherited with numerous components which possess several curative properties. In this chapter, several spices and herbs which are beneficial in treating various neurobiological disorders and their probable mechanisms of action are described. Though various drugs for treating neurological disorders like depression, AD, PD, Schizophrenia and epilepsy are available, treatment with spices and herbs described here may overcome the adverse effects of regular treatment.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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CHAPTER 4

Spices and Herbs in Bacterial and Fungal Resistance

Rashmi V. Trivedi[1,*], Mayur B. Kale[1], Nitu L. Wankhede[1] and **Milind J. Umekar[1]**

[1] *Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur 441002, India*

Abstract: A plethora of pathogenic microorganisms is responsible for several infectious diseases. For many decades, the treatment of microbial infections includes the use of various antimicrobial agents. However, the extensive use of antibiotics has been found to develop multiple drug resistance (MDR) in many pathogens. Furthermore, the rate of MDR is higher in developing countries because of indiscriminate use and self-medication. The emergence of MDR limits the effectiveness and therapeutic options for common infections. As a result, much attention is given to naturally derived products that can be used as potential, with better efficacy, less expensive alternative, and safe antimicrobials for the treatment of common infections.

Herbal medicines have always been used as an alternative to treat diseases due to toxicity and associated side effects of allopathic medicines. In recent years, the use of herbs and spices in therapy has been gradually increasing in many developing countries because of their safety, efficacy, and other beneficial effects. Spices and herbs have been used for thousands of years for flavouring and preserving foods. Many of these herbs and spices, such as thyme, cinnamon, clove, oregano, cardamom, nutmeg, mint, and cumin, are known to exert a range of therapeutic activities, including antioxidant, anti-inflammatory, and anticancerogenic. These are also useful for preventing lipid oxidation and free radical scavenging agents in living organisms.

Spices and herbs demonstrate antimicrobial activity due to the presence of some of the important phytochemicals or essential oils, which are naturally toxic to microbes. The phytochemical screening disclosed the presence of a number of secondary metabolites such as resins, phenols, alkaloids, flavonoids, sterols, reducing sugars, tannins, glycosides, *etc*. and various essential oils which act on a wide range of microorganisms such as fungi, viruses, bacteria, protozoa, *etc*. The antimicrobial activity of the spices depends on the composition, the type of the spices, and various other environmental factors. The mechanism of its action by which these phytoconstituents act is generally complex and mostly depends on the presence of chemical constituents. It is also affected by the different cell wall components, such as its composition and the presence

[*] **Corresponding author Rashmi V. Trivedi:** Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur 441002, India; E-mail: rashmitrivedimishra@gmail.com

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

of different proteins on the cell envelope, as these are the major components that interact with the molecules. Some essential oils in plants cause partial disintegration due to the disruption of the lipopolysaccharide in the outer layer. It also inhibits the synthesis of nucleic acids, polysaccharides, and proteins in bacterial and fungal cells.

Thus, the use of spices and herbs presents a great potential to be used as an alternative or in addition with the allopathic medicine to decrease the side effects and progressively increase the resistance of pathogens induced by the use of allopathic drugs.

Keywords: Alkaloids, Spices, Herbs, Bacterial resistance, Essential oils, Cell wall synthesis inhibition, Protein synthesis.

INTRODUCTION

For centuries, spices and herbs have been used to improve the flavour and aroma of foods. Early cultures also reported the importance of using herbs and spices in the preservation of foods and their medicinal value. Since the late 19th century, as per scientific experiments, the antimicrobial properties or application of some spices, herbs, and their active components have been documented [1, 2]. There are many spices and herbs that are known for their antioxidant activity and importance in the prevention of lipid oxidation in living organisms as well as in foods. For instance, turmeric, oregano, cinnamon, cumin, parsley, garlic, mustard seed, ginger, basil, pepper, and cardamom are stated to possess antioxidant activity. For thousands of years and throughout the world, spices and herbs have been used for different purposes. Specifically, extracts of these crude spices and oils extracted from them have various applications, including alternative medicine, pharmaceutical, raw, and processed food preservation, and natural therapies. In addition, the antimicrobial action of different spices and herb extracts has been studied and reported against many microorganisms. Spices have also been used to combat snakebites, stomach disorders, poor eyesight, poor circulation, sleeping problems, colds, sores, motion sickness, lumbago, muscular aches, gout, and hangover [3 - 5].

Spices possess antibacterial and antifungal activity. Many microbiologists and food-product developers or specialists have conducted laboratory studies that involve diverse and challenging food-borne bacteria, fungi, and yeasts with extracted phytochemicals from spice plants. Several techniques have been used to examine antimicrobial activity, and the primary data vary considerably in quantity and quality among different sp0ices. Hence, it strongly demonstrates potent antimicrobial properties [6 - 8].

Various bacteria show resistance towards many antimicrobial agents, which is called antibiotic resistance. In food contaminated by microbial pathogens, spoilage may occur and risk of foodborne diseases, and the development of multidrug-resistant and disinfectant resistant bacteria like *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Staphylococcus aureus* (*S. aureus*) may increase rapidly, causing an increase in the rate of mortality and morbidity [9]. Weak acids such as sorbic acids and benzoic acids [10] are commonly used in the food industry as preservatives to increase the safety, stability, and overall shelf-life of manufactured foods by controlling pathogenic and food-related spoilage causing microorganisms, that in turn may contribute to the development of microbiological resistance [11, 12]. However, chemical preservatives fail to eliminate several pathogenic bacteria in food products or extend the occurrence of microbial spoilage. Naturally obtained spices can be used as a preservative and are tolerated by the human body compared with synthetic products. The antimicrobial activities of natural products are applied in the food industry [13, 14].

The World Health Organization (WHO) has statistically reported that of the 55 million people who died in 2011 worldwide, one-third of the deaths were due to infectious diseases [15]. Antibiotic-resistant microorganisms can increase the death rate as they are not easily killed by antimicrobial agents [16]. Such situations increase the need for modifications in the structure of synthetic antibiotics that have been marketed [17]. Hence, much attention and importance must be paid to natural products like spices that can be used for treating various infectious diseases, with high efficacy against pathogens and minimal side effects [18]. Various spices such as oregano, clove, turmeric, cinnamon, ginger, cumin, and garlic have been used to prevent and treat infectious diseases and protect food. These spices were experimentally confirmed to exhibit antimicrobial activities against pathogenic fungi and bacteria [19, 20]. The secondary metabolites found in spices are antimicrobial agents that generally have negligible adverse effects [21]. Therefore, spices and herbs could be novel antimicrobial agents against food-derived and human pathogens.

ANTIBACTERIAL AGENTS

Antibiotics are compounds that are ‘against life; are typically antibacterial agents, which interfere with some process or structure essential for bacterial growth or survival without any harm to the eukaryotic host harboring the infecting bacteria. There are two types of antibacterial agents, bactericidal (can kill bacteria) and bacteriostatic (nullify the growth). Mechanism of antibiotic resistance is shown in Fig. (**1**) while targets of spices and herbs for antibacterial activity are shown in Table **1**.

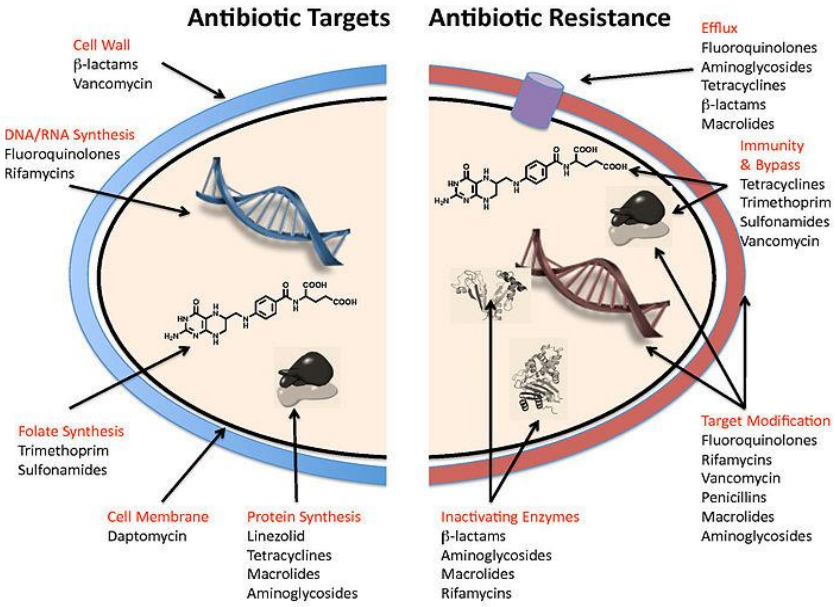

Fig. (1). Mechanism of Antibiotic Resistance.

DEVELOPMENT OF RESISTANCE

Pump Out The Antibiotic

To be effective, antibiotics must specifically target bacteria and get collected in specific effective concentrations that can act in the same sensible time frame. For instance, the protein synthesis machinery is situated in the cytoplasm, so antibacterial agents that are inhibitors of protein synthesis must pass across the cell membrane (inner membrane barriers for Gram-positive bacteria; outer and inner permeability barriers for Gram-negative bacteria) and then accumulate to adequate concentrations to block the target step during protein assembly. Both Gram-positive and negative bacteria that develop resistance to antibiotics (like tetracyclines) usually overproduce related membrane proteins (with comparative molecular masses of 42,000) that can act as an efflux or export pump for the drugs. A drug is pumped out of the cell faster than it can diffuse in, so intrabacterial concentration decreases and becomes ineffective, and bacterial protein synthesis continues at largely unhindered rates [22, 23].

Destroy the Antibiotic Warhead

A second approach to developing resistance is through the destruction of the specific chemical warhead in the synthetic or naturally obtained antibiotic. The classic example is hydrolytic deactivation of the β-lactam ring in the penicillins and cephalosporins through amplification of the hydrolytic enzyme β-lactamase by resistant bacteria. Due to strain, the four-membered lactam ring is the chemically activated functionality in the drugs that acylates and irreversibly modifies the cell wall-crosslinking. The lactamase-producing bacteria discharge this enzyme into the periplasm to destroy β-lactam antibiotics before they can reach PBP targets located in the cytoplasmic membrane [22, 24].

Reprogramme the Target Sructure

The possible third approach of developing resistance against antibiotics does not focus on the destruction or removal of the antibiotic but on reprogramming or masking of the target that is responsible for resistance in bacteria [22, 25].

Mechanism of Action of Spices as an Antibacterial Agent

The major phytoconstituent found in cloves is eugenol, which destroys the cell walls of microorganisms, and permeates the cytoplasmic membranes, and further inhibits the normal protein synthesis [26]. Eugenol can inhibit the production of amylase and proteases and thus causes cell wall deterioration and cell lysis [27]. Thyme is another example of a spice that contains an active compound called thymol, which has the ability to bind to the membrane protein by hydrogen bonding or hydrophobic bonding leading to a change in the permeability of the membrane. It also decreases the intracellular ATP content of *E. coli* and increases extracellular ATP, which disrupts the function of plasma membranes and leads to the death of bacteria [26, 28]. Cinnamon contains cinnamaldehyde as a major component or an active component, which inhibits membrane function, cell wall biosynthesis, and specific enzyme activities. Cinnamon shows antimicrobial activities in a wide range of its species, like MRSA and *A. niger* [29]. Garlic possesses' ability to penetrate the cellular membranes of bacteria and results in the death of different species of bacteria [30]. Fennel seeds can break the permeability of the cell membrane of *S. dysenteriae* and causes leakage of electrolytes, loss of reducing sugars, proteins, *etc*., and further causes decomposition and death of cells. Coriander has the capability to permeate bacterial cell walls, resulting in the loss of all cellular functions [31]. Black pepper causes physical changes in the cell walls of E. coli and further leads to leakage of proteins, electrolytes, ATP, and DNA materials, which results in the death of bacteria [32].

Table 1. Targets of Spices and herbs for antibacterial activity.

S. No	Targets	Spices and Herbs
1	Cellular Metabolism	Cinnamon, Fennel
2	Bacterial Cell wall	Clove
3	DNA and Protein synthesis	Oregano, Black pepper, Nutmeg, Rosemary, Clove
4	Cell apoptosis	Oregano
5	Affects bacterial cellular morphology	Fennel, Mustard, Galangal
6	Cell Proliferation Process	Turmeric
7	Bacterial Cell Membrane	Oregano, Turmeric, Thyme, Cumin, Ginger, Nutmeg, Galangal, Cardamom, Dill, Anise
8	Bacterial Enzymes	Nutmeg, Garlic, Mustard, Asafoetida
9	Biofilm formation	Cumin, Ginger, Cardamom
10	Energy Metabolism Process	Oregano, Black Pepper, Rosemary
11	Bacterial Respiration	Black Pepper, Basil
12	Membrane Potential	Coriander
13	Efflux Pump	Coriander
14	Synthesis of fatty acid	Rosemary
15	Leakage of essential constituents	Cinnamon, Fennel, Rosemary, Basil

ANTIFUNGAL AGENTS

A drug that selectively removes fungal cells from a host with minimal toxicity to the host is known as an antifungal agent. Targets of spices and herbs for antifungal activity are shown in Table **2**.

Table 2. Targets of Spices and herbs for antifungal activity.

S. No	Targets	Spices and Herbs
1	Mycelium Growth	Cinnamon, Thyme, Cumin, Basil, Asafoetida, Anise
2	Destroys Cell Membrane	Cinnamon, Clove, Turmeric, Black Pepper, Coriander, Dill
3	Energy Metabolism	Cinnamon, Clove, Garlic
4	Ergosterol Synthesis	Cinnamon, Clove, Ginger, Thyme
5	Alters the Morphology of Fungal cells	Oregano, Fennel
6	DNA and Protein Synthesis	Black Pepper
7	Fungal Cell Proliferation	Black Pepper

S. No	Targets	Spices and Herbs
8	Spore Germination Process	Black Pepper, Thyme, Anise, Cardamom
9	Targets Biofilm	Coriander
10	Targets Expression Fumonisin Biosynthetic Gene	Cumin
11	Affects Fungal Cell integrity and leakage of constituents	Garlic, Ginger, Black Pepper, Dill, Nutmeg
12	Aflatoxin Synthesis	Rosemary
13	Molds Growth	Mustard
14	Protoplast of Fungi	Galangal
15	Essential enzymes of Fungi	Dill
16	Deposits of ROS	Dill

DEVELOPMENT OF RESISTANCE

Resistance to Azoles

Decrease drug concentration

The development of active efflux pumps results in decreased drug concentration at the site of action. Efflux pumps are encoded by Candida species by two gene families of transporters: multi drug resistance (MDR) genes of the major facilitators class and the Candida drug resistance (CDR) genes of the ATP binding cassette superfamily [33]. Upregulation of CDR1, CDR2, and MDR1 has been proven in azole-resistant C. albicans. Other transporter genes have been noticed in Candida species, like CdCDR1 and CdMDR1 in *Candida dubliniensis* and CgCDR1 and CgCDR2 in *C.glabrata*. While CDR gene up-regulation confers resistance to approximately all azoles, the MDR-encoded efflux pumps are limited for fluconazole [34, 35].

Target site alteration

ERG1 is the gene encoding for the target enzyme lanosterol C14a-demethylase, which prevents the binding of azoles to the enzymatic site. Mutations in ERG11 lead to the development of intrinsic resistance to fluconazole in *C. krusei*, which decreases the affinity of ERG11p to the drug [36]. More than 80 amino acid substitutions in ERG11p have been detected. Similarly, different mutation coexists in the same gene, which leads to the development of resistance against the azole class of drugs [37].

Up-regulation of the target enzyme

Target enzyme up-regulation can be attained through gene amplification, which increases the transcription rate or decreases degradation of the gene product. As compared to other mechanisms described above, this mechanism contributes less to the overall resistance burden, as previously observed in Candida species [38].

Resistance to Polyene

Defect in the ERG3 gene, which is involved in ergosterol biosynthesis, leads to the accumulation of other sterols in the fungi membrane. Therefore, polyene-resistant Candida and Cryptococcus isolates have comparatively low ergosterol content than polyene-susceptible isolates [39]. This indicates the development of resistance against polyene like amphotericin B caused by the defect in the ERG3 gene. Resistance to amphotericin B is also facilitated by increased activity of enzyme catalase, which causes decreased susceptibility to oxidative damage [40].

Resistance to Echinocandin

Fks1 is the gene of β-1, 3-D-glucan synthase complex, that accounts for synthesizing 1, 3-β-glucan chains, one of the major structural polymers of the Saccharomyces cerevisiae cell wall [41]. Mutation in the Fks1 gene, mostly at Ser645 position, leads to the reduction of glucan content of the cell wall and increase in chitin content and also activates the expression of CWP1, which encodes a glycosylphosphatidylinositol (GPI)-dependent cell wall protein. This causes echinocandin resistance in Candida species as well as in other species [42].

Resistance to Flucytosine

Flucytosine is a base pyrimidine analog that is responsible for inhibiting nucleic acid synthesis. Mutation in cytosine permease results in the impairment in cellular uptake, which causes resistance development against flucytosine [43]. Furthermore, a mutation in enzyme-like uracil phosphoribosyltransferase or cytosine deaminase results in a defect in flucytosine metabolism and leads to the development of resistance.

MECHANISM OF ACTION OF SPICES AS AN ANTIFUNGAL AGENT

Oregano contains carvacrol that binds to the sterols, which is the main component of the fungal cell wall and causes the change in the permeability for small cations. By changing the permeability of the fungal cell wall, it causes the death of Candida species [44]. In addition to this, cinnamaldehyde, a vital constituent of cinnamon, inhibits the fungal cell wall biosynthesis and causes the death of different fungal species. Furthermore, garlic has the ability to penetrate the

cellular membrane as well as a mitochondrial membrane which results in the death of fungi like *C. albicans* [29].

DETAILED ACCOUNT OF SOME SPICES AND HERBS HAVING ANTIBACTERIAL AND ANTIFUNGAL POTENTIAL:

Cinnamon

• **Biological source:** The biological source of cinnamon is *Cinnamomum zeylanicum* Nees, which belongs to the family Lauraceae. It comprises the dried inner bark of the shoots of trees [45, 46].

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• **Phytoconstituents and phytochemistry:** The cinnamon barks mainly consist of volatile oil in the range of 0.5-1%. Along with this, it also contains mucilage and phlobatannins. In its essential oil, about 4-10% of eugenol and 60-70% of cinnamaldehyde is present, along with it some traces of phellandrene, caryophyllene, pinene, limonene, (-) linalool is also found [46]. The spicy taste and smell of cinnamon are due to the presence of cinnamaldehyde, and it appears brown due to the uptake of oxygen. The presence of a wide range of essential oils has been documented, such as cinnamyl acetate, trans-cinnamaldehyde, eugenol, terpinolene, and α-thujene L-borneol, caryophyllene oxide, L-bornyl acetate, b-caryophyllene, E-nerolidol, α-cubebene, α-terpineol [45].

• **Antibacterial mode of action of cinnamon:** The cinnamaldehyde causes the leakage of phosphate ions in a time and -dose-dependent manner. Exposure to cinnamon oil or cinnamaldehyde decreases the amount of intracellular ATP. Along with this, cinnamaldehyde also liberates intracellular components like proteins, nucleic acid when subjected to microbes. Due to the lipophilic nature of cinnamon essential oil, it can modify the monolayer structure of the membrane by getting incorporated into it. Also, it enhances the fluidity of the microbe's membrane by decreasing the effectiveness of packing lipid molecules [47].

• **Antifungal mode of action of cinnamon:** It is also active against fungi. In *Rhizopus nigricans*, cinnamon oil suppresses the growth of mycelia as well as modifies the morphology of mycelia so that flattened, empty, shriveled, and collapsed hyphae are generated. Cinnamon oil reduces the activities of succinate dehydrogenase and malate dehydrogenase enzymes in the Krebs cycle, due to which energy metabolism gets altered in *Rhizopus nigricans*. In addition to this, cinnamon oil causes the outflow of proteins and essential ions by damaging the structure of the cell membrane *via* hampering ergosterol biosynthesis. The activities of beta-1, 3-glucan, and chitin synthase get obstructed by cinnamaldehyde which affects the production of fungal cell wall components [48].

• **Other uses of cinnamon:** It is used as an antiseptic, flavoring agent, stimulant, and aromatic. Along with this, cinnamon bark is also used as a mild astringent, stomachic, carminative. Cinnamon is also used commercially in the preparation of candy, perfumes, and dentifrices. Chiefly cinnamon barks are used as spices and condiments [49]. Cassia cinnamon is used most frequently in diabetes [50]. In addition, the main constituents in cinnamon are responsible for numerous therapeutic potentials, which include antiviral, antifungal, anti-microbial, anti-inflammatory, reducing CVS disease, cognition-enhancing, antioxidant, anti-cancer, gastro-protective and blood pressure, cholesterol, and lipid-lowering [51]. It is also used for prediabetes, gas (flatulence), obesity, and many other disorders, although no clear medical evidence is sufficient to support these applications. Cassia cinnamon is used as a flavoring agent in food and beverages. Recent reports have shown that cinnamon can ameliorate organ toxicity induced by chemical toxins through its antioxidant, radical scavenging, anti-inflammatory activities *via* modulation of numerous targets such as mitogen-activated protein kinase (MAPK), tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and nuclear factor-κB (NF-κB) signalling [52].

Clove

• **Biological source:** The biological source of clove is *Eugenia caryophyllus* which belongs to the family Myrtaceae and comprises dried flower buds [49].

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• **Phytoconstituents and phytochemistry:** Clove has been considered as the major source of phenolic molecules such as hydroxybenzoic acids, flavonoids, hydroxyphenyl propane, hydroxycinnamic acids, and eugenol ($C_{10}H_{12}O_2$), which is the largest biologically active molecule, and gallic acid derivatives such as hydrolysable tannins contained in the fresh plant in large amounts. In addition, clove includes flavonoids such as quercetin and kaempferol, as well as phenolic acids such as ferulic, caffeic, ellagic, and salicylic acids. Clove blossoms contain up to 18% of essential oil consisting of eugenol, eugenol acetate, and β-cariofileno. The presence of 36 elements screened by hydro-distillation in the Clove essential oil comprises eugenol, eugenyl acetate, ethyl hexanoate, calacorene, 2-heptanone, β-caryophyllene, α-humulene, humulene, and calamenene [53].

• **Antibacterial mode of action of clove:** Clove belongs to a class of volatile oils, and eugenol is the major chemical substance present in it. It is seen that essential oil present in clove buds exhibits antibacterial activity. It could destroy bacterial cell walls. Due to the lipophilic nature of the essential oil, it can easily interact with the cell wall. Also, it causes the liberation of intracellular materials from microbial cells, which are crucial for the survival of microorganisms; hence it results in bacterial cell death. Clove essential oil enters inside the cell by penetrating through the cytoplasmic membrane, damages the structure of the cell, and inhibits the process of DNA and protein synthesis, which are essential for bacterial growth [53].

• **Antifungal mechanism of action of clove:** Clove suppresses the growth of the various strains of fungi. Eugenol causes metabolic arrest in conidia. It shows the dose-dependent fungicidal action. The mode of action of clove behind fungal cell death comprises - occurrence of primary lesions on the cell membrane, which

results in indirect damage to the membrane and further leads to secondary damage. Also, eugenol hampers the ergosterol biosynthesis and affects the growth of fungi, as ergosterol is necessary for maintaining cell integrity and functions. The properties of clove essential oil, such as hydrophobicity and its ability to partition into the lipid bilayer, are accountable for its antifungal mode of action. In addition to the inhibition of dermatophytes, *Aspergillus,* and *Candida* species, the eugenol is also effective against the fluconazole-resistant *Candida albicans, Candida krusei,* and *Candida glabrata* [54].

• **Other uses of clove:** Clove is being used to give hot drinks aromatic and flavoring characteristics and is often paired with other ingredients such as lemon and sugar. The eugenol-containing clove oil is also useful for toothache and other forms of pain [49, 53]. The alcoholic and aqueous extract of clove in higher concentrations inhibit the larvae stage with a 100% mortality rate [55]. Furthermore, nanocomposite formed from clove essential oil has been used for the preservation of muscle fillets of *Thunnus thynnus* during cold storage [56]. Clove extract containing zinc nanoparticles has been used as an alternative product for its anti-cancer, anti-inflammatory, and antioxidant property [57].

Oregano

• **Biological source:** The biological source of oregano is a flowering plant *Origanum vulgare,* belonging to the mint family *i.e*., Lamiaceae.

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• **Phytoconstituents and phytochemistry:** Oregano contains essential oil. The vital component of its oil, carvacrol is a phenol, which is a natural monoterpene derivative of cymene and thymol. It also contains α- and β-pinene, linalool, myrcene, cineole, and terpinene in a small amount [58].

• **Antibacterial mechanism of action of oregano:** Oregano shows antibacterial action, especially against the methicillin-resistant staphylococcus aureus (MRSA) through various mechanisms. It destroys the cell membrane that leads to the leakage of small molecules such as Na^+, K^+. Oregano affects the normal physiological metabolism of microbial cells by inhibiting the action of intracellular enzymes like beta-galactosidase and others. It also inhibits the Krebs cycle, by which the concentrations of citric acid in MRSA increase and accumulate inside bacterial cells. In MRSA, it decreases the rate of metabolism of some amino acids and also decreases the bacterial content of fumaric acid, succinic acid, malic acid. The basic requirement for the survival of an organism is the energy that is given by ATP. Oregano shows the inhibitory effect on energy metabolism in MRSA, due to which the amount of ATP decreases, eventually reducing the activity of the Na^+ K^+ ATPase enzyme. The genetic material of bacterial cells gets affected by oregano as it decreases the synthesis and causes leakage of DNA and nucleic acid by destructing the cell membrane. It also obstructs the process of DNA replication, transcription, and translation. The extracellular toxin pvl gene, which is an important pathogenic factor in MRSA, is present. The oregano shows the bactericidal effect in MRSA by promoting its apoptosis, by lowering the production of the *pvl* gene [58].

• **Antifungal mode of action of oregano:** In addition to this, oregano essential oil suppresses the growth of fungi. It forms the shrunken hyphae and degrades them. The cytoplasm present in the cell and its organelles depletes due to the presence of essential oils in oregano. It alters the morphology of hyphae and promotes its lysis. Oregano forms crinkled and dehydrated sclerotia and also destroys it [59].

• **Other uses of oregano:** The antioxidants terpinene, limonene, thymol, ocimene, carvacrol, and caryophyllene give the herb its flavor and scent. Oregano is widely used as herbal medicine to treat many ailments, including skin sores, aching muscles, asthma, cramping, diarrhea, indigestion, colds, and to boost up overall health [58, 59]. *in vivo* studies have shown that oregano extract has beneficial effects on gastrointestinal health, specifically by lowering inflammation [60]. Recent studies also highlighted the anti-inflammatory potential of oregano against endotoxemia-induced toxicity [61]. Ileum transcriptomics revealed that 2% oregano extract altered gut-brain axis signaling and also altered other drug targeted gene expression [62].

Fennel

• **Biological source:** The biological source of fennel is *Foeniculum vulgare* Miller, belonging to the family Umbelliferae. Fennel comprises dried, ripe fruits [49].

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• **Phytoconstituents and phytochemistry**: The fenchone, *trans*-anethole, and limonene are the main bioactive components of fennel essential oil. The seeds of *Foeniculum vulgare contain* isolated triterpenes, flavanoid glycosides, smaller terpenes (monoterpenoids, sesquiterpenoids, and diterpenoids), and reduced sugars. The phenolics found in the fruit of this plant are ferulic acid-7--, neochlorogenic acid, gallic acid, chlorogenic acid, p-coumaric acid, chlorogenic acid, quercetin-7-o-glucoside, ferulic acid, 1,5 di-caffeoylquinic acid, caffeic acid, quercetin, and apigenin [63].

• **Antibacterial mode of action of fennel:** Although a culinary spice, the antibacterial activity of fennel is also quite prominent. Because of the hydrophobic nature of fennel essential oil and its components, it can easily penetrate the bacterial cell membrane to accumulate inside it and affect the permeability of bacterial cells, which results in the leakage of intracellular ingredients like Na^{+}, $K^{+,}$ $Ca^{2+,}$ and proteins. The bacterial cell death occurs due to irreversible damage of the cytoplasmic membrane and loss of some vital molecules. It also causes morphological alterations in bacterial cells. It was seen that when bacterial cells were treated with fennel essential oil, the cells became pitted, shriveled, deformed, and got stuck to each other. After that, there occurs leaching of genetic materials and nutrients. All these effects of fennel essential oil increase with an increase in concentration and duration of treatment. Even very small modifications in the structural integrity of cell membrane can affect the metabolism of cells, and this may result in cell death [59, 63].

• **Antifungal mode of action of fennel:** Fennel essential oil suppresses the

growth of fungi and also damages the morphological structure of the hyphae in the same way and by the same mechanism as that of oregano essential oil. It forms shriveled hyphal aggregates and causes degenerative changes to the sclerotia [59].

Turmeric

• **Biological source:** The biological source of turmeric is *Curcuma longa* Linn, the family Zingiberaceae. Turmeric comprises dried and fresh rhizomes.

• **Phytoconstituents and phytochemistry:** Curcumin, demethoxy curcumin, and bisdemethoxy curcumin, classified commonly as curcuminoids (3-6 percent), are major polyphenolic components in turmeric rhizomes. Many phenolic compounds in the turmeric rhizome include 1-(4-hydroxy-3-methoxyphenyl)-7-(3, 4-dihydroxyphenyl)-1, 6-heptadiene-3,5-dione and 1, 7-bis (4-hydroxyphenyl)-1,4, 6-heptatrien-3-one; 1-(4-hydroxy-3, 5-dimethoxyphenyl)-7-(4-hydr-xy-3-methoxyphenyl)-(1E, 6E)-1, 6-heptadiene-3, 4-dione; 1, 5-bis (4-hydroxy-3-methoxyphenyl)-penta-(1E, 4E)-1, 4-dien-3-one; 1-(4-hydrox--3-methoxyphenyl-5-(4-hydroxyphenyl)-penta-(1E, 4E)-1, 4-dien-3-one; 1-hydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl)-(6E)-6-heptene-3,5-dione. A variety of mono- and sesquiterpenes make up the pale yellow to orange-yellow volatile oil (4-6%) acquired from turmeric. Curcumenone was the name of (4 S, 5 S)-germacrone 4, 5-epoxide; bisabola 3, 10-diene 2-one; sesquiterpenes; dehydrocurdione; ar-turmerone [49, 64].

• **Antibacterial mode of action of curcumin:** Curcumin is active against the growth of both gram-positive and gram-negative bacteria. Almost in all bacteria, *FtsZ* (Filamenting temperature-sensitive mutant Z), which is the FtsZ protein, is necessary for the recruitment of other proteins that create a new cell wall (septum) between dividing cells and z-ring formation. Curcumin inhibits the formation of z-ring, which in turn suppresses the cytokinesis and bacterial cell proliferation through inhibiting *FtsZ* protofilaments assembly by binding into *FtsZ* proteins. The role of *FtsZ* protein in cell division resembles that of tubulin in the eukaryotic cell division. Again, curcumin increases the sensitivity of MRSA (Methicillin-resistant staphylococcus aureus) towards the beta-lactam antibiotic's antibacterial action. This is done through the mechanism in which it reduces the expression of PBP-2 alpha protein by inhibiting the transcription of the *mec-A* gene. Curcumin causes the death of bacterial cells by triggering cell membrane damage and cell lysis as it has an affinity for the peptidoglycan. It shows the synergism with various antibiotics against MRSA and MSSA. Glycopeptides, cephalosporins, fluoroquinolones, aminoglycosides, and beta-lactams are the antibiotics classes with which curcumin shows synergistic activity. Along with antibacterial action,

it is also seen that curcumin decreases the resistance of oxaliplatin, 5-fluorouracil, cisplatin, and doxorubicin [65].

• **Antifungal mode of action of curcumin:** Curcumin also possesses antifungal activity. It induces the outflow of various essential components such as K^+ ions, proteins, *etc*. As K^+ ions are important for the survival of the cell by regulating the pH of the cell and maintaining homeostasis, due to its loss, the death of the fungal cell occurs. This outflow of K^+ ions suggests that curcumin causes the lysis of the membrane because of membrane damage, fungi losses 'their cell membrane integrity. It shows the membrane-targeted mode of action against the fungi and increases membrane permeability [49, 66].

• **Other uses of turmeric:** It is used as a spice or condiment and is also used commercially in ointment and creams manufacturing as a coloring agent. Turmeric is also known for having potent antioxidant and anti-inflammatory properties. As inflammation is linked to tumor growth, anti-inflammatory compounds such as curcumin may play a role in treating and preventing a variety of cancer types, including colorectal, pancreatic, prostate, breast, and gastric cancers [66].

Garlic

• **Biological source:** The biological source of garlic is *Allium sativum* Linn. belonging to the family Liliaceae. It comprises bulbs of the plant.

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• **Phytoconstituents and phytochemistry:** A. Sativum bulb is believed to contain hundreds of bioactive compounds such as sulfur-containing compounds like ajoenes (E-ajoene, Z-ajoene), thiosulfinates (allicin), vinyldithins (2-vinyl-(4H)

--,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyl disulfide (DADS), diallyl trisulfide (DATS) and many others that accounted for 82% of the total garlic sulfur content. The key odor molecules in freshly milled garlic homogenates are S-propyl-cysteine-sulfoxide (PCSO), allicin, and S-methyl cysteine-sulfoxide (MCSO) [67].

• **Antibacterial mode of action of garlic:** Garlic is used as an antibacterial and antifungal agent because of the presence of allicin. Garlic has the same antibacterial action as that of penicillin and chloramphenicol. Tuberculosis disease caused due to the *Mycobacterium tuberculosis* develops resistance against various antibiotics at a very great speed, and this can also be treated with garlic because of the Sulphur containing compound in it. In *Entamoeba histolytica*, two enzyme groups are present; these are *alcohol dehydrogenase* and *cysteine proteinase*. From these two, the enzyme which is responsible for infection is the *cysteine proteinase,* whereas *alcohol dehydrogenase* is simply important for the metabolism and survival of the microorganisms. Allicin acts by reacting with the sulfhydryl (SH) or thiol group of these enzymes and blocks both the enzymes [67, 68].

• **Antifungal mode of action of garlic:** When "Caposele" and "Rosato" these two different varieties of garlic were studied for their activities; it was found that Rosato had suppressed the growth of the *Penicillium expansum* while *Aspergillus versicolor* and *Penicillium citrinum* had been inhibited by the Caposel variety. The mechanism by which it shows the antifungal action involves the destruction of the structure of the cell *via* piercing or entering inside cells and their organelles, causing the leakage of essential molecules and cytoplasm. In *Candida albicans*, garlic oil alters the normal metabolic process due to which cell cycle, protein modification process, and oxidative phosphorylation also suffer [67, 68].

• **Other uses of garlic:** Garlic is widely used for several conditions linked to the blood system and heart. Garlic is also used by some people for the prevention of different types of cancers [60]. Also, recent studies reported the anti-obesity property of garlic oil which counteract the effects of an HFD on adipose tissue weight, body weight, and serum lipid profiles *via* preventing excessive adipogenesis [69, 70]. Garlic also possesses a neuroprotective effect *via* altering the caspase-12-dependent pathway and improving spatial acquisition learning in mouse models [71 - 73]. Garlic activates pain-sensing neurons *via* acting on transient receptor potential (TRP) family of cation channels, specifically on TRPA1 and TRPV1 through allicin, showing its involvement in mechanical and inflammatory pain and visceral hypersensitivity [74, 75].

Ginger

• **Biological source:** The biological source of ginger is *Zingiber officinale* Roscoe belonging to the family Zingiberaceae. It comprises of whole or cut and also scrapped or unscraped dried rhizomes of the ginger plant.

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• **Phytoconstituents and phytochemistry:** The volatile oil of ginger is responsible for characteristic fragrance and flavor that comprise 1-3% of the weight of fresh ginger. Primarily volatile oil consists of zingerone, shogaols, and gingerol, which are phenolic ketones of oleoresin. Along with that, it contains 6-gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone), the principal pungent compound [76].

• **Antibacterial mode of action of ginger:** Ginger is one of the most commonly used spices and is employed in the treatment of some medical conditions. It is effective against fungi, bacteria, and viruses. It strongly inhibits the growth of *Pseudomonas aeruginosavia* hampering the biofilm formation process and thus affects the membrane formation. Ginger reduces the level of bis-(3'-5')-cyclic dimeric guanosine monophosphate (c-di-GMP) in *Pseudomonas aeruginosa* PA14 and blocks the biofilm formation. Ginger contains a wide range of active constituents, and from all these, 6-shogoal and gingerenone-A restrict the 6-hydroxymethyl-7, 8-dihydropterin pyrophosphokinase activity in pathogen and inhibit the growth of *Staphylococcus aureus* [77]. The nanofibers from ginger had good microbial activity. Thus, many formulations have been prepared using different methods. One such formulation is transparent cellulose film prepared with chemical treatment, and ultrasonication has been shown to possess good antimicrobial properties [77]. Also, polyvinyl alcohol and ginger bionanocomposites had microbial activity thus can be used as an alternative packaging material for food [78].

• **Antifungal mode of action of ginger:** In fungi, ginger alters the membrane integrity by penetrating inside the cell wall and cytoplasmic membrane by making

it permeable due to the lipophilic nature of ginger essential oil. Also, it obstructs the growth of fungi Fusarium verticillioides by means of affecting membrane integrity, reducing biosynthesis of ergosterol, and decreasing the synthesis of fumonisin-B1 and fumonisin-B2. The powerful antifungal constituents from the ginger essential oil are citral and gamma-terpinene; as they obstruct the ergosterol biosynthesis, the expression of the genes which are associated with aflatoxin biosynthesis also gets hampered, which further results in the suppression of *Aspergillus flavus* growth. In addition to this, it is also effective against the virus as it suppresses the growth of the human respiratory syncytial virus (HRSV) in the respiratory tract cell lines and causes inhibition of plaque formation. The viral attachment and internalization are also affected by ginger. It depletes the level of liver function relevant markers such as *Aspartate aminotransferase* (AST) and *Alanine aminotransferase* (ALT) also alpha fetoproteins (AFP) in the people who are suffering from hepatitis C [76].

• **Other uses of ginger:** Ginger has strong antibacterial activity and can also be used to treat bacterial infections. This is used in colic and atonic dyspepsia and is also used as a stimulant in traditional Chinese medicine. Ginger is described as spicy and sweet rhizome, helping to warm up the body and treat cold extremities, improving a slow and late heart, treating pale skin, and strengthening the body after loss of blood. In Traditional Chinese Medicine it is also used as herbal medicine for several cardiovascular diseases. In traditional medicine, the anti-emetic effect of ginger was recognized as a treatment option. Ginger has a significant role to play in treating headaches, nausea, colds, arthritis, rheumatism, muscle pain, and inflammation. Ginger could be used as an anti-edema drug which is used to cure various ailments, which include nausea, gastrointestinal disorders, respiratory disorders, atherosclerosis, migraine, depression, gastrointestinal ulcer, cholesterol, and other ginger benefits include its use for pain reduction, and to treat rheumatoid arthritis [79]. In addition, regular consumption of ginger has been shown to delay the progression of diabetes and cancer due to the effective antioxidant action of its constituents [80]. A bioactive compound present in the ginger act by a different mechanism that shows anticancer activity, and these molecules can be used as a lead for further drug discovery [81]. Recent studies also revealed that ginger supplementation could alter the composition of gut microbiota and increase survival of Bifidobacterium genus and short-chain fatty acid-producing bacteria, thereby showing anti-obesity activity in mice [82].

Black Pepper

• **Biological source:** The biological source of black pepper is *Piper nigrum* Linn

belonging to the family Piperaceae. It comprises of the fruits which are dried unripe fruits of climbing vine of black pepper.

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• **Phytoconstituents and phytochemistry:** Piperine is an alkaloid that is commonly present in plants relating to the Piperaceae family. This is also categorized as piperidine (E, E)-1- and piperoylpiperidine (E, E)-1-[5-(1, 3-benzodioxol-5-yl)-1-oxo-2, 4-pentdienyl].Piperine, along with chavicine (a piperine isomer), is the alkaloid accountable for the pungency of long pepper and black pepper. This is also used as an insecticide and in certain types of traditional medicine. Piper nigrum leaf extract has shown the presence of tannins, alkaloids, and flavonoids [83].

• **Antibacterial mode of action black pepper:** Black pepper inhibits bacterial growth in various ways. It outrages the cell membrane of bacteria so that the intracellularly present enzymes like transaminase comes into the extracellular space. It elevates the permeability of the cell membrane of bacteria by restricting the activity of the Na^+/K^+ ATPase enzyme. The cellular energy metabolisms of bacteria also get affected through the inhibition of *Hexokinase* and *Pyruvate kinase* enzymes of the glycolysis. This may lead to bacterial cell death as black pepper blocks the production of essential substances and energetic components. In addition to this, black pepper obstructs the aerobic respiration, Krebs cycle, so that bacterial cell undergoes the anaerobic respiration. Due to the anaerobic respiration, the level of lactic acid increases, and it accumulates in the bacterial cell. Hence, bacterial cell death occurs due to a high concentration of lactic acid [84]. Black pepper essential oil (BPEO) has been shown to produce physical and morphological alterations in E. coli by modulating permeability of cell membrane *via* breaks and then leaking electrolytes, proteins, and nucleic acids, which eventually results in the death of E. coli, and thus BPEO can be used as a natural antibacterial agent in food practices [32]. Also, the biocomposite film prepared

from BPEO and ginger essential oil (GEO) fabricated by casting technology has been shown to inhibit microbial growth thus can be used as alternatives to wound dressing [85].

• **Antifungal mode of action of black pepper:**Black pepper contains the active constituents which are extremely fat-soluble and volatile, because of these two properties it exerts antifungal action mainly through the cell membrane. By damaging the cell membrane and inhibiting its synthesis it enters inside the fungal cell, afterward, it invokes the outflow of various ions and molecules from the cell, which results in fungal cell death. In addition to this, black pepper also affects the production of polysaccharides, RNA protein, and DNA. Fungal cell proliferation and spore germination are also gets inhibited by black pepper. It provokes the rupturing of the chitin polymer, beta-1, 3-glycan, and beta-1, 6-glycan [86].

• **Other uses of black pepper:** Dried P. nigrum fruit is considered as "The King of the Genus" because it gives a unique taste to the dish together with its medicinal properties to treat many diseases as well. Herb is widely used for the treatment of gastrointestinal diseases, malaria, respiratory disorders, cold and cough infections, skin cancer, scabies, nerve pain, and other illnesses [87]. Also, recent data has shown that consumption of herbal formulation prepared from piperine along with turmeric extract and ginger for 1 month has beneficial effects in patients with chronic knee osteoarthritis through anti-inflammatory action *via* altering levels of prostaglandin E_2 [88]. Due to antioxidants, the anti-inflammatory activity of piperine can attenuate cardiac injury, hypertension, and cardiac fibrosis, thus showing the cardioprotective effect [89].

Coriander

• **Biological source:** The biological source of the coriander is *Coriandrum sativum* Linn belonging to the family Umbelliferae. It comprises completely dried, ripe fruits.

• **Phytoconstituents and phytochemistry:** Coriander fruits include essential oil and vegetable oil (fixed oil). Coriander contains monoterpenoid linalool, limonene, camphor, and geraniol. The main component described in most studies is linalool (60-70%), often up to 87.54%. Frequently recognized other key elements are α-pinene, camphor which geraniol, and are responsible for the character of the plant's scent and aroma [90].

• **Antibacterial mode of action of coriander:** In coriander essential oil, the active chemical constituent linalool shows the antibacterial action by accelerating penetrability inside the cell. Linalool, naturally present in S (+) enantiomer form, is highly penetrable to the bacterial cell membrane, which is negatively charged, *i.e*., gram-negative bacteria. Due to its alcohol-like properties, the peptidoglycan shrinks and tightens due to dehydration of peptidoglycan. After penetrating inside the cell, coriander oil shows various secondary effects, such as alteration of membrane potential. It also works by restricting the activity of the efflux pump, which is one of the reasons responsible for antibiotic resistance [31, 91].

• **Antifungal mode of action of coriander:** Coriander shows the antifungal activity by causing damage to the cell membrane. Coriander essential oil binds with ergosterol which is the important component of the fungal cell wall and promotes the outflow of essential ions from the cell, which results in fungal cell death. In addition to this, coriander also affects the integrity of biofilm, which is one of the mechanisms through which microbes develop resistance. At the modest inhibitory concentration of coriander essential oil, the reduction in proteolytic activity takes place in *Candida albicans* [31].

Other uses of coriander: Coriander is useful in treating problems associated with the GI tract, nausea, loss of appetite, *etc*. It is used in the treatment of certain bacterial and fungal infections associated with joint pain. It also increases the flow of milk in breastfeeding women [31, 91].

Thyme

• **Biological source:** The biological source of the thyme is *Thymus vulgaris* Linn, belonging to the family Labiatae. It comprises leaves that may be dried or partially dried and also of flowering tops.

• **Phytoconstituents and phytochemistry:** The chemical makeup of the thyme oil is distinguished by significant concentrations of thymol, p-cymene, and ÿ-terpinene [92].

• **Antibacterial mode of action of thyme:** The vital chemical constituent of the thyme essential oil is thymol which has antibacterial efficacy. It acts by rupturing the outward membrane of the gram-negative bacteria. Because of the ruptured cell membrane, the enhancement in the outflow of ATP and liberation of lipopolysaccharides also occurs. This could result in a disturbance in plasma membrane function [93].

• **Antifungal mode of action thyme:** Thyme suppresses the growth of fungi by interacting with ergosterol and affects the normal function and growth of fungal cell membrane. In addition to this, sporangiospores germination and development of mycelia get obstructed because of thymol. It acts as both fungistatic and fungicidal [94].

• **Other uses of thyme:** Thyme, along with other herbs, is used for various ailments of the throat such as bronchitis, whooping cough, and sore throat. Thyme is also taken in dyspraxia (a movement disorder in children), GIT, and skin disorders. It is also used as an appetite stimulant. Other than these, thyme is also used in laryngitis, tonsillitis, sore mouth, and bad breath. In foods industries, thyme is used as a flavoring agent [49, 94].

Cumin

• **Biological source:** The biological source of cumin is the *Cuminum cyminum* belonging to the family Umbelliferae. It comprises dried, ripe fruits of the cumin plant.

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• **Phytoconstituent and phytochemistry:** Cumin seeds are extremely nutritious. The predominant volatile components of cumin are cumin aldehyde, cymene, and terpenoids. Cumin has a strong, distinctive flavor. Its warm fragrance is a consequence of its essential oil content. Cuminaldehyde and cuminic alcohol are the chief components of the aromatic compound. The substituted pyrazines, 2-methoxy-3-methyl pyrazine, and 2-methoxy-3-sec-butylpyrazine2-et-oxy-3-isopropylpyrazine are other important aroma compounds of roasted cumin. Certain constituents include terpinene, saffron, p-cymene, and β-pinene [95].

• **Antibacterial mode of action of cumin:** Cumin is effective against both gram bacteria. It acts by targeting biofilm and decreases its production. Also, it causes the liberation of proteins and DNA from the cells of bacteria by destructing the cell membrane [96].

• **Antifungal mode of action cumin:** Cumin essential oil is also effective against fungi. It inhibits the growth of *Aspergillus flavus*, as cumin has anti-aflatoxigenic activity. Cumin essential oil inhibits mycelial growth completely. It decreases the expression of the fumonisin biosynthetic gene in *Fusarium verticillioides* which is significant for the FUM1 gene [97].

• **Other uses of cumin:** The cumin plant seeds are used for indigestion problems, as a diuretic, as an aphrodisiac. Cumin is used as a flavoring agent in the food industry and as a fragrance in cosmetics [49, 97].

Nutmeg

• **Biological source:** The biological surface of the nutmeg is *Myristica fragrans* Houtt. of family Myristicaceae. It comprises dried kernels of nutmeg seeds.

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•**Phytoconstituents and phytochemistry:** The volatile oil portion of nutmeg comprise phenylpropanoids and terpenes, including d-borneol, l-terpineol, d-pinene, geraniol, limonene, safrol, and myristicin. Myristicin in its pure form acts as a poison and is toxic, and the administration of higher amounts of nutmeg can develop myristicin poisoning. The oil is colorless or may be light yellow, and smells and tastes are similar to that of the nutmeg [98].

• **Antibacterial mode of action of nutmeg:** The gram-negative bacteria are less sensitive to the antibacterial action of nutmeg. This contrast inactivity towards these types of bacteria is due to the difference in their composition of the cell wall. The gram-negative bacteria contain many proteins, lipoproteins, and less concentration of peptidoglycan in its cell membrane than gram-positive bacteria, which reduces their susceptibility towards nutmeg essential oil [98, 99].

• **Antifungal mode of action of nutmeg:** Nutmeg essential oil is also used as an antifungal agent. Its antifungal mode of action is that it causes the outflow of ions and molecules from cells by increasing the porosity of the cell membrane. The multiple cellular processes of fungi get inhibited by nutmeg essential oil [98].

• **Other uses of nutmeg:** Nutmeg is used for GIT disorders and nausea. It is also used to treat insomnia, different types of cancer, and kidney disorder; increase menstrual flow, causing a miscarriage; nutmeg is used as spice and flavoring agent. Nutmeg oil is used in soaps and cosmetics as a fragrance [49, 99].

Rosemary

• **Biological source:** It is a woody, perennial herb with fragrant, evergreen, needle-like leaves and white, pink, purple, or blue flowers belonging to the plant *Rosmarinus officinalis,* family-Labiatae.

.

• **Phytoconstituents and phytochemistry:** Rosemary plants have a polyphenolic profile, distinguished by the presence of carnosol, carnosic acid, and the principal components are rosmarinic acid and hesperidin. The essential oil of rosemary consists primarily of 1, 8-cineole (46.4%), camphor (11.4%), and pinene. The *Rosmarinus officinalis* is a rich source of phenolic compounds. Rosemary extracts also contain many antioxidants, in addition to the volatile constituents, that mostly belong to the class of phenolic acids, flavonoids, and diterpenoids [100].

• **Antibacterial mode of action of rosemary:** Rosemary's inhibitory effect results from the action of carnosol, rosmaridiphenol; rosmarinic acid, carnosic acid, rosmanol, epirosmanol, and isorosmanol. They alter the transportation of electrons, cellular leakage components, and changes in fatty acid production [79].

• **Antifungal mode of action of rosemary:** High proportion of antifungal activity of rosemary oil is correlated with monoterpenes α-pinene as a principle compound. The essential oil from rosemary has a medium anticandidal action. Aflatoxin B1 (AFB1) is potentially a carcinogenic and poisonous metabolite made by the species

Aspergillus and rosemary acts by strongly inhibiting the aflatoxin synthesis. The antifungal effects of Rosemary essential oil can be due to monoterpenes composite, and especially α-Pinene [79].

• **Other uses of rosemary:** The rosemary leaf and its oil are used for making medicine. Rosemary is used to improve memory, indigestion (dyspepsia), joint pain associated with arthritis, hair loss, and other disorders, although there is no clear medical evidence to support any of these applications. The rosemary is used as a seasoning in foods. Rosemary oil is used as a fragrant component in the manufacture of soaps and perfumes [100].

Mustard

• **Biological source:** The mustard consists of the dried ripe seeds of the plant *Brassica nigra* belonging to the family Cruciferae.

.

• **Phytoconstituents and phytochemistry:** Mustard seeds have the compound allyl isothiocyanate (AIT) as their primary pungency ingredient. Isothiocyanates (R –N= C= S) are glucosinolate derivatives in Cruciferae plant cells or the mustard family. Such compounds are formed through the action of the enzyme myrosinase glucosinolates as it injures or mechanically disrupts the plant tissue. Certain side groups of isothiocyanate include ethyl, methyl, benzyl, and phenyl, in addition to the allyl side group. Such compounds were known as potent antimicrobial agents [101].

• **Antibacterial mode of action of mustard:** The isothiocyanates inhibit bacterial cells may be due to enzyme inhibition by direct reaction with disulfide bonds or by anion reaction with thiocyanate (SCN−) to mollify sulfhydryl enzymes [101,

102]. Also, it can be used as a probiotic as it enhances the growth of some microbes except E. coli and thus can be used in livestock nutrition [103]. It can be used for antimicrobial packaging based on its release of allyl isothiocyanate from its seed in a controlled manner [104].

• **Antifungal mode of action of mustard:** Mustard essential oil significantly causes the fungal degradation of shelled groundnuts. Mustard essential oil inhibits growth in molds [101, 105].

• **Other uses of mustard:** Black mustard oil is used to treat severe cold, sore and swollen joints (rheumatism) and arthritis. Black mustard leaves are used in foodstuffs. Black mustard seed is also used as a seasoning in foods and for flavoring mustard condiments. There are about 40 distinct mustard plant species. The mustard condiment is usually made of three different varieties. The most pungent one is the black mustard (*Brassica nigra*) [49].

• The high (200 mg/kg) doses of the crude aqueous extract of the black seeds produce neuronal insult at prefrontal cortex microarchitecture along with alteration of the expression and activities of certain enzymes in the brain due to the production of oxidative stress [106]. Also, mustard seed extract shows anticancer activity against lung cancer *via* stimulation and regulation of proliferation, apoptosis, cell and DNA damage, and invasion [107].

Basil

• **Biological source:** It consists of the flowering shoots of the plant *Ocimum bacsilicum* belonging to the family- Labiatae.

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• **Phytoconstituents and phytochemistry:** The essential European basil oil contains high linalool and methyl chavicol (estragole) concentrations in a ratio of about 3:1. 1,8-cineole, eugenol, and myrcene are some of the constituents. The sweet basil clove-scent is derived from eugenol. Basil's fragrance profile contains 1, 8-cineole, and methyl eugenol [108].

• **Antibacterial mode of action of basil:** It was found that the essential oil of *O. bacsilicum* has moderate antibacterial activity. Bacterial strains considered to be gram-positive are more responsive to basic basil oils as compared to gram-negative bacteria. The inhibition may be accompanied due to enhanced plasma membrane permeability by essential oils and restriction of bacterial respiration. This causes bacterial cell death because of the massive leaching of ions [108].

• **Antifungal mode of action of basil:** The mycelial development of the pathogenic fungus *Botrytis fabae* was substantially decreased by the chemotype oil of methyl chavicol and the linalool. All the components of the oil reduce fungal growth. *Botrytis fabae* and the rust fungus *Uromyces fabae* were also managed *in vivo*, with all oils of both chemotypes and pure methyl chavicol and linalool, greatly reducing the infection of broad bean leaves [109].

• **Other uses of basil:** The parts of the plant rising above the ground are used for medicinal purposes. Basil is widely used for problems with the stomach, such as spasms, lack of appetite, digestive gas, vomiting, constipation, and many other disorders, although there is no sufficient medical evidence to support this usage. Basil is used for flavor in foods [108, 109].

Asafoetida

• **Biological source:** Asafoetida is an oleo-gum resin obtained as an exudation by incision of the decapitated rhizome and roots of *Ferula asafoetida* L, *F. foetida, Royel*, *F. rubricaulis* Boiss, and some other species of Ferula, family- Apiaceae.

• **Phytoconstituents and phytochemistry**: Asafoetida comprises volatile oil, resin, and gum. Owing to the presence of sulfur compounds, it has the oil's garlic-like odor. The resin has three sulfur compounds extracted, such as 1-methyl propyl-1-propenyl disulfide, l-(methylthio)-propyl-1-propenyl disulfide, and l-methyl-propyl 3-(methylthio)-2-propenyl disulfide; the latter two have pesticidal properties. Resin is made up of asaresinotannol ester and ferulic acid, pinene, vanillin and ferulic acid free [110].

• **Antibacterial mode of action of asafoetida:** The preliminary phytochemical analysis of asafoetida extracts showed the presence of terpenoids, tannins, glycosides, alkaloids, flavonoids, and polyphenolic compounds. Tannins inhibit microbial enzymes in distilled forms. It is reported that the astringent property of tannins is due to their complex formation with enzymes and metal ions. Polyphenolic components are found to have antimicrobial activity probably due to suppression of enzymes in the oxidized forms or *via* more nonspecific protein interactions. Many specific secondary plant metabolites are believed to have an antibacterial effect [110].

• **Antifungal mode of action of asafoetida:** Asafoetida oil has shown inhibitory activity against all fungal strains, including *Aspergillus Niger*, *Candida blanki, Candida krusei, Candida glabrata, Candida cylindracea, Candida tropicalis, Candida Albicans,* and *Saccharomyces cerevisiae*, but it shows heavy activity against *Candida Tropicalis*, and the MTCC-227 *Candida albicans, Saccharomyces Cerevisiae, A. Niger while mild to C. blanki, C. cylindracea, C. glabrata, C. krusei, and C. albicans*. The antifungal and allelopathic effects of methanol extract from concentrations of asafoetida oleo-gum resin against Pleurotus spp. and the harzianum and trichoderma were examined. It exhibited fungicidal activity against *T. Pleurotus* and *harzianum* species at greater concentrations. Asafoetida oleo-gum-resin imposes a semispecific antifungal action on the growth of *T. harzianum mycelium* at the minimum concentrations. The inhibition of mycelium production of the asafoetida oleo gum resin towards the fungi has also been reported [111].

• **Other uses of asafoetida:** People use asafoetida resin, a substance similar to gum, as a medicine. Asafoetida has been used by women to restart their menstrual cycles after menstruation has stopped for some reason, for conditions such as breathing or throat problems, digestive problems. Asafoetida is used in the production as a fragrance in cosmetics and as a flavoring agent in foods and beverages. Asafoetida is also used in materials for the repelling of dogs, cats, and wildlife [49, 111].

Galangal

• **Biological source:** Galangal consists of a rhizome used as an herb, *Alpinia galangal* belonging to the family Zingiberaceae.

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• **Phytoconstituents and phytochemistry:** The chemical constituents of the different parts of the medicinal plant Galangal (*Alpinia galanga*) are Monoterpene and sesquiterpene derivatives. β-farnesene and β-caryophyllene (40.5% leaf oil) along with fenchyl acetate (20.7% leaf oil), 1, 8-cineole, and caryophyllene oxide are the main constituents of leaf oils. The key constituent of stem oil is cubenol followed by humulene, germacrene, and cadine. Galangal rhizome oil contains cineole, carotol, 1–8, fenchyl acetate, and rhizome oil contains 1–8 cineole, β-pinene, β-caryophyllene, camphor, methyl cinnamate, fenchyl acetate, limonene, camphor, α-terpineol, and cubenol. The root oil with 1, 8 cineole, and limonene are found to have fenchyl acetate [112].

• **Antibacterial mode of action of galangal:** The galangal extract has the most potent inhibitory effect on *S. aureus*. The galangal extract damages the outer and the inner membrane and causes coagulation of the cytoplasm. Destruction of the cytoplasmic membrane properties causes the discharge of cellular materials, namely nucleic acid, that results in bacterial cell death [113].

• **Antifungal mode of action of galangal:** (E)-8 beta, 17-epoxylabd-12-ene-15, 16-dial is a bioactive component from galangal which lyses the *Candida albicans* protoplast. These findings reveal that antifungal action of (E)-8 beta, 17-epoxylabd-12-ene-15, 16-dial is owing to a shift in membrane porosity caused by the variation of membrane lipids [114].

• **Other uses of galangal:** Alpinia is a ginger-based herb. The rhizome (underground stem) is used to produce the drug. For fevers, muscle spasms,

digestive gas, bacterial infections, and swelling (inflammation), people have been using Alpinia, although there is no clear medical evidence to support such uses [113, 114].

Cardamom

• **Biological source:** Cardamom comprises the dried, nearly ripe fruits of the plant *Elettaria cardamomum* Var. Minuscule belonging to the family Zingiberaceae. The cardamom seeds contain about 3-6% of the volatile oil.

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• **Phytoconstituents and phytochemistry:** The composition of essential oil in the cardamom seeds relies greatly on storage conditions, and it can be as high as 8%. In the crude oil, 45% of α-terpineol was found; others include myrcene, 1, 8-cineol, menthone, β-phellandrene, sabinene, limonene, and heptane [115].

• **Antibacterial mode of action of cardamom:** Cardamom essential oil inhibits growth and triggers dissociation of biofilms in the *Streptococcus mutans,* and it is noted that it could be of interest to periodontal disease. Extracts of cardamom demonstrated good antibacterial activity against major gram-negative periodontal pathogens, including *Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Porphyromonas gingivalis, intermedia,* and *Prevotella intermedia*. Bacterial membrane disturbance was caused by CFE and CSE, affecting the membrane integrity of bacteria. These findings are consistent with previous research that bacteria treated with 1, 8-cineole, one of its key components of cardamom extracts, has shown shrinking cells and weakened membranes [115].

• **Antifungal mode of action of cardamom:** The key component 1, 8-cineole, substantially increased elastase and protease output and dose-dependent motility in *Pseudomonas aeruginosa* PAO1. About 50% of essential oils suppressed elastolytic and proteolytic activity in *P. aeruginosa* PAO1. These oils had also hindered the synthesis of violacein in C. A strain of the violaceum.

Similarly, in large concentrations, the A. corrorima essential oil greatly prevented radish germination [116].

• **Other uses of cardamom:** The cardamom seeds and seed oil are used for preparing medicine. Cardamom is often used in people who consume little to no alcohol (nonalcoholic fatty liver disease) and diabetes. Cardamom is used as a seasoning in foods. It is used even in soaps, creams, and scents [49].

Dill

• **Biological source:** Dill consists of the dried ripe fruits of *Anethum graveolens* Linn., belonging to the family Umbelliferae.

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• **Phytoconstituents and phytochemistry:** The chemical constituents of the volatile dill oil differed according to the parts of the plant. The α-phellandrene and limonene percentage differed in leaves and flowers. Dill is available in either leaves or flowers but is not present in fruit oil. Carvone and limonene are the essential elements of the dill fruit oil, while α-phellandrene occupies the herb oil. Dill apiole and myristicin were other key components of herbal oil. Contents and compositions of dill fruit oil differed with the extraction process [117].

• **Antibacterial mode of dill:** The extract obtained containing carvone as a major component from dill suppresses the strains but is significantly less effective than D-limonene. Elevated membrane permeability of tested microorganisms by exposure to essential oil may be related to proteolytic cleavage and bacterial death induced due to intracellular component leakage, notably electrolyte losses like K^+,

$Ca^{2+,}$ and Na^{+}. The release may be due to the interaction of antimicrobials and the cytoplasmic membrane. A decline in cellular components such as proteins and other important molecules suggests injury to the cytoplasmic membrane [118].

• **Antifungal mode of action of dill:** The antifungal destinations for dill oil are the plasma membrane and the mitochondria. Dill oil shows dose-dependent antifungal activity; the specific harm to the plasma membrane occurs in *A. flavus* cells with a heavy lesion on the membrane, instead of metabolic disability, which destroys the secondary membrane. Dill oil can modify the architecture of the plasma membrane, suggesting that the fungal cells lack integrity. Dill oil can produce substantial ergosterol biosynthesis inability with *Aspergillus flavus* [119].

• **Other uses of dill:** Dill is an herb that is used in soaps and cosmetics, cooking spice, and a fragrance. People also use dill seeds and plant parts that grow just above the ground as medicine. Individuals use dill for issues with digestion, liver disease, urinary tract disorders, infections, and several other illnesses, although there is no clear medical evidence to support such uses [29, 119].

Anise

• **Biological source**: Anise consists of dried ripe fruits of *Illicium verum*, *Pimpinella anisum* Linn., belonging to the family Umbelliferae.

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• **Phytoconstituents and phytochemistry:** Anethole is the main constituent of anise. Other components comprise p-anisaldehyde, 2-methylbutyrate, ϒ-himachalene, cis-pseudoisoeugenyl methylchavicol, and trans-pseudoisoeugenyl 2-methylbutyrate. Flavonoids separated from the anise comprise of quercetin 3-glucuronide, rutin, 7-glucoside luteoline, isoorientin, isovitexin, 7-glucoside apigenin and luteolin glycoside. Sesquiterpenes segregated from the essential anise oil (fruit and shoots) entail gamma-himachalene and neophytadiene diterpene [120].

• **Antibacterial mode of action of anise:** Phenolic substances function as antimicrobials through various mechanisms involving microbial membrane disruption. The exposure of the bacteria to anise extracts has shown that Gram-positive bacteria appear to be more sensitive than Gram-negative bacteria ones. Such action may be due to variations in the arrangements in their cell walls. Gram-negative bacteria possess an additional external hydrophilic membrane that works as a protective shield against hydrophobic substances and prohibits phenolic compounds from accumulating in the goal cell membrane. It usually makes the Gram-negative highly resistant to herb extracts than that the gram-positive bacteria. Anise is a potential antimicrobial for gram-positive and negative bacteria, filamentous fungi, and yeast [121].

• **Antifungal mode of action of anise:** The key component of the oil extracted act against spore germination of *M. oryzae* is trans-anethole. Anise also hinders radial mycelial development. The suppression of spore germination is similar to that for mycelial development reduction [96].

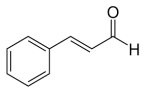
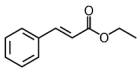
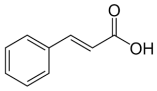
• **Other uses of anise:** Anise is a flowering plant. Seed and oil are used for preparing medicines. Anise is being used to treat stomach upset, intestinal gas, nasal congestion, and increase productive cough as an expectorant. It is often used to boost urination and to boost the desire to eat. Women take anise while nursing to improve milk flow, start the menstrual cycle, alle*via*te menstrual discomfort or pain, ease labor and boost sexual desire. Other applications involve epilepsy control, nicotine dependency, sleeping disorder (insomnia), asthma, diabetes, and constipation. Some people treat lice, scabies, and psoriasis by applying anise directly to the skin. Anise is used as aromatherapy for nausea. Anise is used as a flavoring agent in foods. It has a sweet, spicy taste which is similar to the taste of black liqueur. It is most commonly used in liqueurs and alcohols, such as anisette and ouzo. Anise is also used in dairy products, gelatins, foods, candy, and fresheners for breathing. Anise in soap, creams, perfumes, and sachets is often used as a scent in production (Table **3**) [122, 123].

USE OF HERBS AND SPICES AGAINST CORONAVIRUS

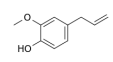
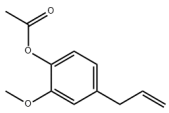
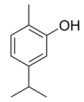
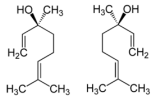
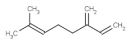
Since December 2019, the novel coronavirus (COVID-19) has spread over the world and has infected more than 2 million people causing more than 100 thousand deaths. People with pre-existing infectious and non-infectious diseases of the lungs are prone to be at more risk of contracting COVID-19 infection owing to their compromised immune system. On the basis of Ayurvedic and scientific literature, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy), India, has issued an advisory in which it has suggested the use of Kadha, *i.e.*, herbal tea or decoction made from *Ocimum*

tenuiorum (Tulsi), *Piper nigrum* (Kalimirch), *Cinnamomum verum* (Dalchini), *Vitis vinifera* (Munakka) and *Zingiber ocinale* (Shunthi) as a preventive measure which enhances immunity against severe infection caused by COVID-19. It has also been recommended to drink golden milk which is made up of a half teaspoon of turmeric *(Curcuma longa)* powder in 150 ml hot milk once or twice daily [142].

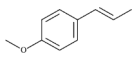
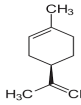
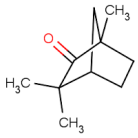
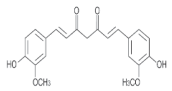
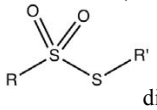
Table 3. Summarization of commonly used antibacterial and antifungal spices and herbs.

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
1	Cinnamon	*Cinnamomum zeylanicum Nees.* Family-Lauraceae	Cinnamaldehyde  Cinnamate  Cinnamic acid 	***As an anti-bacterial agent:** disturbance in cellular metabolism, leakage of cellular constituents. ***As an antifungal agent**: suppresses the growth of mycelia, destroys cell membrane, alters energy metabolism, and hampers ergosterol biosynthesis.	As an antiseptic, flavoring agent, stimulant, aromatic, astringent, stomachic, carminative, preparation of candy, perfumes, dentifrices, spices, and condiments.	[45]

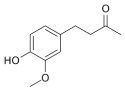
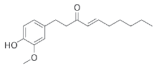
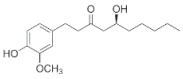
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
2	Clove	*Eugenia caryophyllus* Family-Myrtaceae	Eugenol  Eugenol acetate 	***As an antibacterial agent:** destroy bacterial cell wall, inhibition of DNA and protein synthesis. ***As an antifungal agent**: metabolic arrest, damage to the membrane hampers the ergosterol biosynthesis.	Flavoring agent, as a spice, repellent for ant, for toothache.	[124]
3	Oregano	*Origanum vulgare* Family-Lamiaceae	Carvacrol  α and β pinene, Linalool  Myrcene  Cineole, Terpinene	***As an antibacterial agent:** destroys cell membrane, affects the normal physiological metabolism, inhibits the Krebs cycle, obstructs the process of DNA replication, transcription, and translation, and promotes apoptosis. ***As an antifungal agent:** alters the morphology of hyphae and promotes its lysis.	Bleeding disorders, Wound healing, Asthma, Bronchitis, Cough, Flu, Painful menstrual periods, Arthritis, Headaches, Cardiovascular disorders, Antioxidant, as an insect repellent	[125]

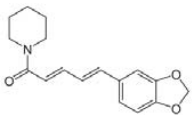
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
4	Fennel	*Foeniculum vulgare Miller* Family-Umbelliferae	trans-Anethole  Limonene  Fenchone 	***As an antibacterial agent:** leakage of intracellular ingredients, morphological alterations, affects the metabolism of cells. ***As an antifungal agent:** suppresses the growth of fungi.	Flavoring agent, a scent, an insect repellent, herbal remedy for poisoning and stomach conditions, as a stimulant to promote milk flow in breastfeeding and induce menstruation.	[126]
5	Turmeric	*Curcuma longa Linn.* Family-Zingiberaceae	Curcuminoids, which is a mixture of curcumin, demethoxycurcumin, and bisdemethoxycurcumin  Curcuminoids	***As an antibacterial agent:** suppresses cytokinesis and bacterial cell proliferation, cell membrane damage. ***As an antifungal agent:** lysis of the membrane.	As spice or a condiment, as a colouring agent, potent anti-inflammatory and antioxidant, Alzheimer's disease, depression, preventing a variety of cancer types, osteoarthritis and also for prevention and treatment of diabetes.	[127]
6	Garlic	*Allium sativum Linn.* Family-Liliaceae	diallyl thiosulfonate(allicin)  diallyl sulfide, diallyl disulfide, diallyl trisulfide, S-ally--cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin)	***As an antibacterial agent**: block the enzymes. ***As an antifungal agent:** destroys the structure of the cell, alters the normal metabolic process.	Atherosclerosis, high cholesterol, heart attack, coronary heart disease, hypertension, as stimulant, expectorant, carminative, rubefacient, disinfectant, aphrodisiac, as a condiment, as anthelmintic.	[67]

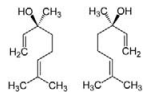
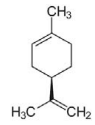
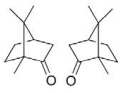
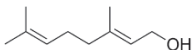
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
7	Ginger	*Zingiber officinale* Family- Zingiberaceae	Zingerone  Shogaols  Gingerol 	***As an antifungal agent:** blocks the biofilm formation, affects the membrane formation, obstructs the glucan synthesis. ***As an antifungal agent**: alters the membrane integrity, reduces biosynthesis of ergosterol.	Used to treat bacterial infections, as a stimulant, an antiemetic agent, headaches, nausea, colds, arthritis, rheumatism, muscle pain, and inflammation, as an anti-edema, as an antioxidant.	[128]

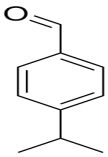
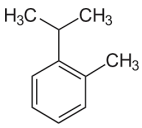
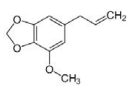
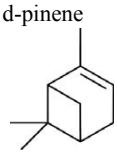
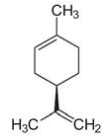
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
8	Black pepper	*Piper nigrum Linn.* Family- Piperaceae	Piperine 	***As an antibacterial agent:** inhibits the process of protein synthesis, affects energy metabolism, reduces ATP biosynthesis, and obstructs aerobic respiration. ***As an antifungal agent**: damages cell membrane and inhibits its synthesis, obstructs the RNA protein and DNA synthesis, inhibits fungal cell proliferation and spore germination, ruptures the chitin polymer, beta-1, 3--, and beta-1, 6-glycan.	Cold and cough infections, skin cancer, scabies, nerve pain, as anti-apoptotic, anti-microbial, anti-pyretic, anti-analgesic, anti-tumor, anti-depressant, anti-inflammatory, anti-arthritic, anti-thyroid, antifibrinolytic, anti-fungal, anti-diarrheal, immunomodulatory, larvicidal.	[129]

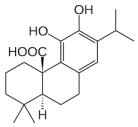
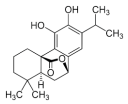
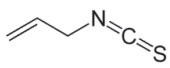
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
9	Coriander	*Coriandrum sativum* Linn. Family- Umbelliferae	Linalool  Limonene  Camphor  Geraniol 	***As an antibacterial agent**: alters the membrane potential, restricts the activity of efflux pump. ***As an antifungal agent**: causes damage to the cell membrane, affects the integrity of biofilm.	GIT and associated disorders used to treat measles, hemorrhoids, toothaches, worms, and joint pain, as well as infections caused by bacteria and fungus, as a culinary spice and to prevent food poisoning, flavoring agent.	[130]
10	Thyme	*Thymus vulgaris Linn.* Family- Labiatae	Thymol  p-cymene, ÿ-terpinene	***As an antibacterial agent**: ruptures the outward membrane. ***As an antifungal agent**: interacts with ergosterol and affects the normal function and growth of fungal cell membrane, obstruct sporangiospores germination and development of mycelia.	Lungs and throat disorders, colic, arthritis, upset stomach, gastritis, diarrhoea, bedwetting, dyspraxia, intestinal gas (flatulence), parasitic worm infections, and skin disorders, as a diuretic, flavoring agent.	[131]

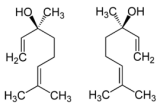
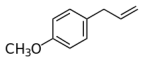
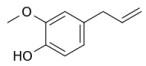
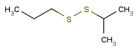
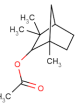
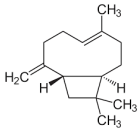
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
11	Cumin	*Cuminum cyminum,* Family-Umbelliferae	Cuminaldehyde  Cymene  Terpenoids	***As an antibacterial agent**: targets biofilm and decreases its production destruct the cell membrane. ***As an antifungal agent**: inhibits mycelia growth, decreases the expression of fumonisin biosynthetic gene in Fusarium verticillioides.	Digestion problems including diarrhoea, colic, bowel spasms, gas, as a diuretic; to start menstruation, as an aphrodisiac, as a flavoring component.	[132]
12	Nutmeg	*Myrestica fragrans Houtt.* Family-Myristicae	Myristicin  d-pinene  Limonene  d-borneol, l-terpineol, Geraniol, Safrol	***As an antibacterial agent:** damages the cell membrane of the bacteria and also sluggish the capability of bacterial adhesion, inactivates the enzymes, and affects the process of protein synthesis. ***As an antifungal agent**: increases the porosity of cell membrane.	Diarrhoea, nausea, stomach spasms and pain, and intestinal gas, rheumatism, mouth sores, and toothache, like spices and flavorings.	[133]

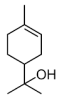
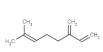
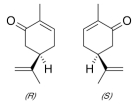
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
13	Rosemary	*Rosmarinus officinalis,* Family-Labiatae	Carnosic acid  Carnosol  Rosmarinic acid, Hesperidine	***As an antibacterial agent**: changes in genetic material, alter the transportation of electrons, cellular leakage components, and the changes in fatty acid production. ***As an antifungal agent**: strongly inhibits aflatoxin synthesis.	Improve memory, indigestion (dyspepsia), joint pain associated with arthritis, hair loss, as a seasoning in foods, as a fragrant component.	[134]
14	Mustard	*Brassica nigra* Family-Cruciferae	Allyl isothiocyanate 	***As an antibacterial agent:** targets the active enzyme, promotes the misfolded protein aggregation. ***As an antifungal agent:** causes fungal degradation, inhibits growth in molds.	Antineoplastic drugs, as a food flavoring, as an emetic, and diuretic, topical treatment, arthritis, and rheumatism. It has shown encouraging pharmacological effects in cancer, cardiovascular disease, and diabetes.	[135]

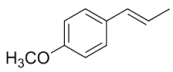
(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
15	Basil	*Ocimum bacsilicum* Family- Labiatae	Linalool  methyl chavicol (estragole)  Eugenol 	***As an antibacterial agent:** restriction of bacterial respiration, leaching of ions. ***As an antifungal agent**: inhibits mycelial development of the pathogenic fungus Botrytis fabae.	Spasms, lack of appetite, digestive gas, vomiting, constipation, flavor in foods.	[136]
16	Asafoetida	*Ferula asafoetida,* Family- Apiaceae	Isobutyl propyl disulfide 	***As an antibacterial agent:** inhibit several microbial enzymes. ***As an antifungal agent:** inhibition of mycelium production, inhibition of mycelium production.	Breathing or throat problems, digestive problems, for corns and calluses, as a fragrance in cosmetics and as a flavoring agent in foods and beverages, used in materials for the repelling of dogs, cats, and wildlife.	[137]
17	Galangal	*Alpinia galangal* Family- Zingiberaceae	Fenchyl acetate  β-caryophyllene  β-farnesene, Caryophyllene oxide, and 1,8-cineole	***As an antibacterial agent:** damage to the outer and the inner membrane and coagulation of the cytoplasm. ***As an antifungal agent:** lyses the fungal protoplast.	Fever, muscle spasms, digestive gas, bacterial infections, and swelling (inflammation)	[138]

(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
18	Cardamom	*Elettaria cardamomum Var. minuscule* Family-Zingiberaceae	α-terpineol  Myrcene  Menthone, Limonene,1,8-cineol, Sabinene, 1,8-cineol, β-phellandrene,	***As an antibacterial agent**: inhibits growth and triggers dissociation of biofilms, affects the membrane integrity. ***As an antifungal agent**: prevented radish germination.	Diabetes, and high cholesterol, as a seasoning in foods, in soaps, creams, and scents.	[139]
19	Dill	*Anethum graveolens Linn.* Family-Umbelliferae	Carvone  α-phellandrene and limonene	***As an antibacterial agent:** Rise in the membrane permeability, destroys membrane integrity. ***As an antifungal agent:** modify the architecture of the plasma membrane, inhibit mitochondrial ATPase, and hinder Mitochondrial dehydrogenase functions, Deposition of ROS.	In soaps and cosmetics, cooking spice, as a fragrance, for issues with digestion, liver disease, urinary tract disorders, infections.	[140]

(Table 3) cont.....

S. No	Name of spices / herbs	Biological Source	Phyto-constituents	Mechanism of Action	Uses	References
20	Anise	*Illicium verum, Pimpinella anisum* Family-Umbelliferae.	Anethole 	***As an antibacterial agent:** microbial membrane disruption. ***As an antifungal agent:** inhibits spore germination, reduces mycelial development.	Stomach upset, intestinal gas, nasal congestion, as an expectorant, to boost urination, alleviate menstrual discomfort or pain, ease labour and boost sexual desire, epilepsy control, nicotine dependency, sleeping disorder (insomnia), asthma, diabetes, constipation, flavoring agent, in dairy products, gelatins, foods, candy and fresheners for breathing.	[141]

CONCLUSION

Bacterial and fungal infections have been a common reason for several diseases in humans. Thus, a lot of antibiotics have been employed for treatment purposes. However, the overuse of antibiotics has led to the emergence of resistant strains of bacteria and fungi. To combat/reduce this problem, some of the spices and herbs can be really helpful. In this chapter, we have discussed the various reasons for the development of resistant strains in bacteria and fungi. Furthermore, the details of various spices and herbs that can be beneficial in the treatment of infections and different possible mechanisms by which they act are described.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 5

Naturally Isolated Compounds from Spices and Herbs and their Medicinal Uses

Archana M. Ramteke[1,*]

[1] *Department of Chemistry, K. D. K. College of Engineering, Great Nag Road, Nandanvan, Nagpur, M.S. 440001, India*

Abstract: Spices and herbs have a long history of medicinal uses. They include turmeric, basil, mace, cinnamon, ginger, *etc*. [1]. Ginseng and Ginkgo biloba are reportedly used to improve stamina and cognitive performance. Spices are used in all the countries for different purposes, such as in cooking and medicines, *etc*. Spice is a seed, fruit, root, bark, or other plant substance primarily used for coloring, flavoring, and preserving food. Herbs are the leaves, flowers, stems from plants used for flavoring or as garnishing. Medicinal and aromatic plants have also been used therapeutically to improve the health and wellbeing of animals; most were used for prophylactic purposes and to improve the growth rate and feed conversion ratio efficiency [2, 3]. The alternatives to antibiotics as growth stimulators from the group of prebiotics, probiotics, organic acids, essential oils, medicinal plants, or parts of plants, such as thyme, basil, oregano, pepper and plenty of others, are numerous [2]. This chapter includes a wide variety of isolated compounds, such as phenolic compounds and flavanoids present in spices, which are now experimentally documented to possess antioxidant, anti-inflammatory, antimutagenic and anticarcinogenic activities. It also includes a list of spices compounds that are experimentally evidenced to control cardiovascular diseases, diabetes, cataract, cancer, *etc*.

Keywords: Herbs, *In-vitro*, Isolated compounds, Spices.

INTRODUCTION

Spices and herbs are an important part of the human diet to enhance the flavor, color and aroma of food. They have also been used from ancient times as traditional medicine to improve the health of animals. Spices and herbs can be classified on the basis of flavor, taxonomy or part of the plant from where they came. Presently there has been a trend to use natural substances present in fruits, vegetables, oil seeds, and herbs as antioxidants and rational foods [4 - 6]. According to the World Health Organization (WHO), essentially 20,000 medicinal plants

[*] **Corresponding author Archana M. Ramteke:** Department of Chemistry, K. D. K. College of Engineering Great Nag Road, Nandanvan, Nagpur, M.S. 440001, India; E-mail: archanamramteke@gmail.com

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reside in 91 countries. The premier steps to make use of the biologically active phytochemicals from plant resources are extraction, pharmacological screening, isolation and characterization of the bioactive compound, toxicological analysis and clinical evaluation [7]. A brief summary of the general approaches in extraction, isolation, and characterization of bioactive compounds from plant extract is presented in Fig. (**1**).

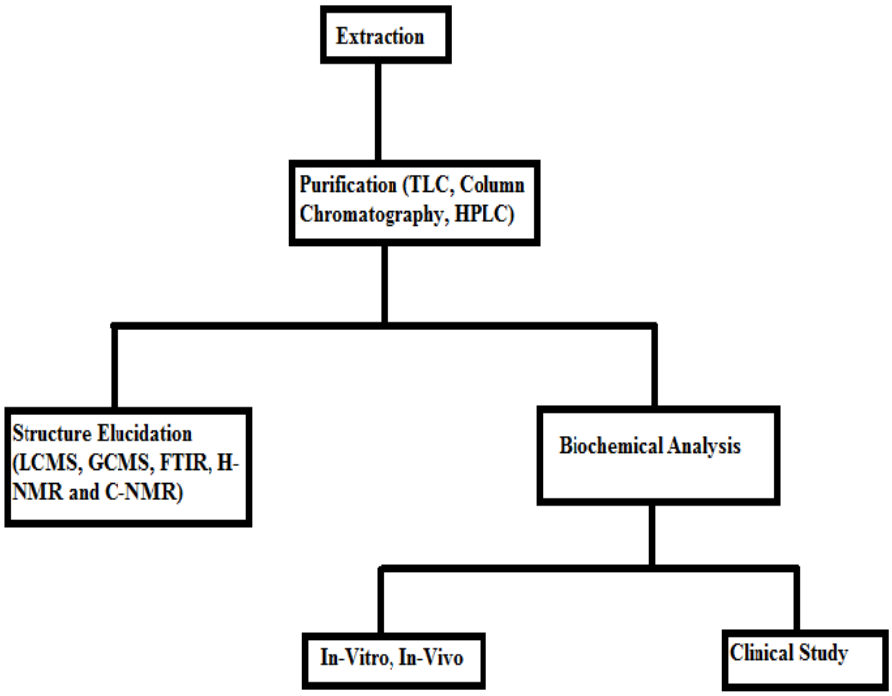

Fig. (1). A brief summary of the general approaches in extraction, isolation, and characterization of a bioactive compound from plant extracts [8].

Spices and herbs are found to be rich sources of phytochemicals [9 - 12]. Phytochemicals are a large group of bioactives derived from plants, which have potential protective effects against diseases. This group consists of flavonoids and other phenolic compounds, carotenoids, plant sterols, glucosinolates and other sulphur-containing compounds. There are more than 6000 known flavonoids (Jaganath & Crozier, 2010). Phenolic chemicals have a variety of activities in plants, including structural and defensive activities, and they serve as pollinators and seed-dispersing animal attractants.

Differences between Spices and Herbs

Spices come from different parts of a plant other than the leaves, while herbs come from the leaves of a plant. They can be classified into various groups based on taste, taxonomy or part of the plant where they came from.

Based on taste, spices and herbs can be classified into the following groups:

a) Hot spices (black and white peppers, Cayenne pepper, mustard, chilies).

b) Mild flavor spices (paprika, coriander), aromatic spices (clove, cumin, dill fennel, nutmeg, mace, cinnamon) and

c) Aromatic herbs and vegetables (thyme, basil, bay leaf, marjoram, shallot, onion, garlic)

Uses and Benefits of Spices

Table **1** enlists the uses and benefits of spices.

Table 1. List of Important Spices with their Uses and Benefits [13 - 16].

Spices	Uses	Benefits
Asafoetida (Hing)	It is used for seasoning food, especially snacks, and has medicinal uses	A good remedy for whooping cough and stomach ache.
Cardamom (Elaichi)	Mostly in all Indian and other sweet dishes, it used to give a good flavor and smell. It is also used widely in the pharmaceutical sector.	It helps to control bad breath and digestive disorders. Also the whole cardamom chewed is good for coping with Diabetes.
Chilly (Lal Mirch)	It is the main ingredient used for adding hot flavor to the food.	The antioxidants present in chilly help cope up with cholesterol, and also help in burning calories.
Cinnamon (*Dalchini*)	It is used mainly for seasoning food and preparing masala. It has medicinal value too.	It supports the natural production of insulin and reduces blood cholesterol.
Clove (Laung)	It is mainly used as a cooking ingredient for seasoning food or preparing the masala.	Clove oil is beneficial for coping with toothache, sore gums, chest pains, fever, digestive problems, cough, and cold.
Coriander (Dhaniya)	Coriander leaves, as well as coriander seeds, are used in cooking. It also has some medicinal uses.	It can be used externally on aching joints and rheumatism. It is also good for coping with soar throat, allergies, digestion problems, hay fever, *etc*.

(Table 1) cont.....

Spices	Uses	Benefits
Cumin (Zeera)	It is used for cooking and it also possesses medicinal properties.	It is a good source of iron and keeps the immune system healthy. Water boiled with cumin seeds is good for coping with dysentery.
Curry leaves(*Curry Patta*)	It is used as the main ingredient for seasoning in some countries. It has many medicinal uses.	These leaves are beneficial for reducing blood sugar. Each part of the plant provides some benefit or the other. The dried leaves are extensively used in herbal medicines.
Fenugreek (*Methi*)	It is mainly used as a green leafy vegetable, and seeds are used for seasoning and preparing *masalas*. It has medicinal uses too.	Fenugreek seed tea or sweet fudge is good for increasing breast milk. It is also helpful for treating diabetes and lowering cholesterol.
Garlic (*Lassan*)	It is used for cooking as well as for medicinal purpose.	It is useful for coping with cough and cold. It also has antibiotic properties.
Ginger (Adrak)	It is used for giving a specific flavor to food and has many medicinal uses.	It helps avoid digestive problems. It is beneficial for coping with cough and cold.
Mustard (Rye)	It is used for seasoningas well as with green leafy vegetables. The use of mustard oil is extensive in India, but it is banned in some countries.	Mustard oil is good for body massage and even for getting good hair. It consists of omega-3 fatty acids. It is an excellent source of iron, zinc, manganese, calcium, protein, *etc*.
Nutmeg (Jaiphal)	It is used in powdered form for garnishing and preparing the masala. It is used in making soaps, perfumes and shampoos. It is also used for medicinal purposes.	It is beneficial for the treatments of asthma, heart disorder, and bad breath problems.
Pepper (*Kaali Mirch*)	It is extensively used in cooking, especially for garnishing. It has many medicinal uses too.	It helps to deal with cold, cough, infections, muscle pains, and digestive problems.
Saffron (Zaffran/Kesar)	It is used for cooking as well as in beauty products. It is mainly used in sweet dishes. It has good medicinal properties.	It helps cope with skin diseases. It is a good remedy for cough, cold, and asthma.
Star anise (Chakra Phool)	It is used in cooking and for medicinal use.	Star anise oil is beneficial for rheumatism, digestion and avoiding bad breath.
Turmeric (Haldi)	It is used in cooking and skincare products. It has a wide range of medicinal use.	It helps to deal with skin problems, and also it makes coping with diabetes easier. Turmeric powder can be used for healing cuts and wounds.

Chemical Compounds in Herbs and Spices

Anise

Anise is a seed spice derived from a flowering plant belonging to the family *Apiaceae*. Flavor and aroma from anise come from anethole. Anethole is a phenylpropene derivative found in anise (*Pimpinella anisum*) and fennel (*Foeniculum vulgare*). Anethole occurs naturally in high concentrations in volatile oils, such as anise oil (80–90%), star anise oil (over 90%), and fennel oil (80%) [17]. Anethole exists in both a *cis* and a *trans* isomer, with the *trans* isomer being more abundant. It is the main component of the anise essential oil (80–90%), with minor components including para-anisaldehyde, estragole, and pseudoisoeugenyl-2-methylbutyrates, among others [18]. Anethole is also used in medicines as an expectorant, an antitussive, and antispasmodic for treating gastrointestinal tract illnesses. As a result, anise is found in a number of pharmaceutical products.

Basil

Basil (*Ocimum basilicum*) is a culinary herb belonging to the botanical family *Lamiaceae*. It has been used traditionally as a medicinal herb for the treatment of headaches, coughs, diarrhea, constipation, warts, worms, and kidney disorders. It is also a source of aroma compounds and essential oils containing biologically active constituents that possess antimicrobial and antifungal properties [19, 20]. Linalool is the main constituent of the essential oil of *O. basilicum* (28.6–60.6%), followed by estragole, methyl cinnamate, epi-α-cadinol, α-bergamotene, γ-cadinene (3.3–5.4%), germacrene D (1.1–3.3%), and camphor (1.1–3.1%). Other compounds, such as myrcene, pinene, terpineol, 1,8-cineole, eugenol, and methyleugenol, have been identified in basil leaves [21].

Caraway

Carvone is found to be the major compound in caraway. It has two mirror-image isomers, one of which smells like caraway, and the other smells like spearmint. Only S-carvone, the isomer smelling of caraway, is found in caraway seeds.

Cardamom

1,8-cineole is the major compound found in small cardamoms. The cardamom aroma is caused by the combination of 1,8-cineole compound and another compound, alpha-terpinyl acetate.

Cayenne

Capsaicin is the major compound present in chili peppers, which gives them their spiciness.

Chili Pepper

The chili pepper is a fruit spice derived from plants from the genus *Capsicum*, originated in Mexico and was brought to Asia by Portuguese navigators during the sixteenth century. Chili peppers have a taste that is pungent, hot, and somewhat sweet (depending on the variety and type). Mild or sweet peppers contain similar constituents as *Capsicum* but with little or no pungent components. Chili peppers are used as food colorants, flavoring agents, predator repellants, and as a source of pain relief. The compounds responsible for the "hot" flavor of chili peppers are called capsaicinoids, with capsaicin being the best known. *Capsicum* contains up to 1.5% (by weight) of pungent compounds, commonly composed of capsaicin, dihydrocapsaicin, and others. Other constituents present in chili pepper are carotenoids, vitamins A, C, and small amounts of volatile oils with more than 125 known components. Another class of capsaicin-like compounds found in chili pepper and non-pungent chili pepper are the capsinoids. Many positive health benefits have been ascribed to both capsaicin and capsinoids, including anticancer, anti-inflammatory, and analgesic effects [22].

Chives

Similar to onions and garlic, sulfur-containing organic compounds gives flavor to chives. One of the major contributors to chives is dipropyl disulfide.

Cloves

Eugenol is one of the main compounds found in cloves. More minor constituents also contribute to the characteristic odour, for example, compounds, such as methylamylketone and methylsalicylate. Eugenol is named after the scientific name for cloves, and along with its derivative compounds, it is used in perfumery & flavoring.

Cinnamon

Cinnamon is a bark spice obtained from the inner bark of several tree species from the genus *Cinnamomum*. Cinnamon is native to India, Sri Lanka, Bangladesh, and Myanmar, and it was imported to Egypt 4000 years ago [23]. In addition to its common culinary, also used as condiment and flavoring material, cinnamon is widely known for its anti-diabetic and glucose-lowering effects [24]. The flavor of cinnamon is due to an aromatic essential oil that is largely

composed of cinnamaldehyde (up to 90%); however, there are at least 80 other compounds known to be present in cinnamon oil, including cinnamyl alcohol, cinnamyl acetate, eugenol, and various coumarins that contribute to its overall flavor and aroma [25].

Coriander Leaves

One of the main component of cinnamon leaf oil extract is 2-decenoic acid. The composition also includes many different aldehydes, primarily those of 9-10 carbons in length.

Coriander Seeds

The main compound in coriander seeds is linalool. It has two mirror-image isomers, one of which is known as coriandrol. The other mirror-image isomer is found in lavender and sweet basil.

Cumin

Cuminaldehyde is the main contributor to cumin's warm aroma. Other constituents include a range of other aldehyde compounds.

Dill

Carvone is the main compound found in dill. The spearmint isomer of carvone is used in the manufacture of chewing gum, spearmint chewing gum. It is produced by being soaked in carvone.

Fennel

Fennel is a seed (and bulb) spice, as well as a leaf herb, that is derived from *Foeniculum vulgare.* Fennel is a highly aromatic and flavorful herb/spice and is one of the primary ingredients of absinthe. The distinctive licorice flavor and aroma from fennel comes from anethole. Other compounds known to be in fennel include estragole, fenchone, 1,8-cineole (eucalyptol), and *p*-allylphenol. In addition to its use in culinary applications, fennel has long been used as a medicinal herb to treat gastrointestinal illness and upper respiratory tract infections as well as to increase milk production in breastfeeding mothers through the consumption of fennel tea.

Ginger

Ginger (*Zingiber officinale*) is a root or rhizome-based spice derived from the ginger plant, a member of the turmeric family (both are from *Zingiberaceae*).

Ginger is believed to have originated in India and is widely used as a culinary additive as a hot, fragrant spice as well as a popular medicine. In addition to ginger's well-known use as a treatment for nausea, many components in ginger have been found to have anti-inflammatory, antibacterial, antipyretic, antilipidemic, antitumorigenic, and antiangiogenic effects [26, 27]. A variety of active components have been identified in the oleoresins of ginger, including zingerone, gingerols (6-, 8-, and 10-gingerols), and shogaols (6-, 8-, and 10-shogaols) [28]. Gingerols (especially 6-gingerol) are the major pungent components in the fresh ginger rhizome.

Lemongrass

Citral is a mix of two different isomeric aldehydes, neral and geranial. Citral is also used in perfumery for its citrus odour.

Mace

Mace's chemical composition is similar to that of nutmeg, as they are both obtained from the same plant. The compound of the highest concentration in the essential oil of mace is terpinen-4-ol. It is also found in the essential oil of the tea tree.

Marjoram

Sabinene hydrate is the main component of the extracted oil of marjoram and is responsible, along with other compounds of the terpene family, for the characteristic flavor of the herb.

Mint

The major compound in mint leaves is menthol. This compound is also a popular flavoring for chewing gum and toothpaste and is also used in menthol cigarettes.

Nutmeg

Nutmeg is a fragrant flavoring spice coming from the seed of *Myristica fragrans (*belonging to the *Myristicaceae* family*),* an evergreen tree indigenous to the Banda Islands in the Moluccas (or Spice Islands) of Indonesia. The nutmeg essential oil is obtained by steam distillation of ground nutmeg, and it is used widely in the perfumery and pharmaceutical industries. This volatile fraction typically contains sabinene (21.38%), 4-terpineol (13.92%), and myristicin (13.5 7%), as well as portions of safrole, elimicin, terpineol, α-pinene d-camphene, limonene, linalool, and isoeugeunol [29].

Paprika

Paprika is a ground spice made from the red, air-dried fruits of larger and sweeter varieties of the plant *Capsicum annuum*, which is also called bell pepper or sweet pepper. Paprika can also be modified with the addition of more pungent chili pepper and cayenne pepper. The red, orange or yellow color of paprika is due to its content of carotenoids. Paprika carotenoids, particularly capsanthin and capsorubin, have been reported to have a strong antioxidant activity [30]. Based on these results, cucurbitaxanthin A, capsanthin, capsanthone, and cryptocapsin could be potential paprika-specific carotenoid biomarkers. However, further analyses using untargeted MS-based approaches should be conducted to evaluate other possible biomarkers of paprika intake.

Parsley

Parsley (*Petroselinum crispum*) is a herb belonging to the *Apiaceae* family. It is native to the central Mediterranean region. Fresh parsley has a clean, green aroma with a versatile, fresh taste that is slightly peppery with an after taste of green apple. Parsley is a source of several flavonoids, especially luteolin and apigenin [31]. Apigenin is associated with anti-inflammatory activities as it appears to downregulate or inhibit cyclo-oxygenoase-2 (COX-2). Apigenin has also been identified as a potential cancer chemopreventive agent [32]. The major essential oil found in parsley leaves is 1, 3, 8-*p*-menthatriene, but other components are also present in lesser amounts, including myristicin and limonene [33, 34].

Pepper

Piperine is the major constituent of the oil that can be extracted from black pepper and is the main compound that gives black pepper its pungency. An isomer of piperine, chavicine, also contributes to the pungency.

Peppermint

Peppermint and spearmint are herbs that belong to the *Laminacea* family. Spearmint (*Mentha spicata*) is believed to be one of the oldest mints. The active constituents of spearmint include spearmint oil, various flavonoids (diosmin, diosmetin), phenolic acids, and lignans. The most abundant compound in spearmint oil is carvone, which gives spearmint its distinctive smell. Peppermint has a high menthol content (40.7%), along with menthone (23.4%), and other essential oils, such as menthyl acetate (4.2%), 1,8-cineole (5.3%), limonene (2. 6%), menthofuran (3.7%), and β-caryophyllene (1.7%) [35]. Peppermint leaves can also be added to herbal tea, ice cream, chewing gum, toothpaste, shampoo, *etc*. , for enhancing their flavor. Peppermint leaves are often used alone or with other

herbs in herbal teas (tisanes, infusions), ice cream, confectionery, chewing gum, toothpaste, and shampoos. Menthol activates cold-sensitive receptors in the skin and mucosal tissues and is the primary source of the cooling sensation that follows the topical application of peppermint oil. Peppermint also contains terpenoids and flavonoids such as eriocitrin, hesperidin, and kaempferol 7-O-rutinoside.

Saffron

Saffron is among the world's most costly spices. It comes from the dried flower stigma of *Crocus sativus*. Saffron contains more than 150 volatile and aroma-yielding compounds. Safranal (2,6,6-trimethyl-1,3-cyclohexadie-e-1-carboxaldehyde) is the major compound (70%) in the volatile fraction of saffron [36]. Saffron also has a number of non-volatile active components, many of which are carotenoids, including zeaxanthin, lycopene, and various α- and β-carotenes. However, the golden yellow-orange color of saffron is primarily the result of the carotenoid α-crocin, a glycosylester of crocetin. Picrocrocin(4-(β-d-glucopyranosyloxy)-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde) has also been found in saffron spice from 0.8 to 26.6% on a dry basis. This compound is responsible for saffron's bitter taste. In addition, saffron contains two important vitamins, riboflavin and thiamine. Saffron extracts and tinctures have been used as antispasmodic agents, gingival sedatives, nerve sedatives, expectorants, stimulants, and aphrodisiacs.

Sage

Sage or *Salvia officinalis* is a medicinal plant belonging to the *Lamiaceae* family. It is an aromatic herb native to the Mediterranean region but is now widely distributed throughout the world. Sage has been used in traditional medicine for the treatment of seizures, ulcers, gout, rheumatism, inflammation, dizziness, tremors, paralysis, diarrhea, and hyperglycemia [37]. Sage has a savory, slightly peppery flavor. It is strongly aromatic and is characterized by a medicinal, lemony, or bitter taste. It is used for seasoning and flavoring in many different foods, including sausages and stuffing. The major components present in sage are α-thujone (11.55–19.23%), viridiflorol (9.94–19.46%), 1, 8-cineole (8.85–15.60%), camphor (5.08–15.06%), manool (5.52–13.06%), β-caryophyllene (2.63–9.24%), α-humulene (1.93–8.94%), and β-thujone (5.45–6.17%) [38]. Some of the major phenolic compounds found in sage are rosmarinic acid, caffeic acid, carnosol, and carnosic acid.

Tarragon

Tarragon (*Artemisia dracunculus*), also known as estragon, is a perennial herb

belonging to the *Asteraceae* (daisy) family. It is widespread across much of Eurasia and North America and is cultivated for culinary and medicinal purposes. *In vitro* pharmacological studies indicate that tarragon has antibacterial, antifungal, and antiplatelet activity [39]. *In vivo* pharmacological studies have shown that tarragon has anti-inflammatory, hepatoprotective, antihyperglycemic, and antioxidant activity [39]. The major components of Russian tarragon are reported to be terpinen-4-ol, sabinene, and elemicin. Methyleugenol and estragole are usually present in tarragon oils at about 10 and 3%, respectively. However, estragole is one of the predominant compounds in the essential oil of French tarragon, constituting up to 82% [39]. *Trans*-anethole (21.1%), α-trans-ocimene (20.6%), limonene (12.4%), α-pinene (5.1%), and allo-ocimene (4.8%) are the other main components of tarragon.

Turmeric

Turmeric is a rhizomatous herbaceous perennial plant (*Curcuma longa*) belonging to the ginger family, *Zingiberaceae.* It is a key ingredient in many Asian dishes and is used mainly as a coloring agent. The most notable phytochemical components of turmeric root include compounds called curcuminoids, such as curcumin (diferuloylmethane), demethoxycurcumin (DMC), and bisdemethoxy-curcumin (BDMC). Curcumin is a polyphenolic molecule that constitutes 3.14% (on average) of powdered turmeric Curcumin is what gives the spice its yellow color [40]. The rhizome oils of turmeric contain more than 40 identifiable compounds, with the major constituents being α-turmerone (30–32%), aromatic-turmerone (17–26%), and β-turmerone (15–18%). This interest is likely due to the multiple biological or health activities attributed to it, including antioxidant, anti-inflammatory, and anti-tumor activities. Recent clinical studies with curcumin have demonstrated additional health benefits relating to treating immune deficiencies, improving cardiovascular health, treating depression [41], combating Alzheimer's disease, treating diabetes, arthritis, and inflammatory bowel disease [42].

Vanilla

The aroma of vanilla is mainly due to the compound vanillin, which accounts for 74-96% of the flavor & aroma compounds. Over 100 other volatile compounds have been detected, including acids, phenolic compounds, alcohols, and aldehydes.

Oregano, Rosemary and Thyme

Oregano, rosemary and thyme are well known for their beneficial health properties. For example, carnosic acid and some of the diterpenes abundant in rosemary and sage appear to exert anti-obesity effects (including body weight and

lipid-lowering effects) [43]. Several compounds found in herbs from the *Laminaceae* family also exhibit antimicrobial activity, such as thymol, carvacrol, carnosol, rosmanol, and caffeic acid [44].

Oregano (*Origanum vulgare*) is a native herb to temperate western and southwestern Eurasia and the Mediterranean region. It has an aromatic, warm, and slightly bitter taste. Among the chemical compounds contributing to the flavor of oregano are carvacrol, thymol, limonene, pinene, ocimene, and caryophyllene. Oregano also contains polyphenols, including caffeic, *p*-coumaric, and rosmarinic acid, which confer antioxidant activity and prevent lipid peroxidation [45].

Rosemary (*Rosmarinus officinalis*) is native to the Mediterranean and Asia. The leaves are used as a flavoring agent in a variety of foods in traditional Mediterranean cuisine. They have a bitter, astringent taste and a very characteristic aroma. Rosemary contains a number of phytochemicals, including rosmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid, carnosic acid, and carnosol [45]. Major essential oils present in rosemary oil are borneol (26. 5%), α-terpinene (15.6%), and α-pinene (12.7%).

Thyme (*Thymus vulgaris*) is also a member of the *Lamiaceae* family, and it has been used in foods mainly for flavor, aroma, and food preservation. Thyme has also been used in folk medicine since the times of the ancient Egyptians, Greeks, and Romans. The leafy parts of thyme are often added to meat, fish, and food products and are also used as herbal medicinal products. The essential oils of common thyme contain 20–58% thymol and *p*-cymene (15–28%) as the most prevalent compounds, followed by linalool (0.7–6.5%), γ-terpinene (4–10%), carvacrol (1–4%), myrcene (1–3%), 1,8-cineole (0.8%), and borneol (0.7–1.7%) [46]. Thymol is the compound that provides the distinct flavor of thyme. It is also found in oregano and is used as one of many additives in cigarettes.

CONCLUSION

Spices and herbs have been used since the early days of humankind and are still used throughout the world for health promotion and treatment of various diseases. Plants are found to be the source of today's modern medicine and contribute largely to commercial drug preparation.

However, in many developing countries, herbal medicine is used as traditional medicine. Interests in food compounds from spices and herbs will continue to increase as well as research and technology that will develop better ways of growing spices and herbs that contain higher amounts of antioxidants. Over the last many years, several bioactive compounds have been isolated from various spices and herbs, which provide a scientific and medicinal basis to include spices

and herbs in our diet.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 6

Naturally-derived Analgesics and Anti-Inflammatory Agents

Shaimaa Fayez[1,#], Mariam I. Gamal El-Din[1,#], Omayma A. Eldahshan[1,2] and **Abdel Nasser B. Singab[1,2]**

[1] *Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, 11566 Cairo, Egypt*

[2] *Center for Drug Discovery Research and Development, Faculty of Pharmacy, Ain-Shams University, 11566 Cairo, Egypt*

Abstract: Medications for the treatment of pain and inflammatory disorders, although effective, their chronic use and/or misuse can lead to serious side effects. In this regard, naturally-derived antinociceptive and anti-inflammatory agents have emerged as alternatives to synthetically marketed drugs. The current review covers all the nutraceuticals and phytochemicals – derived from medicinal plants– which have been reported to possess analgesic and/or anti-inflammatory effects over the period between 2018 up to June 2020.

Keywords: Pain, Inflammation, Marine organisms, Medicinal plants, Natural products.

INTRODUCTION

Inflammation is one of the responses of innate immunity to infection or tissue injury. Despite being essential for maintaining normal homeostasis, prolonged inflammation could likewise be a sign of a pathological condition resulting from chronic diseases, which could be detected by the presence of inflammatory markers [1]. The molecular mechanisms of inflammation are complicated, and they are initiated by the recognition of the allergen by germline-encoded specific pattern recognition receptors such as Toll-like receptors (TLR), retinoic acid-inducible gene-I (RIG-1)-like receptors, C-type lectin receptors (CLR), and the nucleotide-binding oligomerization domain (NOD) like receptor [1, 2]. These inflammatory responses end up with some typical symptoms, including redness,

[#] Authors show equal contribution

[*] **Corresponding authors Abdel Nasser B. Singab and Omayma A. Eldahshan:** Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, 11566 Cairo, Egypt and Center for Drug Discovery Research and Development, Faculty of Pharmacy, Ain Shams University, Egypt; Tel: 002-010-05036231, 002-010-11841951; E-mail: dean@pharma.asu.edu.eg, oeldahshan@pharma.asu.edu.eg

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

swelling, pain, and heat [1, 3]. Activation of these receptors by bacteria triggers the release of inflammatory cytokines, which in turn mediate the production of C-reactive protein (CRP), among others, which promote the secretion of prostaglandins [3]. The latter are responsible for the symptoms of inflammation. Viral infections, on the other hand, trigger the release of type-I interferons, while parasitic infections and other allergens increase the production of histamine and interleukins. The common pathways, which play a major role in inflammation, are the NF-κB, JAK-STAT, and MAPK [3]. Although pain is one of the consequences of inflammation, it could also be a separate sign, even with no existence of an ongoing inflammatory process. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics are among the commonly used medications for pain treatment. However, they show many side effects, which lead to patient discomfort, especially in chronic use [4, 5]. Since the last decade, many natural products have proven efficacy for the management of pain and inflammation [2]. Herein, we report on the latest updates in the field of anti-inflammatory natural products, which have been reported over the interval between 2018 and June 2020.

Medicinal Plant Extracts with Reported Analgesic and/or Anti-Inflammatory Activities (Table 1)

Table 1. List of previously reported spices with anti-inflammatory activities.

Spices/plant Name	Mechanism of Action	Refs.
Acanthus ilicifolis Linn.	*In vivo* analgesic effect for the chloroform and petroleum ether fractions *In vitro* antioxidant activity	[8]
Ajuga laxmannii (Murray) Benth.	Inhibition of phagocytosis and decreasing the total leukocytes *in vitro* *In vitro* antioxidant activity	[9]
Anadenanthera colubrina var. cebil (Griseb.)	*In vivo* anti-inflammatory potential in paw oedema model Reduction of IL-12 production and TNF-α release accompanied by elevation in IL-10 Inhibition of the production of nitric oxide	[10]
Asphodelus microcarpus Salzm. & Viv.	Strong antioxidant capacity Reduction of the *in vivo* paw and ear edema induced by carrageenan and xylene	[11]
Athyrium multidentatum (Doll.) Ching	Decreased the expression of iNOS and COX-2 enzymes Downregulation of the *in vitro* and *in vivo* mRNA expression of IL-6, IL-1β, and TNF-α	[12]
Backhousia citriodora (Lemon myrtle)	Antioxidant properties Reduction of IL6, TNF-α, and NO levels	[13]

(Table 1) cont.....

Spices/plant Name	Mechanism of Action	Refs.
Bistorta officinalis (Bistort)	Inhibition of the release of pro-inflammatory cytokines after LPS stimulation	[14]
Boswellia species oleogum resin	Antioxidant effect Immunomodulatory effects Decreased paw edema, pleural exudates, pain, and fever *in vivo*.	[16]
Buddleja officinalis Maxim.	Suppression of NO, TNF-α, and IL-1β *in vitro*	[17]
Caesalpinia minax Hance	Reduced the proinflammatory cytokines, IL-6, IL-1β, and TNF-α *in vivo*	[18]
Caesalpinia sappan L.	Reduced the production of TNF-α	[20]
Calotropis procera	Reduction of myeloperoxidase activity in neutrophils Reduction of the expression of adhesion molecules ICAM-1 and Iba-1	[21]
Centipeda minima (L.) A.Br.	Inhibition of NF-κB TNF-α, IL-1β, COX-2, NOX-2, NOX-4, ROS, PGE_2, and iNOS *in vitro*.	[22]
Cissus gongylodes (grapevine)	Inhibition of COX and LOX inflammatory pathways and reducing the concentrations of PGE_2 and LTB_4	[23]
Citrus bergamia	Downregulation of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and the inhibition of the release of NO, PGE_2, ROS.	[24]
Cyclamen africanum B. et R.	Strong antioxidant activity	[25]
Elephantopus scaber Linn. herb	Inhibition of the transcription and translation of iNOS and the blockade of NF-κB signaling pathway	[26]
Elsholtzia ciliata (Thunb.) Hyl.	Inhibition of the secretion of the pro-inflammatory cytokines IL-6, TNF-α. and PGE_2	[27]
Epigynum auritum	Inhibition of the release of TNF-α, IL-6, and NO	[28]
Eugenia stipitate McVaugh. *Eupatorium japonicum Thunb.*	Reduction of the volume of edema and the migration of leukocytes and neutrophils *in vivo* Suppressing the expression of IL-1β, the activation of NF-kβ, and the transcription of MMP-9	[29] [30]
Forsythia suspensa (Thunb.)	Inhibition of NF-kβ pathway *via* the activation of A20 protein as well as the stimulation of the Nrf2 signaling cascade	[31]
Galinsoga parviflora Cav.	Reduction of IL-6 levels and strong anti-hyaluronidase activity	[32]
Garcinia cambogia Gaertn. and *Pothos scandens* L.	Suppression for 5-LO in human neutrophils Inhibition for isolated human 5-LO and $mPGE_2S$-1	[33]
Halosarcia indica Willd.	Dose dependent reduction in carrageenan-induced edema and reduction of writhing responses in rats	[34]
Hyusopus cuspidatus Boriss.	Reduction of serum nitric oxide, prostaglandin E_2, IL-6, IL-1β, and TNF-α	[35]
Indigofera argentea Burm. F.	Central action on the opioid receptors and the inhibition of COX and LOX metabolites in the peripheral tissues	[36]
Kadsura heteroclita	Reduction of the cytokines level of TNF-α, IL-1β, and IL-6	[37]

(Table 1) cont.....

Spices/plant Name	Mechanism of Action	Refs.
Kleinia pendula (Forssk.) herb	Significant analgesic and anti-inflammatory properties *in vivo*	[38]
Larrea species and *Zuccagnia punctate* Cav.	Inhibition of lipoxygenase enzyme	[39]
Ligusticum chuanxiong and *Radix Paeoniae lactiflora*	Reduction of the levels of IL-1β, IL-6, IL-12, and IFN-c *in vivo*	[41]
Manilkara zapota	*in vivo* pain-relieving effect	[42]
Mitrella kentia	Inhibition of the production of PGE_2, TXB_2, and its antagonism on PAF	[43]
Mycetia cauliflora Reinw.	Reduction of iNOS, NO, IL-1β, inhibition of the nuclear translocation of the transcription factor p65 and p50 protein	[44]
Niebuhria Apetala Dunn.	Reduction of the thermal-induced pain in rats in a dose dependent manner	[45]
Ocimum forskolei Benth.	Reduction of the carrageenan-induced paw edema	[46]
Opuntia humifusa Raf.	Inhibition of NO production and decreasing the levels of iNOS	[47]
Paeoniae alba and *Atractylodis macrocephalae*	Reduction of NO production and the proinflammatory cytokines like TNF-α, IL-6, and MCP-1	[48]
Panax ginseng	Decreasing the inflammatory symptoms by reducing IL-6 and TNF-α levels *in vivo*	[49]
Phyllanthus amarus Schum. & Thonn.	Inhibition of the production of the pro-inflammatory PGE_2, IL-1β, and TNF-α	[50]
Physalis angulata L.	Inhibition of the proinflammatory cytokines IL-1β, TNF-α, IL-6, IL-12, iNOS, COX-2 and increasing the levels of the anti-inflammatory genes of IL-10, arginase-1, TGF-β	[51]
Phytolacca dodecandra	Reduction of pain sensation and edema in the tested mice *in vivo*	[52]
Picria Fel-Terrae Lour	Downregulation of TNF-α, IL-6, IL-1β, COX-2, and iNOS	[53]
Pituranthos scoparius Coss. and Dur.	Dose-dependant inhibition of edema was observed in mice	[54]
Pterocephalus hookeri (C.B. Clarke) Höeck	Interfering with NF-κB pathway	[55]
Reineckia carnea (Andr.) Kunth	Inhibition of the production of NO	[58]
Rhodiola crenulate (golden root) *Sambucus australis* Cham. & Schltdl	Reduction of the levels of the inflammatory mediators like IL-1β, IL-6, and NO Reduction of interleukins 4 and 5, interferon-γ, nitric oxide, and decreased expression of NF-κB.	[59] [60]
Sarcopoterium spinosum	Increasing the expression of the anti-inflammatory genes IL-10 and Arg-1, the inhibition of the $NF\text{-}_{\kappa}B$ inflammatory pathway and Akt phosphorylation	[61]
Scrophularia megalantha Rech. f.	Reducing the levels of IL-17 and interferon-γ while increasing the levels of IL-10	[62]

(Table 1) cont.....

Spices/plant Name	Mechanism of Action	Refs.
Scutellaria barbata D. Don	Reducing NO, PGE_2, IL-6, and IL-1β production and decreasing the expression of p-JNK and p-ERK	[63]
Sigesbeckiae species	Inhibition of the nuclear factor $_{\kappa}$B (NF-$_{\kappa}$B) signaling pathway and mitogen-activated protein kinases (MAPKs)	[64]
Sinapis semen	Suppressed the protein and mRNA expression of TNF-α, IL-1β, and IL-6	[66]
Sophora flavescens Ait.	Reduction of IL-6, TNF-α, NO, and MCP-1 levels	[67]
Spatholobus suberectus	Strong free radical scavenging potential and the reduction of iNOS and COX-II expression	[68]
Tephrosia linearis (Willd.) Pers.	Interfering with the release of IL-2, GM-CSF, and TNF-α *in vitro*	[70]
Thymus zygis subsp. zygis	Inhibition of the release of nitric oxide	[71]

Acanthus Ilicifolis Linn

The "Holy leaved acanthus", *Acanthus ilicifolis* (Acanthaceae), is a perennial herb native to Australia and South Asia. The herb was traditionally used in China and India as a remedy for numerous ailments. Diverse phytochemicals were isolated from their different parts (leaves, bark, fruits, and roots), including terpenoids, flavonoids, steroids, alkaloids, phenolic compounds, and lignins [6, 7]. The chloroform and petroleum ether fractions demonstrated a significant *in vivo* analgesic effect when evaluated using the acetic acid-induced writhing method compared to the standard diclofenac. The plant extract likewise displayed potential *in vitro* antioxidant activity compared to standard ascorbic acid when evaluated using DPPH assay [8].

Ajuga Laxmannii (Murray) Benth

Ajuga laxmannii (Labiatae) is a Romanian herb used as a galactagogue and as an anti-inflammatory remedy. The latter effect is due to its antiradical capacity, which is attributed to the high phenolic content (total content ca. 67.6 ± 1.5 mg eqivalent of gallic agid/ g ethanol extract), including iridoid glycosides (*i.e.,* harpagide, aucubin, catalpol, harpagoside), flavonoids (*i.e.,* luteolin, apigenin, quercetin, rutin), and phytosterols (*i.e.,* stigmasterol, *β*-sitosterol, ergosterol). The antioxidant effect of *Ajuga laxmannii* ethanolic extract was evaluated using DPPH (showing IC_{50} value of 22.6 ± 0.8 µg/ml) and ABTS free radical assay. Moreover, the extract inhibited phagocytosis and decreased the total leukocytes *in vitro*, which was comparable to the positive control (diclofenac) [9].

Anadenanthera Colubrina Var. Cebil (Griseb.)

The ethanol extract of *Anadenanthera colubrine* (Fabaceaea) leaves exhibited significant *in vivo* anti-inflammatory potential in paw oedema model compared to standard dexamethasone drug. Marked reduction in IL-12 production accompanied by elevation in IL-10 were observed. The extract at 50 µg/mL inhibited the production of nitric oxide by 80% and reduced the release of TNF-α by more than 50%. Anti-oxidant activity of the extract was confirmed by DPPH assay. The anti-inflammatory and anti-oxidant were attributed to the flavonoid and phenolic content of the extract [10].

Asphodelus Microcarpus Salzm. & Viv

Asphodelus microcarpus (Liliaceae) is an Algerian plant commonly used in the traditional medicine for the treatment of pain and inflammation especially in the cases of rheumatoid arthritis, toothache, asthma, and bronchitis. The crude extract is rich in polyphenols and flavonoids with the highest percentage being in the leaves (equivalent to 755 mg gallic acid for polyphenols and 42 mg rutin for flavonoids). This finding corroborates its strong antioxidant capacity in scavenging the free radicals, which initiate inflammatory cascades. The anti-inflammatory effect of the extract was likewise evaluated by its ability to reduce the *in-vivo* paw and ear edema induced by carrageenan and xylene, respectively, within 6 h after the administration of an oral dose of 500 mg/kg [11].

Athyrium Multidentatum (Doll.) Ching

Athyrium multidentatum (Athyriaceae) is a perennial herb widely distributed in China. This nutritional potherb has a strong antioxidant and pain relieving effect due to its flavonoid (total flavonoid content ca. 36 ± 2.3 mg/g extract) and phenolic acids content mainly myricetin, quercetin, and kaempferol. The herbal extract decreased the expression of iNOS and COX-2 enzymes leading to significant reduction in NO and PGE_2, respectively. Downregulation of LPS-stimulated acute lung injury mice models, mRNA expression of IL-6, IL-1β, and TNF-α, decreased phosphorylation of ERK (extracellular signal-regulated kinase s), JNK (c-Jun-N-terminal kinases), and other relevant proteins of the TLR-4 pathway [12].

Backhousia Citriodora (Lemon Myrtle)

The lemon myrtle (Myrtaceae) is a shrub native to the rainforests of Australia and

grows mostly 50-800 m above the sea level. Its alcoholic extract is rich in flavonoids (flavonoid content is 14.5 mg/g extract) and polyphenols (total polyphenol content is 118.7 mg/ g extract). Its anti-inflammatory activity is due to its antioxidant properties and is mediated through the reduction of IL6, TNF-α, and NO levels in LPS-induced murine macrophages *in vitro* [13].

Bistorta Officinalis (Bistort)

The rhizomes of *Bistorta officinalis* (Polygonaceae) are traditionally used in Asia and Europe for topical treatment of skin conditions. Pawłowska *et al.* reported the influence of the infusion of the subterranean parts of *B. officinalis* and their isolated phytoconstituents on the release of pro-inflammatory cytokines after LPS stimulation. The study demonstrated the *in vitro* activity of the infusion to modulate the inflammatory response of human neutrophils involved in wound healing and other skin problems justifying its ethnopharmacological use [14].

Boswellia species oleogum resin (Frankincense, olibanum)

Many studies revealed the therapeutic potential of the frankincense obtained from the trees of *Boswellia* species (family Burseraceae) in the management of many inflammatory and autoimmune disorders and in cancer therapy. It has been cultivated since ancient ages in China, India, and the Arabic peninsula and it has been used traditionally in the treatment of constipation, flatulence, CNS, and other inflammatory diseases. In the Islamic traditional medicine, the plant was used as a remedy for burns, bruises, infections, and eye sores. At the beginning of the 20th Century, the plant was officially used in the management of inflammation around Europe [15]. Although genus *Boswellia* comprises ca. 30 species or even more, only five of which are mainly used for the production of the frankincense namely *B. serrata*, *B. sacra*, *B. frerana, B. carterii*, and *B. papyrifera*. The oleogum resin of the frankincense is a complex mixture of more than 200 phytochemicals of different classes including terpenoids (tetra and pentacyclic), polyphenols, tannins, saponins, alkaloids, and sugars. Despite the diversity of its constituents, its activity is mainly pertained to its pentacyclic boswellic acids. The mechanisms pertaining to its anti-inflammatory effects are [16]:

- Antioxidant effect through its free radical scavenging activity including ROS (reactive oxygen species) and RNS (reactive nitrogen species). Interfering with membrane lipid peroxidation. Inhibition of iNOS, COX-2, 5-LOX, prostaglandins, leukotrienes, and proinflammatory cytokines (TNF-α, IL-1, IL-2, IL-4, IL-6, γ-interferon) *in vitro* and *in vivo*.

- Immunomodulatory effects among them decreasing the immune cells infiltration into the inflamed tissue, enhancing the differentiation of the regulatory T-cells, stabilization of mast cells, and decreasing the adhesion between the leukocytes and endothelial cells *in vitro* and *in vivo*.
- Other phenotypic effects including decreased paw edema, pleural exudates, pain, and fever *in vivo*.
- On the molecular level, many inflammatory pathways have been interrupted among them the NF-κB, MAPK, JNK, WNT/β-catenin, and STAT3.

Buddleja Officinalis Maxim

Buddleja officinalis (Loganiaceae) is a Chinese medicinal plant, which has been used in the traditional medicine for the treatment of conjunctivitis, stroke, and headache. Buddlejae Flos (Mi Meng Hua) is a Chinese medicine composed of the dried flower buds of *B. officinalis*. Ateoside and linarin are among the major phytochemicals in Mi Meng Hua. They have a strong antioxidant and anti-inflammatory activities which are pertained to the suppression of NO, TNF-α, and IL-1β in LPS-induced human umbilical vein endothelial cells *in vitro* [17].

Caesalpinia Minax Hance

The seeds of the Chinese plant *Caesalpinia minax* (Fabaceae) are traditionally used for the remedy of common cold, dysentery, and rheumatoid arthritis. Its chloroform fraction is rich in cassane-type diterpenes, which remarkably reduced the proinflammatory cytokines, IL-6, IL-1β, and TNF-α in the serum of Wistlar rats [18].

Caesalpinia Sappan L

The sappan wood or the Brazilian wood, *Caesalpinia sappan* (Fabaceae), has long been used traditionally for the remedy of inflammatory diseases. Brazilin, the major constituent of the sappan wood, has been reported for its *in vitro* analgesic and anti-inflammatory effects [19]. *C. sappan* was even more potent in lipopolysaccharide-treated bone marrow cells than other related anti-inflammatory herbs as *Machilus thunbergii*, *Agastache rugosa*, and *Saururus chinensis*. The extract of *C. sappan* reduced the production of TNF-α and significantly decreased the metabolic activity as well as the mitochondrial membrane potential of the treated bone marrow cells [20].

Calotropis Procera

Calotropis procera (Apocynaceae) is an Indian medicinal plant that has been used traditionally in wound healing, rheumatism, and in the treatment of different skin diseases. Previous phytochemical investigations revealed that the pharmacological effects of the plant are mainly related to the proteins of the plant latex. A highly homogenous cocktail of laticifer proteins containing peptidases and osmotin was prepared from the latex of *C. procera* and evaluated for its *in vivo* anti-inflammatory activity in treatment of oral mucositis (a severe inflammatory condition of ulceration and severe oral tissue damage). The protein cocktail successfully ameliorated the inflammation in oral mucosa with total reduction of myeloperoxidase activity (an enzyme present in neutrophils usually used as a quantitative marker of neutrophil infiltration in inflammatory conditions). Moreover, the laticifer protein fraction minimized the expression of adhesion molecules ICAM-1 (intercellular adhesion molecule-1) and Iba-1 (ionized calcium binding adapter molecule1), which are important inflammation biomarkers [21].

13. Centipeda Minima (L.) A.Br

The neuroinflammation induced by LPS in BV2 and microglial cells was reduced dramatically by the ethanolic extract of the Chinese herb *Centipeda minima* (Asteraceae). Neuroprotection was mediated through the inhibition of NF-κB (comparable to dexamethasone), TNF-α, IL-1β, COX-2, NADPH-oxidases 2 (NOX-2) and 4 (NOX-4), ROS, PGE_2, and iNOS *in vitro*. Phytochemical investigations on the ethanolic extract of *C. minima* using LC-MS/MS revealed the presence of phenolic acids, *viz.* caffeic acid, chlorogenic acid and its isomers, which contribute to the activity. *In vivo* experiment on LPS-induced neuroinflammatory mouse model showed that the extract was able to ameliorate the neuroinflammation after 3 days of treatment [22].

Cissus Gongylodes (Grapevine)

This plant belongs to family Vitaceae and its growth is restricted to the tropical rainforests of South America, Asia, and Australia. It has been used traditionally as an anti-inflammatory remedy for urolithiasis. The decoction of *Cissus gongylodes* was found to decrease the edema induced by croton oil in the ears of the tested mice *in vivo*. It inhibited both COX and LOX inflammatory pathways as it significantly decreased the concentrations of PGE_2 and LTB_4. The decoction likewise decreased TNF-α levels and interfered with the formation of calcium oxalate crystals and decreased their number and area [23].

Citrus Bergamia

Bergamot (*Citrus bergamia* Risso et Poiteau (Bergamot) is a shrub of the Rutaceae family famous for its winter fruits and has a diverse array of pharmacological and nutritional values. Bergamot essential oil fraction deprived of furocoumarins (BEO-FF) displayed potent *in vivo* anti-inflammatory effect as evidenced by the significant inhibition of carrageenan-induced paw edema after an intra-peritoneal injection of carrageenan. The strong anti-inflammatory activity was confirmed by histological and immunohistochemical analysis and was related to the downregulation of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and the inhibition of the release of NO, PGE_2, ROS. BEO-FF also demonstrated prominent antinociceptive activity as demonstrated by the acetic acid-induced writhing test and the hot plate model. The pronounced effects of BEO-FA were attributed to its major monoterpene content including limonene, linalool, and linalyl acetate [24].

Cyclamen Africanum B. et R

Cyclamen africanum B. et R. (Primulaceae) is the only species, among 20 species belonging to this genus, available in Algeria. This perennial plant displayed strong antioxidant and anti-inflammatory activities as revealed from its free radical scavenging potential (polyphenol content: 43.5 ± 1 mg equivalent gallic acid/g extract; flavonoid content: 2.48 ± 0.08 mg equivalent quercetin/g extract) and its ability to stabilize the membrane of red blood cells (especially at low extract concentrations and up to 200 µg/mL). The antioxidant capacity of the crude extract was evaluated by DPPH assay and its metal chelating (reducing) power [25].

Elephantopus Scaber Linn. Herb

Elephantopus scaber (Asteraceae) is an annual herb widely distributed in the old world and is used in the treatment of many inflammatory disorders as fever, sore throat, and dysentery. Its ethanolic extract was found to inhibit the transcription and translation of iNOS, hence suppressing the production of NO. The suppression extends to include some proinflammatory mediators like TNF-α, MCP-1, IL-6, and IL-1β through the blockade of NF-κB signaling pathway. These investigations were performed *in vitro* using Western blot, RT-PCR, EMSA (electrophoretic mobile shift assay) and *in vivo* through the analysis of the peritoneal lavage fluid of the LPS-stimulated mice using ELISA [26].

Elsholtzia Ciliata (Thunb.) Hyl

Elsholtzia ciliata (Thunb.) Hyl. (Labiatae) is a medicinal plant widely distributed throughout China, Korea, and Europe. A comparative study of the ethanol extracts of its flowers, leaves, stems, as well as the whole plant was conducted for evaluating their *in vitro* anti-inflammatory and antioxidant activities. All extracts demonstrated significant inhibition of the secretion of the pro-inflammatory cytokines IL-6, TNF-α. and PGE_2 in lipopolysaccharide-induced mouse peritoneal macrophage cells. Meanwhile, the leaf extract was the most potent blocker of PGE_2 secretion. The extracts of the flowers and stems exhibited the most significant suppression of TNF-α and IL-6. On the other hand, the stem extract showed the least antioxidant effect upon testing with different assays [27].

Epigynum Auritum

Epigynum auritum Schneid. (Apocynaceae) is a Chinese herb traditionally used as a remedy for arthritis and other inflammatory disorders. Different fractions of the hydroalcoholic extract of *E. auritum* significantly inhibited the release of TNF-α, IL-6, and NO in LPS-induced RAW264.7 macrophages while stimulating the expression of IL-10. The 100% methanolic fraction down regulated the expression of COX-2 and iNOS enzymes. *In vivo* carrageenan-induced paw edema and xylene-induced ear edema models confirmed the potent anti-inflammatory activity of those fractions through the prominent amelioration of inflammatory cytokines [28].

Eugenia Stipitate McVaugh

Genus *Eugenia* (Myrtaceae) harbors more than 1000 species, many of which show antinociceptive, antioxidant, and anti-inflammatory activities. GC-MS analysis of the essential oil obtained from *E. stipitate* leaves showed the presence of numerous terpenes, the predominant of which are guaiol (13.7%), *trans*-caryophyllene (11.3%), γ-eudesmol (6.5%), 10-*epi*-γ-eudesmol (5.9%), and α-eudesmol (5.9%). The oil was tested by Costa *et al.* for its acute toxicity, antinociceptive, antipyretic, and anti-inflammatory activities *in-vitro* and *in-vivo*. The results showed that:

- The essential oil of *E. stipitate* was considered safe (LD_{50} > 2000 mg/kg).
- The antinociceptive activity was based on the acetic acid-induced writhing test,

which showed that the oil significantly inhibited the number of abdominal writhings compared to the control mice *in vivo*.

- The anti-inflammatory activity was assessed by the carrageenan-induced paw edema test, where the oil significantly reduced the volume of edema as well as decreasing the migration of leukocytes and neutrophils in the carrageenan-induced peritonitis model *in vivo*. Moreover, the oil provided protection for the bovine serum albumin (BSA) against denaturation *in vitro*.

The fever induced in mice by the injection of yeast (*Saccharomyces cerevisiae*) was significantly reduced by the oil within the first hour of treatment *in vivo* [29].

Eupatorium Japonicum Thunb

Eupatorium japonicum (Asteraceae) is a Chinese medicinal plant and an effective painkiller. In the rheumatoid arthritis fibroblast-like synoviocytes, *E. japonicum* ethanol extract demonstrated a dose-dependent *in vitro* anti-inflammatory effect. Suppressing the expression of IL-1β, the activation of NF-□B, and the transcription of MMP-9 were the supposed mechanisms underlying its anti-inflammatory effect [30].

Forsythia Suspensa (Thunb.)

The aqueous extract of the fruits of the Asian flowering plant *Forsythia suspensa* (Oleaceae) significantly suppressed inflammation. The molecular mechanism underlying this *in vitro* activity include the inhibition of NF-κB pathway *via* the activation of A20 protein as well as the stimulation of the Nrf2 signaling cascade, which resulted in the activation of NQO1 (NAD(P)H quinone oxidoreductase 1), HO-1 (heme oxygenase-1), and glutamate-cysteine ligase catalytic subunit (GCLC) [31].

Galinsoga Parviflora Cav

Galinsoga parviflora (Asteraceae) is an annual herb used worldwide in the folk treatment of skin inflammation, wound healing, and in the protection against UV radiation. Its essential oil has an antibacterial activity specially against *S. aureus* and *B. cereus*. The extract was found to decrease IL-6 levels induced by IL-1β (up to 33%), however it has no effect on the constitutive levels of IL-6 in the endothelial cells. It has meanwhile a moderate antioxidant effect but a strong anti-hyaluronidase activity (IC_{50} = 0.47 mg/ml) [32].

Garcinia Cambogia Gaertn. and Pothos Scandens L.

A comparative study was performed on seven plants traditionally used in Sri Lanka for the treatment of different inflammatory conditions including *Argyreia populifolia* Choisy (Convolvulaceae), *Garcinia cambogia* Gaertn. (Clusiaceae), *Hibiscus furcatus* Willd (Malvaceae), *Mollugo cerviana* L. (Molluginaceae), *Nyctanthes arbor-tristis* L. Gaertn. (Oleaceae), *Ophiorrhiza mungos* L. (Rubiaceae), and *Pothos scandens* L. (Araceae). The *n*-hexane, dichloromethane, ethyl acetate, and methanol extracts of the seven herbs were assessed for their *in vitro* capability to inhibit major pro-inflammatory mediators *via* cell-free and cell-based assays of 5-lipoxygenase (5-LO), microsomal prostaglandin E_2 synthase-1 ($mPGE_2S$-1), and nitric oxide (NO) scavenging capacity. The *n*-hexane and dichloromethane extracts of *Garcinia cambogia* showed the most significant suppression for 5-LO in human neutrophils with IC_{50} values of 0.92 and 1.39 μg/ml, respectively. The same extracts demonstrated significant inhibition for isolated human 5-LO (IC_{50} = 0.15 and 0.16 μg/mL) and $mPGE_2S$-1 (IC_{50} = 0.29 and 0.49 μg/ml). The potent anti-inflammatory activities of the lipophilic extracts were attributed to the secondary metabolite garcinol, which had a dual 5-LO/$mPGE_2S$-1 inhibitory activity. Moreover, the lipophilic extracts of *Pothos scandens* displayed potent inhibition of $mPGE_2S$-1 [33].

Halosarcia Indica Willd

The aqueous extract of the tropical herb *Halosarcia indica* (Amaranthaceae) demonstrated significant *in vivo* anti-inflammatory activity evidenced by the dose dependent reduction in carrageenan-induced edema with 42% inhibition at the dose of 400 mg/kg compared to the standard indomethacin, which showed a 48% inhibition. The extract likewise reduced the pellets weight in the cotton granuloma assay relative to diclofenac sodium. The analgesic effect was evidenced by the significant reduction of writhing responses in rats at 200 mg/kg and 400 mg/kg compared to aspirin.The prominent activities of *H. indica* extract was most probably related to its phenylpropanoid content [34].

Hyusopus Cuspidatus Boriss

The essential oil of the Chinese herb *Hyusopus cuspidatus* (Labiatae) significantly decreased the inflammatory response of the cotton-ball induced granuloma in mice at a dose of 0.4 mL oil/kg, which is significant to the effect produced by aspirin. The oil reduced serum nitric oxide, prostaglandin E_2, IL-6, IL-1β, and TNF-α levels in serum [35].

Indigofera Argentea Burm. F

The true indigo, *Indigofera argentea* (Fabacceae), has long been used in the folk treatment of headache, vertigo, pain, and inflammation. A recent study showed that its hydroalcoholic extract exhibited *in vivo* dose dependent analgesic activity upon evaluation *via* the capsaicin-induced pain test and the hot plate model. The analgesic activity was also evidenced by the reduction of mice writhes and the inhibition of pain latency at concentrations of 30, 100, and 300 mg/kg. The analgesic effect of the extract was pertained to its central action on the opioid receptors and the inhibition of COX and LOX metabolites in the peripheral tissues. Dose dependent anti-inflammatory activity was exhibited by the extract in carrageenan-induced paw edema test in rats in addition to its *in vitro* good membrane stability with 49.29% maximum percentage hemolysis inhibition in the human red blood cell membrane stabilization anti-inflammatory method. Moreover, the extract at the doses of 100 and 300 mg/kg demonstrated significant reduction in rectal temperature in yeast-induced pyrexia test in rats. Results validated the traditional use of *I. argentea* in pain management and inflammation and attributed its activities to its content of flavonoids, phenols, alkaloids, saponins and tannins [36].

Kadsura Heteroclita

Kadsura heteroclite (Schisandraceae) has long been used in the traditional Chinese medicine for the treatment of rheumatoid arthritis. *In-vivo* investigations showed that *Kadsura heteroclite* stems decrease paw-edema induced by subcutaneous injection of carrageenan, the ear edema induced by xylene, and the abdominal writhings induced by the intraperitoneal injection of acetic acid. *In-vitro* studies showed that the extract reduce the cytokines level of TNF-α, IL-1β, and IL-6 [37].

Kleinia Pendula (Forssk.) Herb

This herbal plant is native to the Southwestern mountains of Saudi Arabia and belongs to family Asteraceae. Its chloroform and ethyl acetate fractions, administered at doses 100, 200, and 300 mg/kg of the mice body weight, displayed significant analgesic and anti-inflammatory properties comparable to diclofenac sodium (10 mg/kg, positive control) *in vivo*. Metabolic profiling by UPLC-MS showed the richness of these fractions with phenolic acids (caffeoylquinic acid derivatives, protocatechuic, and chlorogenic acids), tannins, and flavonoidal glycosides [38].

Larrea Species and Zuccagnia Punctate Cav

María *et al.* has investigated the synergistic antifungal activity of the binary mixtures of *Larrea* (*L. divaricate* Cav., *L. cuneifolia* Cav., and *L. nitida* Cav.) (Zygophyllaceae) and *Zuccagnia* (*Z. punctate* Cav.) (Fabaceae) hydroalcoholic extracts. The antifungal activity of the most active combinations was attributed to their anti-inflammatory effect due to the inhibition of lipoxygenase enzyme with IC_{50} values ranging from 0.078 to 0.56 μg/mL, which were more potent than that of the standard quercetin (IC_{50} value at 0.9 μg/mL). The percentage of LOX inhibition ranges from 94-99%, which was comparable to naproxen (95%) [39].

Ligusticum Chuanxiong and Radix Paeoniae Lactiflora

Ligusticum chuanxiong (Apiaceae) rhizomes have long been used in the folk remedy of cardiovascular and inflammatory disorders. Its main active constituents, including ligustrazine, tetramethylpyrazine, butylidenephthalide, and phthalide lactones, inhibited the release of different pro-inflammatory mediators [40]. Paeoniflorin, the major constituent of *Paeonia lactiflora* (Paeoniaceae) roots, demonstrated prominent therapeutic effect in different *in vivo* inflammatory models. Meanwhile, the combination of *L. chuanxiong* and *P. lactiflora* roots demonstrated superior *in vivo* anti-inflammatory potential on focal cerebral ischaemic stroke. It significantly reduced the levels of IL-1β, IL-6, IL-12, and IFN-c in serum and brain tissues of rats. The anti-inflammatory and antiapoptotic potential of the combination was mediated through TLR4/MyD88/MAPK/NF-κB signalling pathways [41].

Manilkara Zapota (Sapodilla / Chikoo)

Manilkara zapota (Sapotaceae) is a tropical evergreen tree that has long been used as an analgesic for the treatment of common cold, fever, and wounds. The chloroform and methanol extracts of *M. zapota* leaves were investigated for their *in vivo* pain-relieving effect using tail-flick and hot-plate assays. By evaluating three different doses of both extracts (100 mg/kg, 200 mg/kg, and 400 mg/kg), the highest dose (400 mg/kg) displayed the most significant analgesic effect in the two models [42].

Mitrella Kentia Leaf and Stem Extract

Mitrella kentia (Annonaceae), which is commonly distributed in the tropical areas

of Asia-pacific, is traditionally used as remedy for fever. The mechanism of its anti-inflammatory effect is due to the inhibition of the production of PGE_2, TXB_2, and its antagonism on PAF (platelet activation factor) receptor *in vitro* [43].

Mycetia Cauliflora Reinw.

Genus *Mycetia* (Rubiaceae) comprises ca. 30-45 species, of which *Mycetia cauliflora* is famous for the healing of pain, ulcers, and inflammation among the tribal people of Bangladesh. *In-vitro* biochemical investigations on the methanolic extract of *M. cauliflora* showed a significant reduction of iNOS, NO, IL-1β, inhibition of the nuclear translocation of the transcription factor p65 and p50 protein, as well as the suppression of the phosphorylation - hence inactivation – of IκB kinase (IKK), IκBα, and Akt (protein kinase B). These mechanisms are proceeded *via* phosphoinositide-dependent kinase-1 (PDK1), which is thought to be the main target of *M. cauliflora* methanolic extract [44].

Niebuhria Apetala Dunn.

Niebuhria Apetala (*Capparis apetala*) (Brassicaceae), among other caper plants, is famous for the valuable functional phytoconstituents including vitamins, phytosterol, flavonoids, alkaloids, and tannins. The leaf and stem alcohol extracts of the plant significantly reduced the thermal-induced pain in rats in a dose dependent manner using Eddy's hot plate test. Furthermore, the leaf and stem extracts demonstrated significant increase in the tail flick latency upon testing using the heat conduction model. The maximum analgesia was observed at 500 mg/kg comparable to the standard drug diclofenac. Moreover, the leaf extract of *N. apetala* showed more analgesic activity than the stem [45].

Ocimum Forskolei Benth.

Genus *Ocimum* is one of the largest genera in family Labiatae widely distributed in Africa, Asia, and Central America. *Ocimum forskolei* has been used in the folk medicine of the Arabic peninsula for the treatment of cold symptoms like cough and rhinitis as it is rich in flavonoids and phenolic acids. Phytochemical investigations revealed that the hydroalcoholic extract significantly reduced the carrageenan-induced paw edema (with 40% inhibition) in rats even better than the standard drug indomethacin [46].

Opuntia Humifusa Raf.

The methanolic extract of the Korean plant *Opuntia humifusa* (Cactaceae) displayed promising *in vitro* anti-inflammatory effect by the inhibition of NO production and decreasing the levels of iNOS in the LPS-induced RAW264.7 macrophages [47].

Paeoniae Alba and Atractylodis Macrocephalae

This herbal combination of Radix *Paeoniae alba* (RPA) (Paeoniaceae) and Rhizoma *Atractylodis Macrocephalae* (Asteraceae) have been used in China to enhance the blood circulation, in the treatment of diarrhea and other gastrointestinal disorders. The inflammatory responses are suppressed through reduced NO production (by downregulation of iNOS) and by the inhibition of proinflammatory cytokines like TNF-α, IL-6, and MCP-1. On molecular basis, the herbal combination inhibits NF-κB pathway by suppressing the translocation of p65 to the nucleus and prohibiting IκB-α (inhibitor of kappa B) phosphorylation and degradation in murine macrophages *in vitro* [48].

Panax Ginseng

This Asian-Pacific plant belonging to family Araliaceae has long been used in traditional medicine for improving memory and cognitive disorders in Alzheimer's patients as well as a remedy for chronic inflammatory disorders as COPD (chronic obstructive pulmonary disease). Recently, studies showed that *Panax ginseng* could decrease the inflammatory symptoms by reducing IL-6 and TNF-α levels in cancer cachexia mice models *in vivo* due to the active constituent ginsenoside Rb1 [49].

Phyllanthus Amarus Schum. & Thonn.

Phyllanthus amarus (Euphorbiaceae) is a medicinal herb traditionally used for the treatment of various ailments including inflammatory diseases. Its pharmacological effect is due to the diversity of its secondary metabolites among them lignans, tannins, flavonoids, and alkaloids. The ethanol extract of *Phyllanthus amarus* significantly inhibited the production of the pro-inflammatory PGE_2, IL-1β, and TNF-α in LPS-induced human macrophages. Additionally, it suppressed the activation of the inflammatory cascades PI_3K/Akt, MAPKs, and NF-κB [50].

Physalis Angulata L.

The calyces of the Colombian Caribbean annual herb *Physalis angulate* (Solanaceae) displayed significant anti-inflammatory effect in DSS (dextran sulfate sodium)-induced colitis mice. The intestinal inflammation was reduced due to the inhibition of the pro-inflammatory cytokines IL-1β, TNF-α, IL-6, IL--, iNOS, COX-2 and increasing the levels of the anti-inflammatory genes of IL-10, arginase-1, TGF-β (transforming growth factor beta), and MRC-1 (mannose receptor c) *in vitro*. Moreover, the extract improved the histological score and reduced the severity of the inflammatory symptoms in mice with DSS-induced colitis [51].

Phytolacca Dodecandra

This Ugandan herbal plant has traditionally been used for the management of pain and inflammatory disorders. The crude extract of *Phytolacca dodecandra* (Phytolaccaceae) was evaluated for its analgesic and anti-inflammatory activity using the acetic acid-induced writhing test and histamine-induced pw edema test, respectively. The results showed that the extract significantly reduced pain sensation and edema in the tested mice *in vivo* [52].

Picria Fel-Terrae Lour

This Indonesian herb belongs to genus *Picria* (Linderniaceae). Although the plant has antidiabetic, hepato- and cardioprotective effect, recent studies showed that it exerts an analgesic and anti-inflammatory activity through its immunomodulatory effect by the downregulation of TNF-α, IL-6, IL-1β, COX-2, and iNOS in LPS-treated macrophages without inducing cytotoxicity [53].

Pituranthos Scoparius Coss. and Dur

Pituranthos scoparius (Apiaceae) is a medicinal plant well known in Algeria and North Africa for the treatment of measles, rheumatism, spasms, pain, diabetes, hepatitis, and urinary tract infections. The hydroalcoholic extract of the plant was evaluated for its *in vivo* anti-inflammatory activity using carrageenan-induced paw edema, xylene, and croton oil-induced ear edema. A dose dependant inhibition of edema was observed in mice (stimulated with xylene and croton oil) at concentrations of 100, 300, and 600 mg/kg, however in those stimulated with carrageenan the anti-edematous effect was seen at doses of 100, 250, and 500 mg/kg. Moreover, the analgesic activity of *P. scoparius* extract was investigated

using the acetic-acid-induced writhing model. The extract exhibited potent effect with 69.92% writhing inhibition at 500 mg/kg [54].

Pterocephalus Hookeri (C.B. Clarke) Höeck

Pterocephalus hookeri (Caprifoliaceae) is a herbal plant distributed in the area of Tibet and is known among the native people as "pang-ziduo-wo". It is traditionally being used for the treatment of cold and flu symptoms as well as rheumatoid arthritis. Recent investigations showed that the plant extract is rich in bis-iridoids, which display potent analgesic and anti-inflammatory effects. The extract significantly reduced the writhing effect induced by acetic acid in mice (measure of acute pain) and decreases the ear and paw edema induced by xylene and carrageenan, respectively (measure of inflammation). These compounds primarily work by interfering with NF-κB pathway [55, 56].

Qing Re Zao Shi Liang Xue Decoction (QRZSLXF)

The Chinese decoction is composed of 11 different herbs, namely *gypsum fibrosum*, *Rhizoma Anemarrhenae, Flos Lonicerae*, *Fructus Forsythiae Suspensae*, *Radix Scutellariae Baicalensis*, *Radix Salviae Miltiorrhizae*, *Folium Phyllostachydis Henonis*, *Cortex Moutan Radicis*, *Radix Rehmanniae, Fructus Gardeniae,* and *Cornu Saigae Tataricae.* The formulation showed strong efficacy in the treatment of inflammatory bowel disease by decreasing the expression of interleukin-6, the transcription factor STAT3, and RAR-related orphan receptor gamma (RORγt) *in vitro* as evidenced by Western blotting and quantitative real time PCR [57].

Reineckia Carnea (Andr.) Kunth

This Chinese herb, *Reineckia carnea* (Asparagaceae) is rich in saponin glycosides, which displayed significant *in vitro* anti-inflammatory activity by inhibiting the production of NO in LPS-stimulated RAW 264.7 cells [58].

Rhodiola Crenulate (Golden Root)

Rhodiola crenulata (Crassulaceae) is a medicinal plant traditionally used in Asia and East Europe for the treatment of various epidemic diseases. The water extract of the plant demonstrated *in vitro* anti-inflammatory activity on LPS-stimulated macrophage cells. On extract treatment, the levels of the inflammatory mediators like IL-1β, IL-6, and NO were diminished. The activity was related to the

inhibiting capacity of the extract for the expression of NF-$_K$B, iNOS, and MAPK proteins in addition to its induction for autophagy related molecules [59].

Sambucus Australis Cham. & Schltdl

Elderberry (*Sambucus australis*) (Adoxaceae) is commonly used in Brazil for the treatment of various inflammatory disorders due to its richness with flavonoids, triterpenoids, volatile oil, and phenolic acids. *In-vivo* and *in-vitro* investigations on its methanolic extract revealed significant reduction of interleukins 4 and 5, interferon-γ, nitric oxide, and decreased expression of NF-κB. On the other hand, the extract increased the production of the anti-inflammatory cytokine IL-10 [60].

Sarcopoterium Spinosum

Sarcopoterium spinosum (Rosaceae) is a Mediterranean plant, which is used in the Beduin traditional medicine for the treatment of diabetes and inflammation. Its anti-inflammatory effect is mediated by increasing the expression of the anti-inflammatory genes IL-10 and Arg-1, the inhibition of the NF-κB inflammatory pathway and Akt phosphorylation in RAW264.7 cells (as evidenced by real time PCR and Western blot analysis), and by the inhibition of NO secretion (using Griess reagent) *in vitro*. The plant was also found to decrease the expression of several adipocytokines involved in metabolic inflammation like fetuin-1, resistin, lipocalin-2, PAI-1 (plasminogen activator inhibitor-1), RBP-4 (retinol binding protein-4), and ICAM-1 (intercellular adhesion molecule-1). Reduction of inflammation by *S. spinosum* aqueous root extract is not restricted to the adipose tissue but is also observed in the liver of obese diabetic mice [61].

Scrophularia Megalantha Rech. f

Scrophularia megalantha (Scrophulariaceae) is a medicinal herb growing mainly in the city of Kelardasht in the North of Iran. It has traditionally been used for the treatment of eczema, goiter, stomach ulcers, and gall bladder infections. The 80% ethanol extract of the aerial parts reduced the infiltration of inflammatory cells to the CNS and decreased disease progression in the multiple-sclerosis mice model. *In-vitro* studies revealed that the extract reduced the levels of IL-17 and interferon-γ while increasing the levels of IL-10 [62].

Scutellaria Barbata D. Don

Scutellaria barbata (barbed skullcap) is a flowering plant commonly grown in

Asia and belongs to the mint family (Labiatae) with reported anti-cancer and anti-inflammatory activities. Recent phytochemical investigations showed that the ethanol and ethyl acetate extracts of *S. barbata* are rich sources of phenolics/flavonoids and carotenoids, respectively. Biological studies *in-vitro* revealed that *S. barbata* extracts displayed dose-dependent anti-inflammatory activity by reducing NO, PGE_2, IL-6, and IL-1β production and decreasing the expression of p-JNK and p-ERK [63].

Sigesbeckiae Species

Sigesbeckiae Herba is a Chinese herbal medicine with known anti-inflammatory activity. Linghu *et al.* [64] performed a comparative study on three different species viz. *S. pubescens* Makino (SP), *S. orientalis* L. (SO), and *S. glabrescens* Makino (SG) to investigate the underlying molecular mechanisms. Immunofluorescence staining accompanied with ELISA test showed that the three species *in-vitro* inhibited the nuclear factor κB (NF-κB) signaling pathway and mitogen-activated protein kinases (MAPKs). They likewise suppressed the inflammatory enzymes cyclooxygenase-2 (COX-2) and the inducible nitric oxide synthase (iNOS) - hence the release of NO - in the order of SP > SO > SG. They also decreased the secretion of post-inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). In another study conducted by Zhong *et al.*, the anti-inflammatory activity of *S. glabrescens* was related to in vitro reduction of NO, MCP-1, IL-6 secretion in the addition to inhibition of NF-κB activation. *In-silico* investigations showed that toll-like receptor-4 (TLR-4) as well as transcription factors 65 and 105 (p65 and p105) could likewise be potential anti-inflammatory targets for *S. glabrescens* [65].

Sinapis Semen

Sinapis semen is the dried ripe seeds of *Sinapis alba* L. (white mustard) or *Brassica juncea* (L.) Czern. (yellow mustard) (Brassicaceae). The study of the *in vivo* anti-inflammatory potential of sinapis semen in acute and chronic mouse models revealed that it suppressed the protein and mRNA expression of TNF-α, IL-1β, and IL-6 as well as inhibiting the myeloperoxidase activity in the ears of the treated mice [66].

Sophora Flavescens Ait

Sophora flavescens (Fabaceae) is one of 52 species belonging to genus *Sophora*,

which is distributed in Asia and the pacific. It is used in the traditional Chinese medicine as a strong antipyretic agent due to its flavonoid and alkaloid content. The extract reduced xylene-induced ear edema (with inhibition of 41% and 29% for extract doses of 100 and 200 mg/kg, respectively, compared to 47% inhibition with indomethacin) and carrageenan-induced paw edema in mice. *In-vitro* studies on the LPS-induced RAW 264.7 cells showed that the extract significantly decreased IL-6, TNF-α, NO, and MCP-1 levels [67].

Spatholobus Suberectus

Spatholobus suberectus (Fabaceae) is a Chinese medicinal herb, which has traditional uses for the treatment of rheumatism, menstrual abnormalities, anemia as well as being used as a dietary supplement in tea and soup. DPPH (2,2-diphenyl-1-picrylhydrazyl) and nitric oxide *in-vitro* assays showed that the hot aqueous extract of *S. suberectus* has a strong free radical scavenging potential (due to its high gallic acid content which is ca. 108.4 mg/g extract), nitric oxide reducing ability (in a dose-dependent manner with no significant difference at 200 μg/mL), and reduction of iNOS and COX-II expression in murine RAW 264.7 cells treated with LPS [68].

Swertia punicea Hemsl

Swertia punicea (Gentianaceae) is a medicinal herb traditionally used in China for the alleviation of fever, jaundice, and hepatitis. Enzyme linked immunosorbent assay (ELISA) method was adopted for investigating the *in vitro* anti-inflammatory activities of its isolated compounds. All metabolites demonstrated promising anti-inflammatory activities with IC_{50} values ranging from 1.237 to 3.319 mM. Insights into the structure-activity relationships of the isolated xanthone glycosides revealed better anti-inflammatory activity of compounds with increased methoxy (OCH_3) substitution and a sugar residue [*O*-glc-(6-1)-glc] at C-1. However when the sugar part was replaced by [*O*-glc-(6-1)-xyl] at the same carbon atom, the activity was enhanced only in compounds with less number of methoxy (OCH_3) groups [69].

Tephrosia linearis (Willd.) Pers

The flavonoidal content of the tropical plant *Tephrosia linearis* (Fabaceae) interferes with the release of IL-2, GM-CSF (granulocyte-macrophage colony stimulating factor), and TNF-α *in vitro*. Some metabolites can meanwhile further inhibit the production of IL-1β and IL-6 with superior activity than the standard

anti-inflammatory drug ibuprofen. The percentage of the cytokines release were lowered to 80% (for IL-2), 46% (for IL-6), 47% (for GM-CSF), and 12% (for TNF-α) compared to the control (LPS) [70].

Thymus zygis subsp. zygis

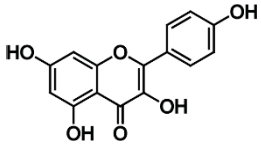
Thymus zygis Loefl. (Labiatae) is a famous Portuguese spice and a medicinal herb that grows in ountries around the Mediterranean Sea. *Thymus* zygis *subsp. zygis* is considered one of the thyme species of highest commercial value. Both the aqueous decoction and the hydroalcoholic extract of the herb demonstrated promising *in vitro* anti-inflammatory activities at their non-cytotoxic concentrations (50 µg/ml). The aqueous decoction and the hydroalcoholic extract inhibited the release of nitric oxide in lipopolysaccharide (LPS)-stimulated RAW264.7 cells by 48% and 89% respectively [71].

Isolated Natural Products with Reported Analgesic and/or Anti-Inflammatory Activities

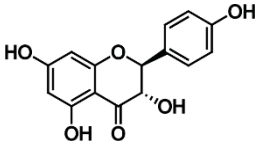
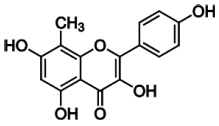
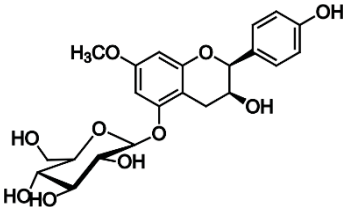
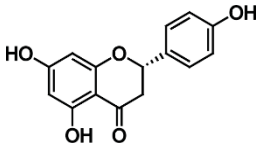
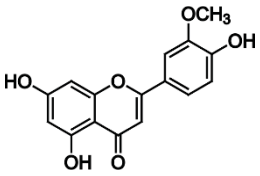
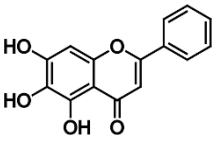
Flavonoids and Phenolic Acids

The hydro-alcoholic extract of the leaves of the Brazilian plant *Licania rigida* (Chrysobalanaceae) is rich in flavonoids and phenolic acids like **kaempferol** (Table **2**) and **chlorogenic acid** (Table **3**). The latter is known to reduce CRP (C-reactive protein), iNOS, and COX-2. The anti-inflammatory effect is observed *via* the reduction of paw edema (induced by arachidonic acid) in mice, which is due to the inhibition of leukocytes migration, the reduction of vascular permeability, and preventing the action of vasoactive amines *in vivo* [72].

Table 2. List of previously reported flavonoids with anti-inflammatory activities.

Compound (Structure / Name)		Isolated From	Mechanism	Refs.
	Kaempferol	*Licania rigida* (Chrysobalanaceae)	- CRP (C-reactive protein), iNOS, and COX-2 reduction - Inhibition of leukocytes migration - Reduction of vascular permeability - Preventing the action of vasoactive amines	[72]

(Table 2) cont.....

Compound (structure / name)		Isolated from	Mechanism	Ref.
	Dihydrokaempferol	*Hosta plantaginea* (Liliaceae)	- COX-1 and COX-2 inhibition - Antioxidant	[73, 74]
	Plantanone D			
	Hostaflavanol A			
	Naringnin			
	Chrysoeriol	*Lonicera japonica* (Caprifoliaceae)	- NO production inhibition - Inhibited production of IL--, IL-1β, TNF-α, PGE_2 - Reduction of iNOS, COX-2	[75]
	Baicalein	*Scutellaria baicalensis* (Lamiaceae)	- interference with NO, IL-6, and TNF-α - Inhibition of COX-2 and NF-κB/p65 expression	[77]

(Table 2) cont.....

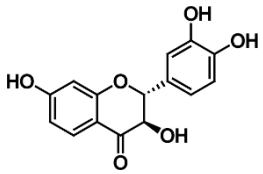
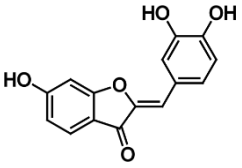
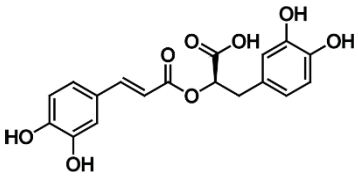
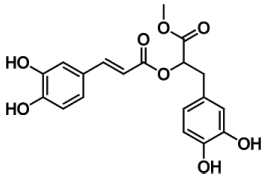
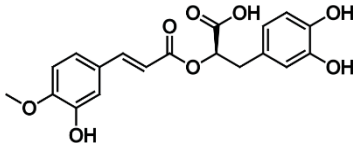
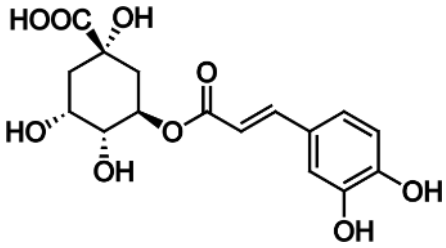
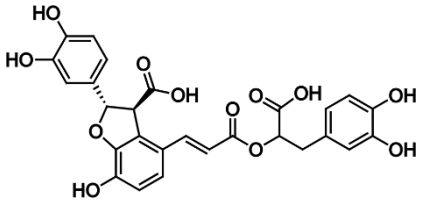
Compound (structure / name)		Isolated from	Mechanism	Ref.
	Dihydrofisetin	*Cotinus coggygria* (Anacardiaceae) *Gleditsia sinensis* (Fabaceae) *Capsella bursa-pastoris* (Brassicaceae)	• Decreased release of NO and PGE_2 • Inhibition of iNOS and COX-2 expression. • Inhibition of TNF-α, IL-1β, IL-6, and MCP-1 expression • Inhibition of IκB-α phosphorylation and decreased the concentration of p65. • Antioxidant activity	[78]
	Sulphuretin	*Gueldenstaedtia verna* (Fabaceae)	- NO production inhibition - Downregulation of IL-6, 1β, and PGE_2	[79]

Table 3. List of phenolic acids previously reported for their anti-inflammatory effects.

Compound (structure / Name)		Isolated from	Mechanism	Refs.
	Rosmarinic acid	*Thymus atlanticus* (Lamiaceae) *Origanum majorana* (Lamiaceae)	Inhibition of TNF-α and IL 6 and 1β in THP-1	[80, 81]

(Table 3) cont.....

Compound (structure / Name)		Isolated from	Mechanism	Refs.
	Rosmarinic acid methyl ester	*Salvia miltiorrhiza* Bunge (Labiatae)	- COX-2 and iNOS inhibition - induction of HO-1expression	[82]
	Shimobashiric acid B	*Salvia miltiorrhiza* Bunge (Labiatae)		
	Chlorogenic acid	*Licania rigida* (Chrysobalanaceae)	- CRP (C-reactive protei n), iNOS, and COX-2 reduction - inhibition of leukocytes migration - reduction of vascular permeability - preventing the action of vasoactive amines	[72]
	Lithospermic acid	*Salvia miltiorrhiza* (Lamiaceae)	Inhibition of IL-1β, IL-6, TNF-α, TLR-4, phosphorylated p65, and IκB-α expression	[83]

The flowers of *Hosta plantaginea* (Liliaceae) have long been used in the traditional Chinese medicine for the treatment of various inflammatory disorders. **Plantanone D** is a methylated flavonoid isolated by Yang *et al.* from *H. plantaginea* flowers along with three other flavonoids, **hostaflavanol A, dihydrokaempferol, and naringnin** (Table **2**). These compounds are responsible for the *in vitro* anti-inflammatory activity of the plant, which was due to the inhibition of COX-1 (IC_{50} at 37.2 ± 3.2 μM) and to less extent COX-2 (IC_{50} at 50.2 ± 3.5 μM) enzymes compared to celecoxib (IC_{50} of 9.0 ± 0.6 μM for COX-1 and 1.0 ± 0.1 μM for COX-2). Moreover, they displayed antioxidant activities

with IC_{50} values at 35.2 ± 0.8 μM and 9.12 ± 0.3 μM as measured by the DPPH and ABTS free radical scavenging assays, respectively [73, 74].

The anti-inflammatory activity of *Lonicera japonica* Thunb. (Caprifoliaceae), an ornamental plant native to East Asia – is due to its content of the flavone **chrysoeriol** (Table **2**). The latter decreased ear edema in the mouse model *in vivo*, decreased NO production, inhibited IL-6, IL-1β, TNF-α, PGE_2, lowered the levels of iNOS, COX-2, and suppressed the phosphorylation of IκB and p65, hence interfering with JAK2/STAT3 and NF-κB pathways [75].

The traditional Chinese herb, *Scutellaria baicalensis* Georgi belonging to family Labiatae has been used in the treatment of several neurodegenerative diseases [76]. One important constituent, **baicalein** (Table **2**), a flavone with promising antioxidant and anti-inflammatory activities. The Antioxidant effect originates from its ability to scavenge the free radicals (ROS) while the anti-inflammatory effect is due to the interference with the production of NO, IL-6, and TNF-α as well as the inhibition of COX-2 and NF-κB/p65 expression in the LPS-treated microglial cells *in vitro* [77].

Dihydrofisetin (Table **2**) is a naturally-occurring flavanonol in many vegetables among them *Cotinus coggygria* (smoke tree) (Anacardiaceae), *Gleditsia sinensis* (Chinese honey locust) (Fabaceae), and *Capsella bursa-pastoris* (shepherd's purse) (Brassicaceae). The mechanisms of its anti-inflammatory effects are [78]:

- Decreased release of NO and PGE_2 by inhibiting the expression of iNOS and COX-2 in EAW 264.7 macrophages *in vitro*.
- Decreased *in-vitro* expression of the proinflammatory cytokines TNF-α, IL-1β, IL-6, and MCP-1.
- Inhibition of IκB-α phosphorylation and decreased the concentration of p65.
- Inhibition of the phosphorylation of ERK and p-38 mitogen-activated protein kinase.
- Increased the expression of the antioxidant protein, HO-1 (heme-oxidase).
- Inhibition of the carrageenan-induced paw edema *in vivo*.

Gueldenstaedtia verna (Fabaceae) is a perennial herb commonly distributed in Asia. Although it is traditionally used for the treatment of inflammatory ailments, recently it was found that the flavonoidal compound, **sulphuretin** (Table **2**) significantly inhibited NO production in LPS-induced RAW 264.7 cells and caused downregulation of interleukins-6, 1β, and prostaglangin E_2*in vitro* [79].

Rosmarinic acid (Table **3**) is one of the major metabolites in the crude extract of the Moroccan plant *Thymus atlanticus* (Labiatae). The aqueous extract and the

polyphenols-rich fraction of *T. atlanticus* significantly reduced the levels of the chemokine MCP-1 *in vitro*. They also reduced the edema induced by carrageenan in Wistar rats *in vivo* [80].

The anti-inflammatory effect of the culinary herb *Origanum majorana* (Labiatae) is attributed to the high phenolic and flavonoid content especially **rosmarinic acid** (Table **3**). Studies showed that the latter significantly inhibited the production of TNF-α and interleukins 6 and 1β in THP-1 human macrophages *in vitro* [81].

The roots of *Salvia miltiorrhiza* Bune (Labiatae) have been traditionally used in Chinese medicine for the treatment of chronic inflammatory ailments. Hyun *et al.* evaluated the *in vitro* anti-inflammatory activities of ten isolated caffeic acid derivatives using inducible nitric oxide synthase (iNOS), nitric oxide (NO), cyclooxygenase (COX)-2 inhibition assays and by investigating the expression of heme oxygenase (HO)-1. **Rosmarinic acid methyl ester** and **shimobashiric acid B** (Table **3**) inhibited NO production at IC_{50} values of 0.6 and 1.4 μM, respectively. Rosmarinic acid methyl ester exhibited more pronounced concentration-dependent inhibition of COX-2 and iNOS generation than that of shimobashiric acid B. Besides, it demonstrated dose-dependent induction of HO-1expression [82].

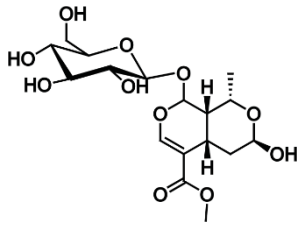
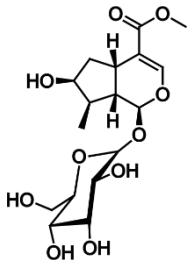
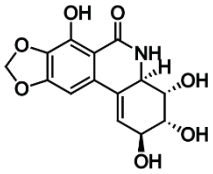
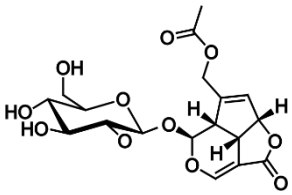
Salvia miltiorrhiza (Labiatae) is a Chinese herb, which is used since decades in the folk medicine for the treatment of thromboangiitis obliterans (an inflammatory thrombotic disorder of the small/medium arteries and veins of the hands and feet). The plant is rich in phenolic acids among them **lithospermic acid** (Table **3**), which showed a strong immunomodulatory potential by decreasing the expression of the inflammatory proteins IL-1β (with 45%, 56%, and 67% inhibition at 1, 5, and 25 μM, respectively), IL-6 (with 40%, 55%, and 75% inhibition at 1, 5, and 25 μM, respectively), TNF-α (with 19%, 35%, and 54% inhibition at 1, 5, and 25 μM, respectively), TLR-4 (using ELISA), phosphorylated p65, and phosphorylated IκB-α in LPS-induced THP-1 macrophages (using qRT-PCR and Western blot) [83].

Iridoids

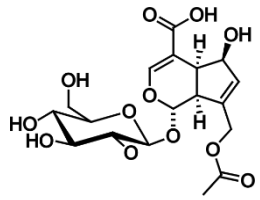
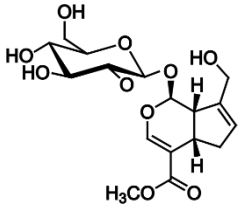
Yuan *et al.* attributed the anti-inflammatory activity of the Chinese medicinal plant *Cornus officinalis* (Cornaceae) to its iridodial glycosides content. Studies done on **morroniside** and **loganin** (Table **4**) showed that they were effective in the treatment of ulcerative colitis *in vivo* due to their antioxidant, anti-inflammatory, and antiapoptotic activities. They maintained the integrity of the intestinal mucosa by suppressing the proinflammatory cytokines, IL-1β, TNF-α,

IFN-γ, and IL-6 in the mouse model. On a molecular basis, they inhibited the NF-κB/STAT3 signaling pathway [84].

Table 4. List of previously reported iridoids with anti-inflammatory activities.

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	Morroniside	*Cornus officinalis* (Cornaceae)	Suppression of IL-1β, TNF-α, IFN-γ, and IL-6 release	[84]
	Loganin			
	Camptoside	*Camptosorus sibiricus* (Aspleniaceae)	Inhibition of NO production	[85]
	Asperuloside	*Hedyotis diffusa* (Rubiaceae)	Reduction of NO, PGE_2, IL-6, and TNF-α	[86]

(Table 4) cont.....

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	Asperulosidic acid			
	Geniposide	*Gardenia jasminoides* (Rubiaceae)	- interference with the production of IL-4, IL-17, IL-1, TGF-β1 - TNF-α, MMP-13 and NO inhibition	[87]

Camptosorus sibiricus Rupr. (Aspleniaceae) is indigenous to North China and is rich in flavonoids and iridoid glycosides like **camptoside** (Table **4**). The latter was found to exert significant anti-inflammatory activity, similar to curcumin, through the inhibition of NO production in RAW 264.7 cells *in vitro* [85].

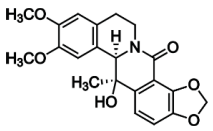
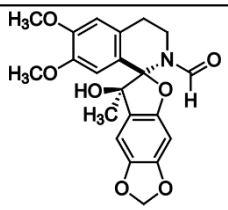
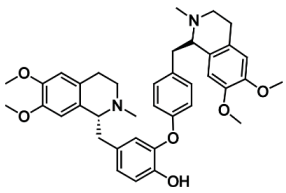
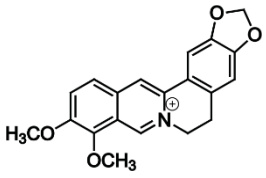
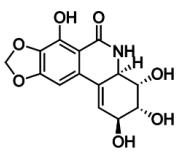
Hedyotis diffusa (Rubiaceae) herb is widely distributed in many Asian countries and is famous in the folk remedy of several inflammatory diseases like nephritis, bronchitis, and arthritis. Recent studies showed that it is rich in iridoids, among them, **asperuloside** and **asperulosidic acid** (Table **4**), which were found to reduce the levels of NO (*via* decreased expression of iNOS enzyme), PGE_2 (*via* decreased expression of COX-2 enzyme), IL-6, and TNF-α in the LPS-stimulated RAW 264.7 cells *in vitro*. On the molecular level, the compounds affected the NF-κB/ MAPK signaling pathway by suppressing the phosphorylation of IκB-α, p38, ERK, and JNK kinases [86].

Geniposide (Table **4**) is an iridoid glycoside isolated from the fruits of the medicinal herb *Gardenia jasminoides* (Rubiaceae), which is traditionally used for the treatment of rheumatism and neurodegenerative disorders due to its anti-inflammatory potential. In-depth biochemical studies showed that it is a potent p38-MAPK inhibitor since it interferes with the production of IL-4, IL-17, IL-1, TGF-β1 (transforming growth factor β1), TNF-α, MMP-13 (matrix metallo-proteinase-13), and NO in the chondrocytes isolated from osteoarthritic rabbit models *in vitro* [87].

Alkaloids

The neuroprotective activity of the Chinese herb, *Corydalis tomentella* (Papaveraceae) is attributed to its anti-inflammatory isoquinoline alkaloids viz. **(13*R*,14*R*)-13-hydroxy-13-methyl-8-oxosinactine** and **(13*S*,14*S*)-tomentelline E** (Table **5**). The neuroprotective effects exerted by **10** and **11** against the LPS-induced BV2 microglial cells were mediated by decreasing the levels of TNF-α, IL-6, and IL1β in cultured cells *in vitro* [88].

Table 5. List of previously reported alkaloids with anti-inflammatory activities.

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	(13*R*,14*R*)-13-Hydroxy-13-methyl-8-oxosinactine	*Corydalis tomentella* (Papaveraceae)	Reduction of TNF-α, IL-6, and IL1β levels	[88]
	(13*S*,14*S*)-Tomentelline E			
	Dauricine	*Menispermum* species (Menispermaceae)	- Suppression of TNF-α, IL-1β, IL-6 secretion - Interference with the activity of COX-2 and iNOS enzymes	[89]
	Berberine	*Berberis vulgaris* (Berberidaceae)	- Downregulation of IL-1β, IL-6, and TGF-β - Reduction of IL-17 and BAFF production	[90]
	Narciclasine	*Lycoris radiata* (Amaryllidaceae)	Inhibition of TNF-α, IL-1β, IL-6, COX-2, iNOS, and NF-κB	[91]

Dauricine (Table **5**) is an isoquinoline alkaloid isolated from *Menispermum* species (Menispermaceae) distributed in Asia and North America. Although the compound is famous for its strong cytotoxicity by inducing cell cycle arrest and apoptosis, recently group of scientists in the city of Wuhan discovered its significant anti-inflammatory effect in acute lung injury. The alkaloid works by inhibiting the inflammatory NF-κB cascade as well as suppressing the secretion of the proinflammatory cytokines TNF-α, IL-1β, IL-6, interfering with the activity of COX-2 and iNOS enzymes in a dose-dependent manner *in vitro* [89].

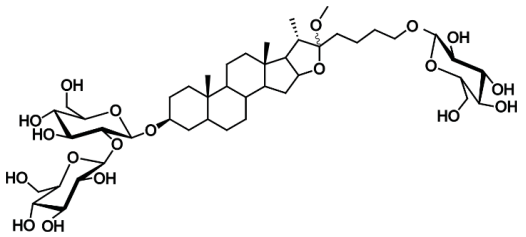
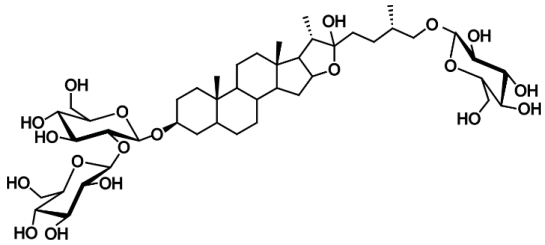
Berberine (Table **5**) is a benzylisoquinoline alkaloid present in many medicinal plants among them *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric), *Rhizoma coptidis* (huang lian), *Mahonia aquifolium* (Oregon grape), *Cortex phellodendri* (huang bai), *Hydrastis canadensis* (goldenseal), and *Phellodendron amurense* (Amur cork tree). Although it is known for its antimicrobial, anti-diabetic, and antitumor activity, recent *in-vitro* studies showed that it displays good anti-inflammatory effect. It is used in the treatment of chronic gastritis induced by *Helicobacter pylori* through the up-regulation of IL-10 and down-regulation of IL-1β, IL-6, and TGF-β in the gastric mucosa. Berberine decreases the production and the expression of IL-17 (up to 50%) and BAFF (B-cell activating factor cytokine which belongs to the TNF family), therefore attenuating Th-17 (T-helper 17 cell) response [90].

Lycoris radiata (Amaryllidaceae) is a Chinese herb commonly used in the folk medicine for the treatment of Alzheimer's disease. Recent studies by Shen *et al* [91] revealed that the plant has an anti-inflammatory activity which is attributed to its alkaloid **Narciclasine** (Table **5**). It inhibits the inflammatory cytokines TNF-α, IL-1β, IL-6, enzymes as COX-2, iNOS, and signaling pathways as NF-κB in human RAW 264.7 macrophages *in vitro*.

Saponins

The rhizome of *Anemarrhena asphodeloides* (Asparagaceae) is native to China, Japan, and Korea. It has traditionally been used in China for the treatment of fever, allergies, and Alzheimer's disease. Recent studies performed on LPS-induced RAW 264.7 cells revealed significant *in vitro* anti-inflammatory activity of the aqueous extract of *A. asphodeloides*, which is attributed to its steroidal saponins **timosaponin B** and **timosaponin B-II** (Table **6**). They inhibited the expression of the proinflammatory cytokines genes (as revealed by real-time PCR) like IL-6, IL-1β, TNF-α, COX-2, interfered with the secretions of NO and ROS, and inhibited the phosphorylation of p38 (class of MAPKs), JNK (c-Jun-N-terminal kinases), IκBα, and the p65 subunit of NF-κB, with timosaponin B-II being more potent than timosaponin B [92].

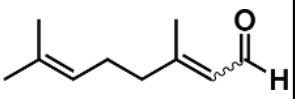
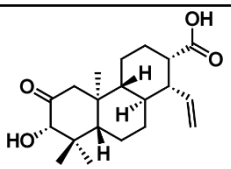
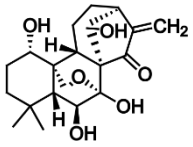
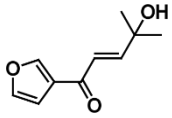
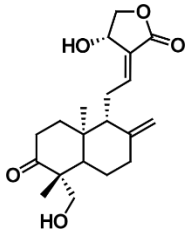
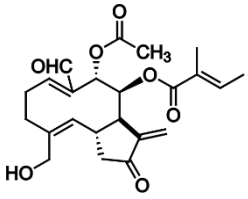
Table 6. List of previously reported saponins with anti-inflammatory activities.

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	Timosaponin B	*Anemarrhena asphodeloides* (Asparagaceae)	- Inhibition of IL-6, IL-1β, TNF-α, COX-2 production - Interference with NO and ROS formation	[92]
	Timosaponin B-II			

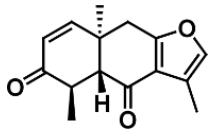
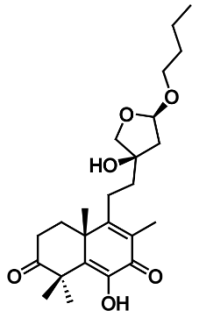
5. TERPENOIDS

Citral (Table **7**) is a common ingredient in *Cymbopogon citratus* (lemongrass) (Poaceae) and it is a tautomeric mixture of the *cis* and *trans* isomers. Phytochemical investigations by Gonçalves *et al* revealed the molecular mechanisms of the analgesic and anti-inflammatory effects of citral. Beside its anti-oxidant activity and its NF-κB and COX-2 inhibition, the compound blocks the transient receptor potential channels of the vanilloid type 1-3 (TRPV1-3) and of the melastatin type-8 (TRPM8) in a sustained form *in vitro*. It reduces paw edema and thermal allodynia induced by carrageenan, LPS, and zymosan upon oral treatment of mice with a dose of 50-300 mg/kg. The analgesic and immunomodulatory activity of citral is dependent on toll-like receptor-4 (TLR-4) (in LPS-induced inflammation) and TLR2/dectin-2 (in zymosan-induced inflammation) modulation [93].

Table 7. List of previously reported terpenoids with anti-inflammatory activities.

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	Citral	*Cymbopogon citratus* (Poaceae)	- Antioxidant activity - NF-κB and COX-2 inhibition - Blockade of TRPV1-3 and TRPM8	[93]
	Malloconspur B	*Mallotus conspurcatus* (Euphorbiaceae)	- Inhibition of prostaglandin E_2, NO - COX-2, TNF-α, and NF-κB/p65	[94]
	Oridonin	*Rabdosia rubescens* (Labiatae)	- Suppression of IL-6 and TNF-α - Inhibit the assembly of NLRP3	[95]
	9-hydroxyisoegomaketone	*Perilla frutescens* (Lamiaceae)	Suppression of nitric oxide, IL-6 and TNF-α production	[96]
	3-dehydroandrographolide	*Andrographis paniculata* (Acanthaceae)	- Attenuation of TNF-α and IL-6 release - Inhibition of NF-κB and protein kinase B	[97]
	Lecocarpinolide	*Sigesbeckiae Herba* (Asteraceae)	- Inhibition of NO, TNF-α, PGE_2, IL-6, MCP-1, and ROS release - Suppression of the expression of iNOS and COX-2	[98]

(Table 7) cont.....

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	Salviplenoid A	*Salvia plebeia* (Lamiaceae)	- Inhibition of proinflammatory mediators induced by the MAPK pathway - Inhibition of NF--, iNOS and COX-2	[99]
	leojaponin E	*Leonurus japonicus* (Lamiaceae)	Inhibition of PGE_2	[100]

Terpenoids like **malloconspur B** (Table **7**) obtained from the Chinese plant *Mallotus conspurcatus* (Euphorbiaceae) were found to exert an anti-inflammatory action through the *in vitro* inhibition of prostaglandin E_2, NO (through interference with iNOS; $IC_{50} = 10.4 \pm 0.3$ μM), COX-2, TNF-α, and NF-κB/p65 in RAW 264.7 macrophages. The cell viability was maintained up to 90% along its different concentrations (from 0 to 50 μM) [94].

Rabdosia rubescens (Labiatae) is an OTC herbal medicine commonly used in China for the treatment of several inflammatory disorders. One of its major constituents is the diterpene compound, **oridonin** (Table **7**). The latter inhibits the *in-vitro* activation of NF-κB and MAPK so the release of IL-6 and TNF-α are suppressed. It was also found to inhibit the assembly of NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome by covalently binding NLRP3 at cys-279, therefore preventing the activation of caspase-1 and decreasing the release of IL-1β [95].

Perilla frutescens (Labiatae) commonly known as the Korean perilla is an annual edible herb distributed in Southeast Asia including South China, Japan, Korea, and India. Hundreds of constituents belonging to different classes of phytochemicals (*i.e*. terpenes, flavonoids, phytosterols, fatty acids) have been isolated from its seeds, stems, and leaves. They contribute to its nutritional and medicinal uses as anti-inflammatory, antioxidant, and as an antidote for fish and crab allergy. Detailed phytochemical study of the *in vitro* anti-inflammatory effect

of its metabolites revealed the monoterpene, **9-hydroxyisoegomaketone** (Table **7**) to exhibit a remarkable suppressing effect on the production of nitric oxide (IC_{50} value of 6 μM) and the inflammatory cytokines IL-6 (IC_{50} value of 5.7 μM) and TNF-α (IC_{50} value of 20.5 μM) [96].

Andrographis paniculata (Acanthaceae) is a bitter herb commonly cultivated in South Asia especially in China, India, and Srilanka. The whole herb (in particular its leaves and roots) has long been used in the traditional Chinese medicine as a remedy for the constipation, sore throat, fever, and the respiratory disorders associated with common cold. One potent anti-inflammatory agent is 3-dehydroandrographolide (Table **7**), which attenuates the *in vitro* release of proinflammatory cytokines like TNF-α and IL-6. This is also supported by the inhibition of NF-κB (by preventing the nuclear translocation of its p65 subunit) and protein kinase B (through prevention of its phosphorylation at the Ser-473 position) in LPS-induced RAW 264.7 macrophages, which is closely related to the activation of the expression of α7 nicotinic acetylcholine receptors (α7nAchR) that showed a potential role in reducing the inflammatory signs in patients with stroke, Alzheimer, and myocardial infarction [97].

The Chinese medicine *Sigesbeckiae Herba* has long been used for the treatment of rheumatoid arthritis. Its anti-inflammatory activity is attributed to the sesquiterpene lactone, **lecocarpinolide** (Table **7**), which significantly inhibits the production of NO, TNF-α, PGE_2, IL-6, MCP-1, and ROS and suppresses the expression of the inflammatory enzymes iNOS and COX-2 in LPS-induced RAW264.7 *in vitro*. On the molecular basis, it interfered with NF-κB signaling pathway through blocking the activation of p65. Its antioxidant effect is mediated through increasing the expression of nuclear factor erythroid 2-related factor-2 (Nrf2) protein and heme oxygenase-1 (HO-1) enzyme. The *in vitro* investigations were carried out using ELISA, flow cytometric analysis, immunofluorescence microscopy, and Western blotting [98].

Salvia plebeia (Labiatae) is an annual herb growing in wide areas of Asia. It is used as a folk remedy for hepatitis, cough, and diarrhea in China. The anti-inflammatory effects of the ethanolic extract of the aerial parts of *S. plebeian* are pertained to a group of eudesmane-type sesquiterpenes, among them **salviplenoid A** (Table **7**), which significantly reduced the release of the proinflammatory cytokine TNF-α at an IC_{50} value of 8.0 μM. Moreover, it decreased the expressions of iNOS and COX-2 proteins, suppressed the activity of NF-κB (IC_{50} = 5.0 μM) through preventing its p50/p65 nuclear translocation and IκB phosphorylation, and inhibiting the proinflammatory mediators induced by the MAPK (mitogen-activated protein kinase) pathway by preventing the phosphorylation of Erk 1/2 (extracellular signal-regulated kinases 1/2) [99].

The Chinese motherwort *Leonurus japonicus* (Labiatae) is distributed in many Asian countries and it has traditionally been used for improving blood circulation and treatment of edema. The latter activity was attributed to the existence of diterpenoids of the labdane type viz. **leojaponin E** (Table **7**), which inhibit the *in vitro* production of prostaglandin E_2 in LPS-induced RAW 264.7 cells [100].

Polysaccharides

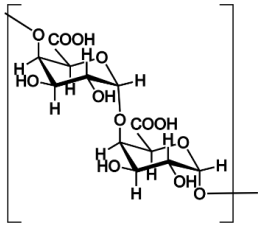
Wang *et al.* reported in 2018 the isolation of the anti-diabetic polysaccharide macromolecule **GPP** (molecular weight of 4.070×10^4 Da) from *Gynostemma pentaphyllum* (Cucurbitaceae) herb. It consists of rhamnose, arabinose, galactose, glucose, xylose, mannose, galacturonic acid, and glucuronic acid subunits [101]. One year later, they reported on the anti-inflammatory activity of GPP, which was due to its antioxidant and its radical scavenging activity. *In-vitro* tests showed that the compound reduced the levels of TNF-α and IL-6 while increasing the levels of IL-4 and IL-10 [102].

Zizyphus jujube (Rhamnaceae) is commonly known as the Chinese date or the jujube. Its fruits have numerous culinary and medicinal applications in the traditional Chinese medicine. The plant is rich in polysaccharides among them **ZPJ** (Table **8**), which is a peptide polysaccharide composed of glucuronic acid units linked at 1,4-position. ZPJ suppresses the production of IL-17 (at dose of 50 µg/ml), NO (in a dose-dependent manner up to 300 µg/ml), TNF-α (at dose of 50 µg/ml), IFN-γ (at dose of 100 µg/ml), and COX-2. On the molecular level, it inhibits MAPK signaling pathway through the preventing the phosphorylation of p38 and JNK [103].

Table 8. Reported polysaccharides with anti-inflammatory activities.

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
Rhamnose-Arabinose-Galactose-Glucose-Xylose-Mannose-Galacturonic acid-Glucuronic acid (in the ratio of 4.11: 7.34: 13.31: 20.99: 1.07: 0.91: 4.75: 0.36)	GPP	*Gynostemma pentaphyllum* (Cucurbitaceae)	- Antioxidant - Improve the anti-inflammatory cytokines IL-4 and IL-10 - Reducing the levels of TNF-α and IL-6	[102]

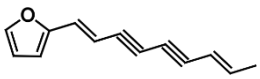
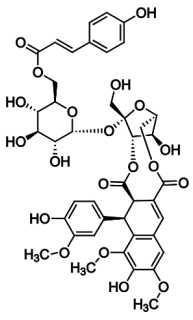
(Table 8) cont.....

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	peptide polysaccharide ZPJ	*Zizyphus jujube* (Rhamnaceae)	Suppression of IL-17, NO, TNF-α, IFN-γ, and COX-2 production	[103]

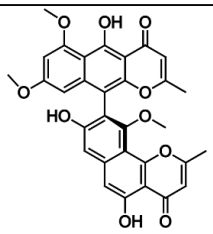
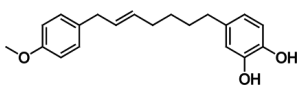
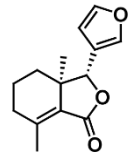
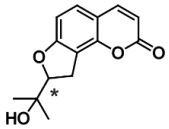
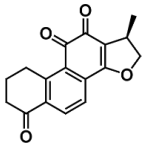
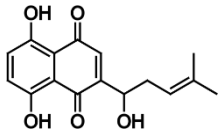
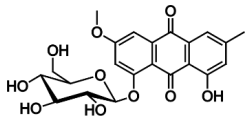
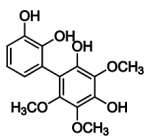
7. MISCELLANEOUS COMPOUNDS BELONGING TO OTHER PHYTOCHEMICAL CLASSES

Atractylodes chinensis Koidzumi (Asteraceae) is one of two *Atractylodes* species (the other is *A. lancea* De Candolle) present in the Japanese crude drug, *Sojutsu*. The rhizomes of *Atractylodes* species have been reported to possess anti-inflammatory effects due to the inhibition of iNOS activity, NO, and prostaglandin E_2 production. **Atractylodin** (Table **9**) isolated from the ethyl acetate fraction of the rhizomes of *A. chinensis* was the most potent constituent, which significantly decreased the expression of iNOS in the IL-1β-treated rat hepatocytes *in vivo* [104].

Table 9. List of miscellaneous natural products with anti-inflammatory activities.

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	Atractylodin	*Atractylodes chinensis* (Asteraceae)	- Inhibition of NO and PGE_2 production - Reduction of iNOS expression	[104]
	3f 3a:6f 2a-[(3*R*, 4*R*)- 4',6-dihydroxy-3', 5,7-trimethox--4,10-cycloligna-1-en-2a,3adicarbonyl]-6g-(*p*-courmaroyl) sucrose	*Corispermum mongolicum* (Amaranthaceae)	Suppression of NO, L-6 and TNF-α production	[105]

(Table 9) cont.....

Compound (Structure / Name)		Isolated from	Mechanism	Refs.
	(*S*)-Asperpyrone A	*Chaetomium nigricolor* (Chaetomiaceae)	- Inhibition of NO production - Suppression of NF-κB and JNK activation	[106]
	1-(4”-Methoxyphenyl)-7-(3',4'-di-hydroxyphenyl)-(*E*)-hept-2-ene	*Pleuranthodium racemigerum* (Zingiberaceae)	Suppression of NO and TNF-α production	[107]
	Fraxinellone	*Dictamnus dasycarpus* (Rutaceae)	- Inhibition of NO production - Reduction of IL-6, TNF-α, iNOS, COX-2, and NF-κB expression	[108]
	Columbianetin	*Angelicae pubescentis* (Apiaceae)	Reduction of TNF-α, IL-6, IL-1β, MCP-1	[109]
	Dihydronortanshinone	*Salvia miltiorrhiza* (Lamiaceae)	Suppression of NO, TNF-α, IL-6, ROS	[110]
	Shikonin	*Lithospermum erythrorhizon* (Boraginaceae)	- Reduction of TNF-α, IL-1β and IL-6 - Interference with NF-κB signaling cascade	[111]
	Physcion 8-*O*-*β*-glucopyranoside	*Polygonum cuspidatum* (Polygonaceae)	Suppression of TNF-α, IL-1β, IL-6, IL-8, IL-12, and IL-17A expression	[112]
	3',5',6'-Trimethoxy[1,1'-biphenyl]-2,2',3,4'-tetraol	*Crataegus dahurica* (Rosaceae)	Inhibition of NO release	[113]

The Aryldihydronaphthalene-type lignan, **3f 3a:6f 2a-[(3*R*, 4*R*)- 4',6-dihydrox--3',5,7-trimethoxy-4,10-cycloligna-1-en-2a,3a dicarbonyl]-6g-(*p*-courmaroyl) sucrose** (Table **9**) isolated from the ethanol extract of the Chinese plant *Corispermum mongolicum* (Amaranthaceae) displayed significant *in vitro* anti-inflammatory activity by the suppression of nitric oxide production and other proinflammatory mediators as IL-6 and TNF-α in LPS-stimulated RAW 264.7 cells without affecting the cell viability even at concentration of 100 μM. Significant inhibition of NO and TNF-α was observed at concentrations of 10, 30, and 100 μM in a dose-dependent manner [105].

From the potato dextrose broth of *Chaetomium nigricolor* (Chaetomiaceae) fungal extract, a quinoid metabolite, **(*S*)-asperpyrone A** (Table **9**) was isolated. The compound inhibited NO production in LPS-induced RAW 264.7 macrophages *in vitro* by suppressing the activation of NF-κB and JNK (c-Jun-N-terminal kinases) [106]

Family Zingiberaceae is famous for its anti-inflammatory perennial herbs like *Curcuma longa* and *Ginger officinalis*. Raju *et al.* investigated the anti-inflammatory potential of the rhizomes of *Pleuranthodium racemigerum* growing in Australia. The results showed that the extract is rich in diarylheptanoids, as in **1-(4"-Methoxyphenyl)-7-(3',4'-di-hydroxyphenyl)-(*E*)-hept-2-ene** (Table **9**), which significantly decreased NO (IC_{50} = 25 ± 2 μM) and TNF-α (IC_{50} = 16 ± 9 μM) production in RAW 264.7 macrophages and N-11 microglial cells *in vitro* in comparison to curcumin having IC_{50} values of 12.3 ± 1.1 μM (for NO) and 11.2 ± 2.2 μM (for TNF-α) [107].

Cortex dictamni (*Dictamnus dasycarpu)* is a perennial herb which belongs to family Rutaceae. The latter - together with family Meliaceae - are rich sources of oxygenated tetranorterpenoids known as limonoids. The root bark of *C. dictamni* has been used to treat rheumatic pain and other inflammatory diseases. **Fraxinellone** (Table **9**) is one member of the limonoid family present in *C. dictamni* showing anti-inflammatory effects. The compound, among others, inhibited NO (nitrile relative concentration = 56.5 ± 3.5% expressed as a percentage of the control group with LPS) production in LPS-treated RAW 264.7 cells and reduced the expression levels of IL-6, TNF-α, iNOS, COX-2, and NF-κB *in vitro* [108].

Columbianetin (Table **9**) is a furanocoumarin and one of the major constituents of the Chinese medicinal plant *Angelicae pubescentis* (Apiaceae). It has been used since long as a prescription remedy for arthritis and asthma in China. *In-vitro* studies showed that the compound reduced the levels of TNF-α, IL-6, IL-1β,

MCP-1 in a dose-dependent manner and downregulated the NOD-1 (nucleotide-binding and oligomerization domain-1) / NF-κB pathway [109].

Dihydronortanshinone (Table **9**) is a diketone natural product isolated from *Salvia miltiorrhiza* Bunge (Labiatae), which is commonly used in China and Japan for the treatment of cardiovascular and circulatory problems. The compound has a strong potential to suppress the inflammatory responses by reducing the levels of iNOS (hence NO), TNF-α, IL-6, ROS (reactive oxygen species) in murine macrophage model *in vitro*. The compound suppressed NF-κB/p65 translocation and inhibited MAPK/p38 and JNK-1/2 activation induced by LPS [110].

The gromwell (Boraginaceae) is a Chinese herb used to alleviate several inflammatory disorders. In a recent study by Wang *et al.*, they described the main bioactive metabolite of *Lithospermum erythrorhizon* as **shikonin** (Table **9**), which is a naphthoquinone with significant anti-inflammatory potential as demonstrated from its ability to reduce the proinflammatory cytokines TNF-α and IL-1β and 6 *in vitro*. It decreases the migration of neutrophils to the mammary glands in the LPS-induced mastitis mice *in vivo* and mechanistically, it interferes with the NF-κB signaling cascade [111].

Physcion 8-*O*-β-glucopyranoside (POGD) (Table **9**) is an anti-proliferative anthraquinone glycoside isolated from the roots of *Polygonum cuspidatum* (Polygonaceae). Its anti-inflammatory activity was evaluated using *in vivo* type II collagen-induced arthritis rat model. POGD reduced the levels of the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IL-8, IL-12, and IL-17A causing marked reduction in the mRNA expression levels of VEGF (vascular endothelial growth factor), MMP-9 (matrix metalloproteinase-9), MMP-3, MMP-2, and COX-2 through the inhibition of NF-κB, MAPK, and TGF-β (transforming growth factor-β) signaling pathways [112].

Crataegus is a large genus belonging to family Rosaceae. It is a rich source of phytochemicals including mono, sesqui, and triterpenoids as well as flavonoids and phenylpropanoids. Recently, it has been reported that the petroleum ether fraction of *C. dahurica* fruits showed anti-inflammatory activity, which was attributed to its biphenyl constituents. The most active of them is **3',5',6'-trimethoxy[1,1'-biphenyl]-2,2',3,4'-tetraol** (Table **9**), which inhibited nitric oxide production in RAW264.7 cells *in vitro* without showing cytotoxicity. It was isolated from the petroleum ether fraction having an IC_{50} value of 46.1 μM, which was even stronger than indomethacin (IC_{50} 53.2 μM), which was the positive control in this study [113].

CONCLUDING REMARKS

Inflammation is a pathological condition involved in several disorders like cancer, Alzheimer's, autoimmune diseases (rheumatoid and multiple sclerosis), ulcers, pneumonia, gall bladder infections, diabetes, cardiovascular diseases, and eczema. Natural products play a key role in combating inflammation due to the presence of a diverse pool of anti-inflammatory secondary metabolites, including flavonoids, iridoids, glycosides, phenolic acids, polysaccharides, quinones, and alkaloids. These compounds act by decreasing the formation of pro-inflammatory cytokines like interleukins (1β, 2, 4, 5, 6, 12, 17), TNF-α, CRP, IFN-γ, prostaglandins (PGE_2), thromboxanes (TXB_2), leukotrienes (LTB_4), NO, GM-CSF and by increasing the release of anti-inflammatory cytokines as IL-10, Arg-1, TGF-β, MRC-1. Some of these secondary metabolites suppress the inflammatory proteins like fetuin-1, resistin, lipocalin-2, RBP-4, ICAM-1 and reduce the levels of inflammatory enzymes as COX-2, LOX, iNOS, HO-1, MMP, NOX-2/4. The majority of these compounds exhibit antioxidant activity by scavenging and reducing the concentration of free radicals as peroxides and superoxides. Moreover, they significantly decrease edema, vascular permeability, leukocytes migration, neutrophils infiltration, and vasoactive amines. On the molecular level, several inflammatory signalling pathways were the common target of these natural products, including NF-κB, MAPKs, JAK/STAT, WNT/β-catenin, and PI_3K/AkT.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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Declared none.

GLOSSARY

Akt	Protein kinase B
PAF	Platelet activation factor
Arg-1	Arginase
COX	Cyclooxygenase
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
DSS	Dextran sulphate sodium
Iba-1	Ionized calcium-binding adapter molecule

NO	Nitric oxide
p65	Transcription factor p65
ICAM-1	Intercellular adhesion molecule-1
PAI-1	Plasminogen activator inhibitor-1
IFN-γ	γ-interferon
PGE2	prostaglandin E2
IL	Interleukin
PI3K	Phosphatidylinositol 3-kinase
IκB	Inhibitor of κB
RBP-4	Retinol binding protein-4
iNOS	Inducible nitric oxide synthase
ROS	Reactive oxygen species
JAK-STAT	Janus kinases-signal transducer and activator of transcription
TGF-β	Transforming growth factor beta
TNF	tumor necrosis factor
LOX	Lipoxygenase
TXB2	Thromboxane B2
LPS	Lipopolysaccharide
UPLC-MS	Ultraperformance liquid chromatography-mass
VEGF	Vascular endothelial growth factor
LTB4	Leukotriene B4
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein -1
MMP	Matrix metallopeptidases
mRNA	messanger Ribonucleic acid

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CHAPTER 7

Phenolic Compounds and their Biological and Pharmaceutical Activities

Ajay Kumar[1,2], Feroz Khan[1,*] and **Dharmendra Saikia[1,*]**

[1] *CSIR-Central Institute of Medicinal & Aromatic Plants, P.O.- CIMAP, Kukrail Picnic Spot Road, Lucknow 226015 U.P., India*

[2] *Government Pharmacy College, BRD Medical College Campus, Gorakhpur-273013, U.P., India*

Abstract: Phenolic compounds play an essential role in plants and foods. These compounds are well known for their biological and pharmaceutical activities. These compounds act as colorants and antioxidants. Research on phenolic compounds is mainly focused on their antioxidant properties. These compounds showed significant effects on chronic degenerative diseases, such as central neurodegenerative disorders, cataracts, macular degeneration (age-related), diabetes mellitus, cardiovascular complication, and cancer. These compounds also showed implications on human health since increased exposure to free radicals might lead to an increased risk of degenerative diseases. Fruits and vegetables are rich in phenolic compounds. The phenolic compound consists of one (phenolic acids) or more polyphenols aromatic structures attached to a hydroxyl group. The phenolic compound is found in combination with mono or polysaccharides, and they can occur in the group as an ester or methyl ester. Their biological and pharmaceutical activities are based on their phenolic ring and a hydroxyl group. Apart from antioxidant activity, they have many other therapeutic effects on human health. Among the several classes of phenolic compounds, flavonoids, tannins, and phenolic acids are considered as main dietary phenolic compounds. In this chapter, we have summarized the biological and pharmaceutical activities related to different classes of phenolic compounds.

Keywords: Antioxidant activity, Biological activity, Cardio-protective, Flavonoids, Oxidative stress, Pharmaceutical activity, Polyphenols.

INTRODUCTION

Phenolic compounds are very common and widespread groups of plant secondary metabolites. The “phenolic” or “polyphenol” substances possess one aromatic ring, and one hydroxyl (phenol), or multiple hydroxyls (polyphenol), which

* **Corresponding authors Feroz Khan and Dharmendra Saikia:** CSIR-Central Institute of Medicinal & Aromatic Plants, P.O.- CIMAP, Kukrail Picnic Spot Road, Lucknow –226015 (U.P.), India; E-mail: f.khan@cimap.res.in, d.saikia@cimap.res.in

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

includes functional groups (esters, glycosides, methyl ethers) that are biogenetically derived from shikimate phenylpropanoids- flavonoids pathways [1, 2]. Various classes of phenols have been classified on the presence of their basic skeleton: C6 (simple phenol, benzoquinones), C6-C1 (phenolic acids like gallic acid, ellagic acid, protocatechuic acid, syringic acid, vanillic acid, hydroxybenzoates and p-hydroxybenzoic acid), C6-C2 (phenylacetic acid and acetophenone), C6-C3 (aesculatin, caffeic acid, coumaric acid, ferulic acid, hydroxycinnamic acid derivatives, chlorogenic acid, curcumin, phenylpropanes, chromones, umbelliferone), C6-C4 (napthoquinones), C6-C1-C6 (xanthones), C6-C2-C6 (stilbenes, resveratrol, anthroquinones), C6-C3-C6 (flavonoids, isoflavonoids, isoflavones, flavanones, anthocyanidins, apigenin, (+)-catechin, (---epicatechin, cyanidin, daidzein, delphinidin, erodictoyl, Isorhamnetin, genistin, glycitien, hesperetin, kaempferol, luteolin, malvidin, myricetin, narengenin, pelargonidin, petunidin, peounidin, quercetin), $(C6\text{-}C3)_2$ (lignans, neolignans, lariciresinol, matairesinol, medioresinol, pinoresinol, secoisolariciresinol), $(C6\text{-}C3\text{-}C6)_2$ (bioflavonoids), $(C6)_n$ (catechol, melanins), $(C6\text{-}C3\text{-}C6)_n$ (condensed tannins, catechin polymers, epicatechin polemers, hydrolysable tannins, casuarictin, punicalagin, gallotannins) [2 - 4]. Polyphenols are further divided into two main groups; one is a flavonoid, and the other is a non-flavonoid [5]. Flavonoids are the most studied and largest group amongst plant phenols. Anthocyanidins, flavones, isoflavones, flavanones, flavonols, dihydroflavonols, flavan-3-ols, proanthocyanidins, and chalcones are all members of the flavonoid group, which includes compounds with the C6-C3-C6 structure. The non-flavonoid group includes simple phenols, acetophenones, hydrolyzable tannins, benzophenones, benzoic aldehydes, coumarins, stilbenes, lignans, xanthones, secoiridids, and phenolic acids, such as gallic acid. Because of their potential free radical scavenging activity [6], anti-inflammatory activity [7], and capacity to lower oxidative stress, polyphenols can be an important part of the human diet, preventing neurodegenerative disorders [8], cancer [9], and other diseases. In plants, they are responsible for the development of resistance to pathogens, growth, pigmentation, and reproduction. Polyphenols also show a protectant nature against bacterial and viral pathogens. They form main classes of secondary metabolites, and almost 8150 flavonoids have been identified, having different structures, such as monomeric, dimeric, and polymeric [10, 11]. They are abundantly present in leaves or bark together with other metabolites. As far as the activity is concerned, almost all the flavonoids possess strong antioxidant activity, and these are commonly present in vegetables and fruits. Therefore, plant containing polyphenols are rich source of compounds having beneficial effect on health and are indicated in chronic diseases related to oxidative stress [2]. After ingestion, these are either absorbed through intestine (small percentage up-to 5- 10 %) or found unchanged in the colon. After absorption, polyphenols exert

biological action or works as a prodrug. These compounds are metabolized through phase I (oxidation, reduction, or hydrolysis) or phase II reaction (conjugated reaction) to form the water-soluble metabolite and excreted through the urine [12].

Food Sources of Polyphenols

Phenolic compounds are abundantly present in plants (whole grains, legumes, fruits, and vegetables, coffee and tea beverages). In fruits, they are mainly found in apples, berries, cherries, citrus fruits, grapes, peaches, *etc*. The most common polyphenols are phenolic acids (benzoic acids, gallic acid, cinnamic acid, sinapic acid, vanillic acid, and ferulic acid, *etc*.), flavonoids, coumarins, tannins, lignans, stilbenes, and proanthocyanidins [13].

Biological and Pharmaceutical Activities of Polyphenols

Plant polyphenols received scientific attention due to their beneficial effect on human health. As per the literature reviewed, plant phenolic compounds bear strong antioxidant activity. These compounds are used in the treatment of several diseases such as cancer and other oxidative stress related human diseases. Multiple studies supported that oxidative stress plays a vital role in the occurrence of neurodegeneration, cancer, cardiovascular complication, muscular degeneration, antibacterial effect, immune system promoting effect, anti-inflammatory effect, UV radiation protective effect, *etc*. The reactive oxygen species include superoxide radical, nitric oxide radical, peroxynitrite anion, hydroxyl-peroxyl, peroxyl, alkoxyl, and hydroxyl free radicals. These oxidative species cause damage to vital biomolecules such as lipids, DNA, and proteins. Polyphenols are divided into different classes such as flavonoids, stilbenes, coumarins, lignans, tannins, curcuminoids, phenolic acid, *etc*. Flavonoid is the largest class and is further subdivided into flavones, isoflavones, flavonols, flavanones, flavanonols, flavanols, anthocyanidins, and anthocyanins. Table **1** enlisted the types of polyphenols, and Table **2** enlisted the detailed biological and pharmaceutical activities of individual polyphenolic compounds. Flavonoids have a 15-carbon skeleton structure with two phenyl rings and a heterocyclic ring. Brief details of flavonoids are as follows:

• **Anthocyanidins:** They are commonly present in fruits, flowers, leaves, and tubers. The main sources are red, purple, and blue berries, pomegranates, plums, red wine, red and purple grapes. These are plant pigments. Change in pH may lead to a change in its colour, such as red, purple, black, blue, *etc*. These compounds have flavylium and oxonium ions. These compounds showed benefits to heart health, antioxidant, anti-obesity, and anti-diabetic effects. Example- Cyanidin, Delphinidin, Pelargonidin, *etc*.

• **Flavones:** They are commonly present in spices, fruits, and vegetables, *e.g*., celery, various herbs, hot peppers, and parsley. Studies showed protective effects in cardiovascular complications and neurological disorders. *In vitro* and *in vivo* studies confirmed the neuroprotective effect and antioxidant benefits. These compounds delay drug metabolism. Example- Apigenin, Luteolin, Tangeritin, Chrysin, *etc*.

• **Flavonols:** They are commonly present in fruits and vegetables, *e.g*., onions, leeks, brussels sprouts, broccoli, tea, berries, beans, apples, *etc*. These compounds have a 3-hydroxy flavone backbone. These compounds have antioxidant, antihistamine property and also help in the treatment of inflammatory bowel disease. Example- 3-Hydroxyflavone, Azaleatin, Fisetin, Galangin, Gossypetin, Kaempferide, Kaempferol, Myricetin, Quercetin *etc*.

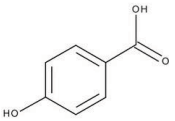
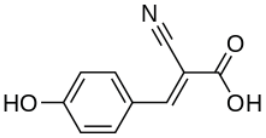
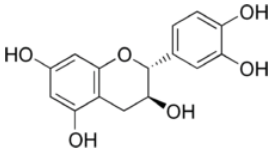
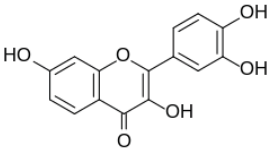
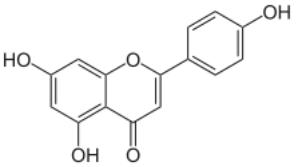
• **Flavan-3-ols (or Flavanols):** They are commonly present in teas, cocoa, grapes, apples, berries, fava beans, and red wine. These compounds are derived from flavans. Structurally, these compounds have a 2-phenyl-3,4-dihydro-2H-chomen-3-ol skeleton. These compounds have anti-mutagenic, anti-diabetic, hypolipidemic, and anti-thrombogenic properties. Example- proanthocyanidins, thearubigins, catechin, theaflavins, epicatechin gallate, epigallocatechin gallate, epigallocatechin, *etc*.

• **Flavanones:** They are commonly present in citrus fruits. These are derived from flavone. These compounds are aromatic and colourless ketones. These compounds have a positive effect on cardiovascular problems, antioxidant and anti-inflammatory activity. Example- Naringenin, Hesperetin, Homoeriodictyol, Eriodictyol, *etc*.

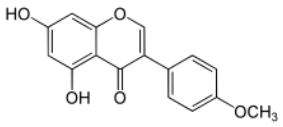
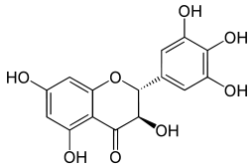
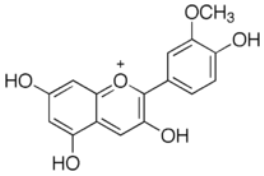
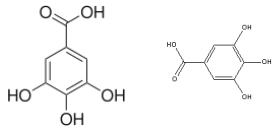
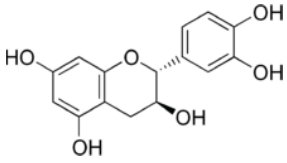
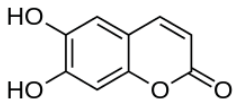
• **Flavanonols:** They are commonly present in plants. These compounds have 3-hydroxy-2,3-dihydro-2-phenylchromen-4-one backbone. Example- Aromadedrin (Dihydrokaempferol), Taxifolin (Dihydroquercetin) *etc*.

• **Isoflavones:** They are commonly present in soybeans and legumes (Fabaceae or Leguminosae family plants). These are derived from isoflavone and act as phytoestrogens. These are bioactive nonsteroidal polyphenolic metabolites with antioxidant properties and showed an estrogenic effect. It showed oxidants as well as antioxidants effects. Thus, the effect on cancer (breast, endometrial, prostate cancer) is still doubtful and a subject of further research work. Example- Genistein, Daidzein, Glycitein, *etc*.

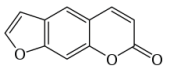
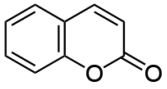
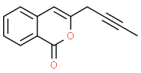
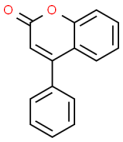
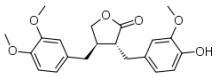
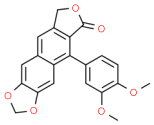
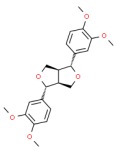
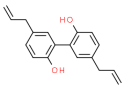
Table 1. Categories of phenolic compounds and representative chemical structures.

Chemical Class	Categories	Chemical Sub-Type	Compounds	Chemical Structure
Phenolic Compounds	Phenolic acids	Hydroxybenzoic acid	4-hydroxybenzoic acid, gallic acid, gentisic acid, salicylic acid, syringic acid, vanillic acid, β- resorcylic acid, protocatechuic acid	 4-hydroxybenzoic acid CAS Number: 99-96-7
		Hydroxycinnamic acid	α-Cyano-4-hydroxycinnamic acid, chlorogenic acid, caffeic acid, cichoric acid, ferulic acid, isoferulic acid, sinapic acid, trans-cinnamic acid, p-coumaric acid	 α-Cyano-4-hydroxycinnamic acid CAS Number: 28166-41-8
	Flavonoids	Flavan-3-ols (flavanols)	(+)-catechin, (-)-gallocatechin, (-)-gallocatechin gallate, (-)-epigallocatechin, (-)-epigallocatechin gallate, (-)-epicatechin gallate, (-)-epicatechin	 Catechin CAS Number: 7295-85-4
		Flavonols	Fisetin, flavonol, galangin, datiscetin, hyperoside, Kaempferol, morin, myricetin, quercitin, isorhamnetin, robinetin, rutin, quercetagetin	 Fisetin CAS Number: 528-48-3
		Flavones	Apigenin, aposide, baicalein, baicalin, chrysin, chrysoeriol, diosmetin, luteolin, vitexin, sinensetin	 Apigenin CAS Number: 520-36-5

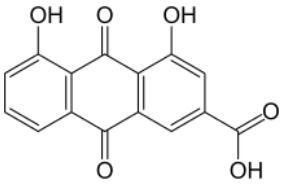
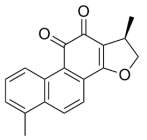
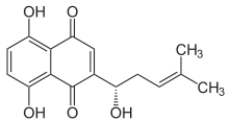
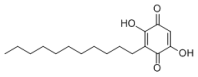
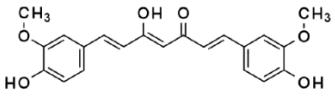
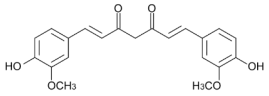
(Table 1) cont.....

Chemical class	Categories	Chemical sub-type	Compounds	Chemical structure
Phenolic Compounds	Flavonoids	Isoflavones	Biochanin A, daidzein, genistein, genistin, glycetin, glycitein, puerarin	 Biochanin A CAS Number: 491-80-5
		Flavanones	Dihydromyricetin, eriodictyol, hesperetin, hesperidin, liquiritin, liquiritigenin, naringin, naringenin, narirutin, (+)-taxifolin	 Dihydromyricetin CAS Number: 27200-12-0
		Anthocyanidins	Peonidin, malvidin, delphinidin, petunidin, cyanidin, pelargonidin, propelargonidin	 Peonidin CAS Number: 134-01-0
	Tannins	Hydrolyzable tannins	Gallotannins [**Aglycones:** Digallic acid, Gallic acid; **Galloyl glucoses:** Glucogallin, 1,6-Digalloyl glucose, 1,2,3-Trigalloyl glucose, 1,2,3,6-tetragalloylglucose, 1,2,3,4,6-Pentagalloyl-glucose, Hexagalloyl glucose; **Galloyl quinic acids:** theogallin, 1,4-Di-O-galloylquinic acid, 1,3,4-Tri-O-galloylquinic acid; **Galloyl shikimic acids:** 4-O-Galloyl shikimic acid; **Others:** 1,2,6-trigalloyl alloside], ellagitannins	 Gallic acid CAS Number: 149-91-7; 5995-86-8
		Condensed tannins	Proanthocyanidin, leucoanthocyanidin	 Catechin CAS Number: 7295-85-4
	Coumarins	Simple coumarins	7-hydroxycoumarin (Umbelliferone), 6,7-dihydroxy coumarin (Aesculetin), 7-methoxycoumarin (Herniarin)	 Aesculetin CAS Number: 305-01-1

(Table 1) cont.....

Chemical class	Categories	Chemical sub-type	Compounds	Chemical structure
Phenolic Compounds	Coumarins	Furanocoumarins	Psoralen, bergapten, imperatorin	 Psoralen CAS Number: 66-97-7
		Pyranocoumarins	Khellactones, calanolides	 CAS Number: 91-64-5
		Isocoumarins	Capillarin, artemidin	 Capillarin CAS Number: 3570-28-3
		Neoflavones	4-Phenylcoumarin	 4-Phenylcoumarin CHEBI:71972
	Lignans	Lignanolides	Arctigenin kaerophyllin	 Arctigenin CAS Number: 7770-78-7
		Cyclolignanolides	Chinensin	 Chinensin ChemSpider ID: 4475036
		Bisepoxylignans	Eudesmin, isoeudesmin	 Eudesmin CAS Number: 29106-36-3
		Neolignans	Magnolol, Burseneolignan	 Magnolol CAS Number: 528-43-8

(Table 1) cont.....

Chemical class	Categories	Chemical sub-type	Compounds	Chemical structure
Phenolic Compounds	Quinones	Anthraquinones	Rhein (cassic acid), dantron, emodin, aloe emodin, alizarin, munjistin, parietin (physcion)	 Rhein CAS Number: 478-43-3
		Phenanthraquinones	Tanshinone: dihydrotanshinone, tanshinone I, or tanshinone IIA; denbinobin	 Dihydrotanshinone CAS Number: 87205-99-0
		Napthoquinones	Alkannin, shikonin (enantiomer of alkannin), shikalkin (racemic mixture)	 Alkannin CAS Number: 517-88-4
		Benzoquinones	Embelin, embelinol	 Embelin CAS Number: 550-24-3
	Curcuminoids		Curcumin, demethoxycurcumin, bis-demethoxycurcumin, ginerol	 Curcumin (Enol form)  Curcumin (Keto form) CAS Number: 458-37-7

(Table 1) cont.....

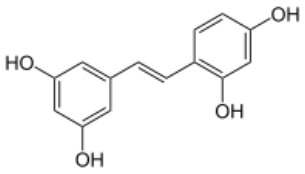
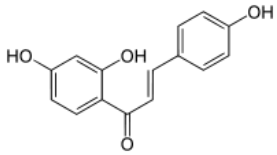
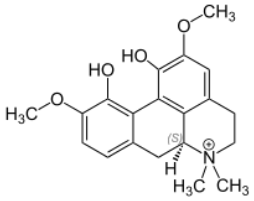
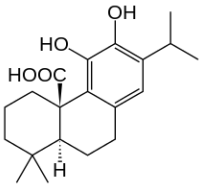
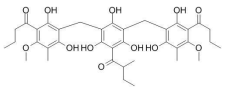
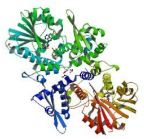
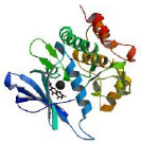
Chemical class	Categories	Chemical sub-type	Compounds	Chemical structure
Phenolic Compounds	Stilbenes		Oxyresveratrol, Isorhapontigenin, piceid, piceatannol, pinostilbene, pterostilbene, resveratrol	 Oxyresveratrol CAS Number: 29700-22-9
	Others	Chalcone derivatives	Isoliquiritigenin (phenolic compound of licorice), butein, phloretin	 Isoliquiritigenin CAS Number: 961-29-5
		Phenolic alkaloids	Demethylsalsoline, magnoflorine (benzylisoquinoline alkaloid), oleracein A, oleracein B, oleracein E	 Magnoflorine CAS Number: 2141-09-5
		Phenolic terpenoids	Carnosic acid (a benzenediol abietane diterpene found in rosemary & common sage), carnosol, thymol	 Carnosic acid CAS Number: 3650-09-7
		m-benzo-triphenol derivatives	Agrimol A, Agrimol B, filicic acids	 Agrimol B CAS Number: 55576-66-4

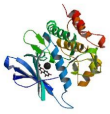
Table 2. Food sources, biological and pharmaceutical activities of some phenolic compounds.

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Gallic acid, Ellagic acid, p Ellagic acid acid, Protocatechuic acid, Hydroxybenzoates, Syringic acids, Vanillic acid	blueberry, blackberry, cashew nut, grapes, hazelnut, mango, plums, strawberry, tea, walnut, wine [14, 15]	Anti-inflammatory [16], Cardio-protective effect [17 - 19], Hepatoprotective [20], Anti-neoplastic activity [21], Metabolic disease [22], urogenital disease [23], dermal disease [24], respiratory disease [25], oral health [26]	Example- Gallic acid: Enzyme (Lyase, Oxidoreductase, Hydrolase, Protease, Transferase, Kinase, Cytochrome P450, Phosphodiesterase), Transcription factor, unclassified proteins, epigenetic regulator, adhesion, transporter, membrane receptor, other cytosolic proteins, other nuclear proteins	Example- Gallic acid: Alpha-(1,3)-fucosyltransferase 7, Fucosyltransferase 4, UDP-glucuronosyltransferase 1-1, Carbonic anhydrase (I, II, III, IV, VI, VII, IX, XII, XIV, VA, VB), LDL-associated phospholipase A2, Aldose reductase, Angiotensin-converting enzyme, Glyceraldehyde-3-phosphate dehydrogenase liver, ADAM17, Cytochrome P450 19A1, Dipeptidyl peptidase IV, Hepatocyte growth factor receptor, Cyclooxygenase-2, DNA polymerase kappa, Thrombin, Endoplasmic reticulum-associated amyloid beta-peptide-binding protein, Glutaminase kidney isoform, mitochondrial, MAP kinase ERK2, 15-hydroxyprostaglandin dehydrogenase [NAD+], Isocitrate dehydrogenase [NADP] cytoplasmic, DNA-(apurinic or apyrimidinic site) lyase, Aldehyde dehydrogenase 1A1, Tyrosyl-DNA phosphodiesterase 1	Example- Gallic acid: Human immunodeficiency virus type 1 protease, Human immunodeficiency virus type 1 reverse transcriptase, Influenza A virus Neuraminidase	Example- Gallic acid: Anthrax lethal factor (Bacillus anthracis), 4'-phosphopantetheinyl transferase fŤp (Bacillus subtilis)	Example- Gallic acid: 4Z5X, 3WRB, 3WR9, 3WR4, 3WR3, 3WPM, 3WKU, 4IC0, **4J0H**  Tannin acyl hydrolase in complex with gallic acid (PDB: 4J0H)
Caffeic acid, Chlorogenic acid, p-Coumaric acid, Curcumin, Ferulic acids, Hydroxycinammates, Hydroxycinnamic derivatives	Apples, apricots, Blueberry, carrots, cereals, citrus fruit, cherry, coffee beans, grape, kiwis, oil seeds, orange, peaches, plum, potato, spinach, sweet pear, spices, tomato, wheat bran [27 - 29]	**Caffeic acid** (Anti-carcinogenic activity [30], Anti-inflammatory [31], Anti-oxidant activity [32], cosmetic use [33]); **Chlorogenic acid** (Antidiabetic and antiobesity activity [34], antihypertensive [35], antioxidant and anti-inflammatory effect [36], antimicrobial effect [37], neuroprotective effect [38]; p-Coumaric acid [UV protective, hypopigmentation and anti-melanogenic effect [39], immuno-modulatory and anti-inflammatory activity [40], anti-platelet activity [41], Antidiabetic and antihyperlipidemic activity [42])	Example- Caffeic acid: Enzyme, epigenetic regulator, unclassified protein, transcription factor, other cytosolic protein, ion channel, membrane receptor, transporter, other nuclear protein	Example- Caffeic acid: Cerebroside-sulfatase, Carbonic anhydrase (I, II, III, IV, VI, VII, IX, XII, XIV, VA, VB), DNA polymerase beta, DNA polymerase kappa, Protein-tyrosine phosphatase LC-PTP, Matrix metalloproteinase-1, Egl nine homolog 1, Protein-tyrosine phosphatase 2C, Tyrosyl-DNA phosphodiesterase 1, MAP kinase ERK2, Epidermal growth factor receptor erbB1, Acetylcholinesterase, DNA-(apurinic or apyrimidinic site) lyase, Tyrosinase, Protein-tyrosine phosphatase 1B, Endoplasmic reticulum-associated amyloid beta-peptide-binding protein, Matrix metalloproteinase 9, Lysosomal alpha-glucosidase, Aldose reductase, Matrix metalloproteinase-2,	Example- Caffeic acid: Integrase (Human immunodeficiency virus 1), Neuraminidase (Influenza A virus), Large T antigen (Simian virus 40)	Example- Caffeic acid: 4'-phosphopantetheinyl transferase fŤp (Bacillus subtilis), Endonuclease 4 (Escherichia coli K-12), 2-heptyl-4(1H)-quinolone synthase PqsD (Pseudomonas aeruginosa)	Example- Caffeic acid: 1KOU, 2O7D, 3HOF, 3S2Z, 4EYQ, 4FB4, 4N0S, 4YU7, 5VFJ, 6AWU, 6I72  Structure of Fragaria ananassa O-methyltransferase in complex with S-adenosylhomocysteine and caffeic acid (PDB: 6I72)
		; **Curcumin** (Anti-HIV activity [43], anti-mutagenic and anti- carcinogenic [44], Antiaflatoxin and antifungal acti-vity [45] Anti-athero-sclerotic [46], Anti-angiogenic [47], Antioxidant [48], Anti-ischemic [49], fibrinolytic [50], hepatoprotective [51], Ornithine decarboxylase inhibitor activity [52], Protease inhibitor action [53], Protein kinase inhibitor action [54])		Cyclooxygenase-1, Cyclooxygenase-2, Dipeptidyl peptidase IV, Aldo-keto reductase family 1 member (C1, C2, C3, C4, B10), Hyaluronidase-1, Xanthine dehydrogenase, DNA--methyladenine glycosylase, Alpha-galactosidase A, Aldehyde dehydrogenase 1A1, 15-hydroxyprostaglandin dehydrogenase [NAD+], LDL-associated phospholipase A2, Dual specificity protein phosphatase 3, Cytochrome P450 3A4, Arachidonate 5-lipoxygenase, Thrombin, Alanine aminotransferase 1, Glutaminase kidney isoform, mitochondrial,			

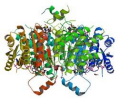
(Table 2) cont.....

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Flavonols: **Kaempferol** Isorhamnetin, Myricetin, Quercetin, Azaleatin, Fisetin, Galangin, Gossypetin, Kaempferide, Morin, Natsudaidain, Pachypodol, Rhamnazin, Rhamnetin	*Allium cepa*, apples, almond, broccoli, buckwheat, celery stalks, chives, cranberries, dillweed, endive, fennel leaves, grapes, kale, leeks, lettuce, olive, pears, pepper, plums, red wine, strawberries, tea, tomatoes, and turnip.	**Isorhamnetin** (Antimicrobial activity [55, 56], anti-diabetic effects [57], hepatoprotective activity [58], anti-inflammatory activity [59], anti-coagulant activity [60], cardiovascular protection [61], anticancer activity [62], neurological effects [63]); **Kaempferol** (Cardioprotective activity [64], anticancer activity [65], anti-diabetic activity [66],	Example- Kaempferol: Enzyme, Transcription factor, unclassified protein, transporter, other cytosolic protein, epigenetic regulator, ion channel, membrane receptor, other nuclear protein, structural protein	Example- Kaempferol: Carbonic anhydrase (I, II, IV, VII, XII), DNA polymerase (eta, iota), Receptor-type tyrosine-protein phosphatase S, Cytochrome P450 (2D6, 2C9, 2C19, 1A1, 1A2, 1B1, 3A4), Cyclin-dependent kinase 1/cyclin B, Prolyl endopeptidase, Tyrosyl-DNA phosphodiesterase 1, Beta-secretase 1, Epidermal growth factor receptor erbB1, Serine/threonine-protein kinase PIM1, Sialidase 2, Acetylcholinesterase, DNA-(apurinic or apyrimidinic site) lyase, Myeloperoxidase, Estradiol 17-bet--dehydrogenase (1, 2),	Example- Kaempferol: Avian myoblastosis virus polyprotein II, Reverse transcriptase, integrase (Human immunodeficiency virus 1), Neuraminidase (Influenza A virus-strain A/USSR/90/1977 H1N1; A/Puerto Rico/8/1934(H1N1))	Example- Kaempferol: Anthrax lethal factor (Bacillus anthracis), Sialidase (Clostridium perfringens), Oleandomycin glycosyltransferase (Streptomyces antibioticus)	Example- Kaempferol: 5AUX, 5AV2, 4REL, 6M8B, 1H1M, 2C1Z, 5AV3, 4DET, 3QWH  Crystal structure of DAPK1 in complex with kaempferol (PDB: 5AUX)
		neuroprotective activity [67]); **Myricetin** (antioxidant activity [68], antiphotoaging activity [69], anticancer activity [70], anti-platelet aggregation activity [71], antihypertensive activity [72], immunomodulatory activity [73], anti-inflammatory activity [74], anti-allergic activity [75], analgesic activity [76], hepatoprotective and hypouricemic activities [77], anti-cataract [78], anti-diabetic and anti-obesity activities [79], antimicrobial activity [68]). **Quercitin** (anti-inflammatory activity [80], cardiovascular disease prevention [81], neuroprotective activity [82], cancer and apoptasis [83], ulcer and gastritis [84], antimicrobial activity [85], for the treatment of allergies, asthma and hay fever [86]).		Salivary alpha-amylase, Superoxide dismutase, Tyrosinase, Death-associated protein kinase 1, Arachidonate 15-lipoxygenase, type II, Carboxy-terminal domain RNA polymerase II polypeptide A small phosphatase 1, Endoplasmic reticulum-associated amyloid beta-peptide-binding protein, Ubiquitin carboxyl-terminal hydrolase 1, Aldose reductase, Glycogen synthase kinase-3, DNA topoisomerase II alpha, Casein kinase II, Cyclooxygenase (1, 2), Cyclin-dependent kinase 5/CDK5 activator 1, CDK6, Dipeptidyl peptidase IV, Tyrosine-protein kinase receptor FLT3, Xanthine dehydrogenase, Flap endonuclease 1, DNA--methyladenine glycosylase, NADPH oxidase 4, Beta-glucocerebrosidase, Aldehyde dehydrogenase 1A1, Arachidonate 5/15-lipoxygenase, 15-hydroxyprostaglandin dehydrogenase [NAD+], Isocitrate dehydrogenase [NADP] cytoplasmic, Butyrylcholinesterase, Serum paraoxonase/arylesterase 1, Glyoxalase I, Catalase			

(Table 2) cont.....

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Flavones: Apigenin, Luteolin, tangeritin, chrysin, 6-hydroxyflavone)	*Allium cepa, Allium sativa,* artichoke, artemisia, achillea, citrus fruits, celery, chamomile tea, matricaria, olive, oregano, parsley, rosemary, spinach, sweet peppers, Tanacetum, thyme	**Apigenin** (As nutraceuticals [87], as anticancer [88], as antioxidant and anti-inflammatory [89], in the treatment of Alzheimer's disease [90], insomnia [91], knee osteoarthritis [92], anxiety disorder and depression [93], anti-diabetic activity [94]); **Luteolin** (In the treatment of ageing, atherosclerosis, anti-inflammatory cardiovascular disease, diabetes mellitus, hypertension, ischemia/ reperfusion injury, neurodegenerative disorders rheumatoid arthritis, anti-allergic [95 - 97], anticancer activity [98], antimicrobial activity [99], antioxidant activity [100])	Example- Apigenin: Enzyme, transcription factor, unclassified protein, transporter, other cytosolic protein, epigenetic regulator, ion channel, membrane receptor, secreted protein, others	Example- Apigenin: Cerebroside-sulfatase, Casein kinase I, Ubiquitin carboxyl-terminal hydrolase 2, DNA polymerase eta/iota, Serine/threonine-protein kinase VRK1, DNA polymerase kappa, CaM kinase I gamma, CaM kinase II gamma, Poly [ADP-ribose] polymerase-1, Cytochrome P450 (2D6, 2C9, 2C19, 1A1), RAF2- and NCK-interacting kinase, Pyruvate kinase isozymes M1/M2, CaM kinase II delta, Death-associated protein kinase 3, Serine/threonine-protein kinase MST1, Cyclin-dependent kinase 1/cyclin B, Serine/threonine-protein kinase PAK6, Tyrosyl-DNA phosphodiesterase 1, Breast cancer type 1 susceptibility protein, MAP kinase ERK2, Serine/threonine-protein kinase PIM2, AMP-activated protein kinase, alpha-2 subunit, Serine/threonine-protein kinase PAK7, Cyclin-dependent kinase-like 1, Phosphodiesterase 5A, MAP kinase p38 alpha, Beta-secretase 1, Epidermal growth factor receptor erbB1, Serine/threonine-protein kinase PIM1, and other signalling proteins	Example- Apigenin: Integrase, Reverse transcriptase (HIV- 1), Neuraminidase (Influenza A virus), Replicase polyprotein 1ab (SARS coronavirus)	Example- Apigenin: 4'-phosphopantetheinyl transferase ffp (Bacillus subtilis), Sialidase (Clostridium perfringens), D-alanylalanine synthetase, Endonuclease 4, DNA gyrase, (Escherichia coli K-12), Urease subunit alpha/Urease subunit beta, D-alanine--D-alanine ligase (Helicobacter pylori strain ATCC 700392 / 26695/ strain HPAG1)	Example- Apigenin: 4WO0, **5AUV**, 5I2H, 4DGM, 4DER, 4HKK, 3AMY, 3CF9, 5UQT  Crystal structure of DAPK1 in complex with apigenin (PDB: 5AUV)
Flavanl struc Flavanols: Catechin, Epicatechin gallate, Epigallocatechin, Epigallocatechin gallate, Proanthocyanidins, Theaflavins, Thearubigins	apples, apricots, barley, cereal, beer, chocolate, cocoa, grapes and blackberrie, apples, peaches, nectarines, nuts, plums, red wine, sour cherries, and tea	For antimutagenic activity [101], antioxidant activity [102], antihypertensive activity [103], anti-platelet activity [104], cardio-protective activity [105], anti-thrombogenic activity [106], hypolipidemic and antidiabetic activity [107], anti-allergic [108], antibacterial and antiviral effect [109], anti-tumor effect [110]	Example- Catechin: Enzyme, unclassified protein, epigenetic regulator, ion channel, other cytosolic protein, transcription factor	Example- Catechin: Carbonic anhydrase (I, II, III, IV, VI, VII, IX, XII, XIII, XIV, VA, VB), Lymphocyte differentiation antigen CD38, ATP-dependent DNA helicase Q1, Ribonuclease pancreatic, DNA polymerase kappa, DNA polymerase iota, Tyrosyl-DNA phosphodiesterase 1, MAP kinase ERK2, DNA-(apurinic or apyrimidinic site) lyase, Salivary alpha-amylase, Ubiquitin carboxyl-terminal hydrolase 1, Intestinal alkaline phosphatase, Aldehyde dehydrogenase 1A1, Arachidonate 15--, 15-hydroxyprostaglandin dehydrogenase [NAD+], UDP-glucuronosyltransferase 1-1, Alkaline phosphatase, tissue-nonspecific isozyme, LDL-associated phospholipase A2, Serum paraoxonase/arylesterase 1, Alkaline phosphatase placental-like, Glutaminase kidney isoform, mitochondrial,	Example- Catechin: Neuraminidase (Influenza A virus), Large T antigen (Simian virus 40)	Example- Catechin: 4'-phosphopantetheinyl transferase ffp (Bacillus subtilis), Urease subunit alpha/Urease subunit beta (Helicobacter pylori strain ATCC 700392 / 26695)	Example- Catechin: 3I52, **4C94**, 4C9I  Crystal Structure of the Strawberry Pathogenesis-Related 10 (PR-10) Fra a 3 protein in complex with Catechin (PDB: 4C94)

(Table 2) cont.....

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Flavanones: Hesperetin, Eriodictyol, Naringenin, Sakuranetin, Blumeatin, Butin, Hesperidin, Homoeriodictyol, Isosakuranetin, Naringin, Pinocembrin, Poncirin, Sakuranin, Sterubin, Pinostrobin	Citrus fruits: grapes, lemons, orange, and tomatoes (Naringenin)	**Naringenin** (anticancer and antiatherogenic properties [111], prevention of osteoporosis [112], cardioprotective activity [113], Antimutagenic activity [114], anti-inflammatory activity [115], hepatoprotective activity [116], anti-fibrotic activity [117], antimicrobial activity [118], anti-diabetic activity [119], hypolipidemic activity [120], antidepressant activity [121]); **Eriodictyol** (for the treatment of cancer [122], anti-inflammatory properties [123], antioxidant activity [124], cardioprotective properties [125], immunomudulatory effect [126], neurotrophic, and anti-melanogenesis and anti-genotoxic properties [127]); **Hesperetin** (antioxidant activity [128], cardioprotective activity [129], vasodilatory effect [130], neuroprotective effect [131], anti-allergic activity [132], dermatitis inhibiting effect [133], antibacterial activity [134]); **Sakuranetin** (anticancer properties [135], antiviral effect [136], anti-mutagenic properties [137], anti-diabetic activity [138], antimicrobial activity [139]).	Example- Hesperetin: Enzyme, unclassified protein, epigenetic regulator, transcription factor, membrane receptor, transporter	Example- Hesperetin: Carbonic anhydrase (I, II, IV, VII, XII), Ras-related protein Rab-9A, Cytochrome P450 (2D6, 2C9, 2C19, 1A1, 1A2, 1B1, 3A4), Tyrosyl-DNA phosphodiesterase 1, MAP kinase ERK2, c-Jun N-terminal kinase (1, 2), Acetylcholinesterase, Estradiol 17-bet--dehydrogenase 1, Salivary alpha-amylase, Endoplasmic reticulum-associated amyloid beta-peptide-binding protein, Serine-protein kinase ATM, Dipeptidyl peptidase IV, Glycogen synthase kinase-3 beta, Estradiol 17-bet--dehydrogenase 2, Aldehyde dehydrogenase 1A1, Serum paraoxonase/arylesterase 1, Aldo-keto reductase family 1 member B10, Thrombin, TGF-beta receptor type II,	Example- Hesperetin: Replicase polyprotein 1ab (SARS coronavirus)	Example- Hesperetin: Beta-lactamase AmpC (Escherichia coli K-12)	Example- Hesperetin: **5JDC**  *Trypanosoma brucei* PTR1 in complex with inhibitor NP-13 (Hesperetin) (PDB: 5JDC)

(Table 2) cont.....

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Anthocyanidins (**Cyanidin**, Delphinidin, Malvidin, Pelargonidin, Peonidin, Aurantinidin, Capensinidin, Europinidin, Hirsutidin, Petunidin, Pulchellidin, Rosinidin)	Anthocyanidin present in fruits is cyanidin□3 glucoside, Grapes, blueberry, red onions, oranges, and red wine. Blackcurrant, blackberry, and elderberry (only cyanide), present in epidermal tissues of fruits and flower	**Cyanidin** (anticarcinogenic activity [140], vasoprotective nature [141], anti-inflammatory properties [142], anti-obesity [143], antidiabetic activity [144]); **Delphinidin** (anti-mutagenic activity [145], anti-cancer [146], anti-angiogenic activity [147], anti-inflammatory activity [148], anti-fibrotic activity [149], antioxidant [150]); **Malvidin** (anti-cancer activity [151], anti-obesity [152], antioxidant and anti-inflammatory activity [153]); **Pelargonidin** (anti-inflammatory activity [154], anti-septic effect [155], anti-tumour activity [156], antiobesity activity [157], anti-thrombotic and antiplatelet activity [158], antiseptic properties [159], anti-diabetic activity [160]); **Peonidin** (antioxidant and prebiotic activity [161], anti-inflammatory activity [162], anti-tumour activity [163], Antimutagenic activity [164]);	Example- Cyanidin: Enzyme, transcription factor	Example- Cyanidin: Lymphocyte differentiation antigen CD38, Death-associated protein kinase 1, Cyclooxygenase-1, Dipeptidyl peptidase IV, Cyclooxygenase-2, Glyoxalase I, Thrombin	Not found	Not found	Example- Cyanidin: **6QCH**  Human Sirt6 in complex with ADP-ribose and the activator cyaniding (PDB: 6QCH)
Isoflavones (**Daidzein**, Genistin, Glycitein)	Soybeans and soy products are almost the sole dietary source of isoflavones. It is also in small amounts in chickpeas.	Daidzein (antithrombotic and anti-allergic activity [165], anticancer activity [166], anti-arthritogenic and cardioprotective action [167], anti-oxidant activity and anti-inflammatory activity [168], anti-osteoporosis activity [169], anti-diabetic activity [170], anti-aging activity [171], anti-hypoxia activity [172], **estrogenic and genotoxic** activity [173]).	Example- Daidzein: Enzyme, unclassified protein, epigenetic regulator, ion channel, other cytosolic protein, transcription factor, transporter, membrane receptor, other nuclear protein, structural protein	Example- Daidzein: Cerebroside-sulfatase, Carbonic anhydrase (I, II, IV, VII, XII), Ras-related protein Rab-9A, Bloom syndrome protein, Cytochrome P450 (2D6, 2C9, 2C19, 1A2, 19A1, 3A4), Pyruvate kinase isozymes M1/M2, Tyrosyl-DNA phosphodiesterase 1, Epidermal growth factor receptor erbB1, DNA-(apurinic or apyrimidinic site) lyase, Estradiol 17-bet--dehydrogenase 1, Salivary alpha-amylase, Endoplasmic reticulum-associated amyloid beta-peptide-binding protein, Aldose reductase, DNA topoisomerase II alpha, Aldehyde dehydrogenase, Xanthine dehydrogenase, Estradiol 17-bet--dehydrogenase 2, Aldehyde dehydrogenase 1A1, UDP-glucuronosyltransferase 1A4, 15-hydroxyprostaglandin dehydrogenase [NAD+], UDP-glucuronosyltransferase 1-1, Serum paraoxonase/arylesterase 1, DNA topoisomerase I, Aldo-keto reductase family 1 member B10, Monoamine oxidase, UDP-glucuronosyltransferase 1-10, UDP-glucuronosyltransferase 1-9	Example- Daidzein: Neuraminidase (Influenza A virus), Replicase polyprotein 1ab (SARS coronavirus)	Example- Daidzein: Urease subunit alpha/Urease subunit beta (Helicobacter pylori strain ATCC 700392 / 26695), Oleandomycin glycosyltransferase (Streptomyces antibioticus)	No PDB ID found. Molecular interactions found with human genes: TRPC5 (transient receptor potential cation channel, subfamily C, member 5), ESRRB (estrogen-related receptor beta), IBSP (integrin binding sialoprotein), PIK3CG (Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform), ESRRA (estrogen-related receptor alpha), LIF (interleukin 6 family cytokine), FOS (fos proto-oncogene, ap-1 transcription factor subunit)

(Table 2) cont.....

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Stilbenes (**Resveratrol**, Pinosylvin, Pterostilbene)	Found in berries, grapes, plums and pine nuts, peanuts, spinach, red wine, and red cabbage.	**Resveratrol** (antioxidant activity [174], anticancer activity [175], neuroprotective activity [176], cardioprotective activity [177], anti-diabetic effect [178], non-alcoholic fatty liver disease [179], anti-allergic activity [180], anti-inflammatory activity [181], immunomodulatory activity [182]).	Example- Resveratrol: Enzyme, membrane receptor, transcription factor, unclassified protein, epigenetic regulator, transporter, ion channel, other cytosolic protein, secreted protein, others	Example- Resveratrol: Cerebroside-sulfatase, FAD-linked sulfhydryl oxidase ALR, Carbonic anhydrase (I, IV, VI, VII, VA, VB, IX, XII, XIV), Lymphocyte differentiation antigen CD38, DNA polymerase beta, Bloom syndrome protein, DNA polymerase kappa, DNA polymerase iota, Cytochrome P450 (2D6, 2C9, 2C19), Matrix metalloproteinase-1, Serine/threonine-protein kinase PAK 1, Thromboxane-A synthase, Tyrosyl-DNA phosphodiesterase 1, Breast cancer type 1 susceptibility protein, MAP kinase ERK2, Phosphodiesterase 5A, MAP kinase p38 alpha, Beta-secretase 1, Epidermal growth factor receptor erbB1, Leukocyte elastase, Monoamine oxidase B, Bcr/Abl fusion protein, *etc*.	Example- Resveratrol: Large T antigen (Simian virus 40)	Example- Resveratrol: ATP-dependent Clp protease proteolytic subunit (Bacillus subtilis strain 168), Beta-lactamase AmpC (Escherichia coli K-12)	Example- Resveratrol: **4QER**, 1SG0, 5CR1, 4QOH, 1CGZ, 4QOJ, 5J54, 5U90, 1DVS, 1U0W, 3CKL, 4Q93, 3MNQ, 4PP6, 2JIZ, 3FTS, 5NZL, 4DPN, 6JEM, 4HDA, 2YDX, 4JAZ, 1Z1F, 5BTR, 2L98  Crystal Structure of the Complex of Phospholipase A2 with Resveratrol at 1.20 Å Resolution (PDB: 4QER)
Stilbenol (**Piceatannol**, Astringin)	Found in grapes, fruit, white tea and red wines	**Piceatannol** (anti-inflammatory activity [183], anti-cancer activity [184], anti-atherogenic activity [185], anti-oxidant, neuroprotective and anti-allergic activity [186], anticariogenic activity [187], anti-platelet aggregation activity [188]); **Astringin** (antioxidant activity [189], anti-inflammatory activity [190]).	Example- Piceatannol: Enzyme, unclassified protein, epigenetic regulator, ion channel, other cytosolic protein, transcription factor	Example- Piceatannol: PIK3CG (Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform), CYP1A2 (Cytochrome P450 1A2), ATP synthase subunit alpha, mitochondrial,	Not found	Not found	Example- Piceatannol: **5U97**, 4HD8, 2JJ1  Crystal structure of Co-CAO1 in complex with piceatannol at 1.85 Å resolution (PDB: 5U97)
Lignan (Medioresinol, **Pinoresinol**, Matairesinol, Lariciresinol, Secoisolariciresinol, Hydroxymatairesinol, Syringaresinol, Sesamin)	Flaxseed is the richest source Buckwheat, sesame seed, rye, and wheat	**Lignans** (anti-tumour activity [191], anti-mitotic activity [192], anti-viral activity [193], insecticidal activity [194], antioxidant activity [195], antidiabetic activity [196], antiallergic activity [197], cardioprotective activity [198], hypolipidemic activity [199], esterogenic activity [200])	Example- Pinoresinol: unclassified protein, transcription factor	Example- Pinoresinol: Peroxisome proliferator-activated receptor (delta, alpha, gamma); Antineuroinflammatory activity (in mouse BV2 cells), Cytotoxicity against human PANC1 cells,	Not found	Not found	Not found

(Table 2) cont.....

Phenolic compound	Food source	Biological & Pharmaceutical activities	Target class	Human Target	Virus Target	Bacteria Target	PDB Entries & 3D Protein complex crystal structure
Tannins/tannoids (Condensed tannin: Catechin, Epicatechin; Hydrolyzable tannins-Gallic acid; Ellagitannins: Punicalagin, Casuarictin)	Lentils, pear, grapes, peaches, plums, mangosteens, pears, red and white wine and apple juice Strawberries, blackberries, raspberries, walnuts, pecans, pomegranate bark, leaf and the fruit husk	Antiulcer activity [201], antimicrobial activity [202], anti-viral activity [203], cardioprotective activity [204], histamine release inhibition [205], cytotoxic effect, antimicrobial and antioxidant activities [206], anti-diabetic activity [207], anti-obesity effect [208], protecting effects on bone marrow hematopoietic stem cell [209], wound healing [210], inhibition of skin-tumor promotion [211].	Example- Catechin: Enzyme, unclassified protein, epigenetic regulator, ion channel, other cytosolic protein, transcription factor	Example- Catechin: Carbonic anhydrase (I, II, III, IV, VI, VII, IX, XII, XIII, XIV, VA, VB), Lymphocyte differentiation antigen CD38, ATP-dependent DNA helicase Q1, Ribonuclease pancreatic, DNA polymerase kappa, DNA polymerase iota, Tyrosyl-DNA phosphodiesterase 1, MAP kinase ERK2, DNA-(apurinic or apyrimidinic site) lyase, Salivary alpha-amylase, Ubiquitin carboxyl-terminal hydrolase 1, Intestinal alkaline phosphatase, Aldehyde dehydrogenase 1A1, Arachidonate 15--, 15-hydroxyprostaglandin dehydrogenase [NAD+], UDP-glucuronosyltransferase 1-1, Alkaline phosphatase, tissue-nonspecific isozyme, LDL-associated phospholipase A2, Serum paraoxonase/arylesterase 1, Alkaline phosphatase placental-like, Glutaminase kidney isoform, mitochondrial	Example- Catechin: Neuraminidase (Influenza A virus), Large T antigen (Simian virus 40)	Example- Catechin: 4'-phosphopantetheinyl transferase ffp (Bacillus subtilis), Urease subunit alpha/Urease subunit beta (Helicobacter pylori strain ATCC 700392 / 26695)	Example- Catechin: 3I52, 4C94, 4C9I  Crystal Structure of the Strawberry Pathogenesis-Related 10 (PR-10) Fra a 3 protein in complex with Catechin (PDB: 4C94)

CONCLUSION

Oxidative stress and accumulation of free radicals play an essential role for the development of life threatening conditions such as cancer, cardiovascular complications, and neurodegeneration. The quest for efficient prevention has become the first concern for clinical science. Polyphenols have been considered as alternative therapeutics and have shown to be effective in various treatments, especially in cancer, neurodegeneration, and cardiovascular complications. It has already been well demonstrated that phenolics are able to exert protective effects on the heart, brain, tumor cells, and other organs. Their effects can be due to antioxidant properties, and they also interact with the basic cellular mechanisms. Polyphenols, such as curcumin, resveratrol, quercetin, and many others, have been shown to promote apoptosis induction in different types of cancers (*e.g.*, skin, breast, lung, colon, prostate, melanoma, or leukemia). They also act as suppressing agents and inhibit the formation of tumors from initiated cells. However, the exact mechanisms of actions are not fully understood to date, require further consideration. Polyphenols are the potential candidates of natural origin in pharmaceutical sectors to promote human health, prevent and cure various diseases. However, intense research and profiling are required for the characterization of each compound on the basis of its mechanism of action.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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CHAPTER 8

Structure-Activity Relationship of Flavonoids: Recent Updates

Shruti Khare[1], Rikeshwer Prasad Dewangan[2] and **Ajay Kumar[3,*]**

[1] *Advance Institute of Biotech & Paramedical Sciences, Kanpur-209217, (U.P.), India*

[2] *Department of Pharmaceutical Chemistry, School of Pharmaceutical Education and Research, Jamia Hamdard (Deemed to be University), New Delhi, India*

[3] *Department of Pharmacology, Government Pharmacy College, BRD Medical College campus, Gorakhpur, U.P. India*

Abstract: The biological, physicochemical, and environmental properties of substances are anticipated by utilizing structure-activity relationships (SARs). A SAR is a (qualitative) correlation between a chemical substructure and the potential for one of the chemicals in the substructure to have a particular biological property or effect. We are familiar with the term SAR which is a powerful concept in the discovery of any active pharmaceutical ingredient with both qualitative and quantitative associations that relate to the chemical structure and biological activity of any chemical compound. Due to their safety and medicinal efficacy, plant-derived functional foods are of great interest. In this chapter, the different types of biologically active compounds, their chemistry and SAR, and the different biologically active compounds from daily dietary supplements, foods, and fruits, which contain polyphenolic compounds, have been discussed. SAR of flavonoids like anthocyanidins, which is the principal component of the majority of fruits, vegetables, and flower petals, flavonols, usually called catechins, and isoflavones, are also discussed. Other polyphenolic compounds like tannins with their subtypes like hydrolysable and non-hydrolysable tannins are well covered.

Keywords: Flavonoids, Polyphenols, Stilbenes, Structure-activity relationships, Tannins.

INTRODUCTION

Herbal or medicinal plants have gained exceptional importance around the world. Plant products have been noticed for nutrition, cosmetics preparations, diagnostic agents, and mitigating diseases of human beings. Therefore, a plethora of studies have been done on different plant species, and their effects have been investigat-

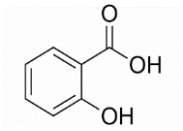
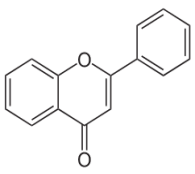
* **Corresponding author Ajay Kumar:** Department of Pharmacology, Government Pharmacy College, BRD Medical College campus, Gorakhpur, U.P. 273013, India; E-mail: ajaykumarbp@gmail.com

Pankaj Kumar Chaurasia and Shashi Lata Bharati (Eds.)

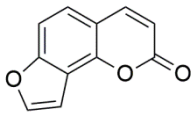
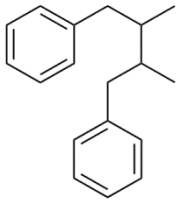
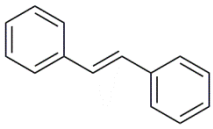
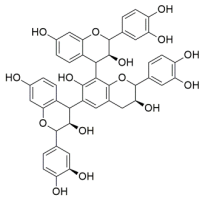
ed. Due to their safety and medicinal efficacy, plant-derived functional foods are of great interest.

Many researchers have already conducted studies on secondary metabolites of plants because of their importance as dietary supplements. The first scientist who discovered the presence of secondary metabolites in plants was Kossel. Among secondary metabolites, 'Polyphenols' are diverse in nature and found in large varieties of plants with antioxidant, anti-inflammatory, and antimicrobial properties. They have gained importance as they have evolved in growth and reproduction, and they provide resistance to plants against pathogens and predators. Moreover, they protect crops from plague and preharvest seed germination [1, 2]. They are polyhydroxylated phytochemicals with common structures. Polyphenols are the secondary metabolites derived from the two main synthetic pathways: shikimic acid and acetate pathway. Chemical structures of natural polyphenols vary from basic phenolic acids to strongly polymerized compounds like tannins. Three main subclasses of phytochemicals that add abundant micronutrients to the diet are phenolic acids (derivatives of cinnamic acid and benzoic acid), flavonoids, and stilbenoids (stilbenes). Phenolic compounds are the most complex classes of chemicals present in the plants. More than 8000 compounds are assumed to have been isolated [3, 4]. They are widely distributed in fruits like berries, apricots, cherries, apples, grapes, and pears, vegetables such as onion, garlic, carrot, tomato, cabbage, and celery, beverages like chocolates, wine, tea, and coffee, and are consumed as dietary supplements [5]. Structural diversity of different polyphenolic compounds has been reviewed in this chapter. The different types of phenolic compounds, their food sources, and their biogenetic pathways have been summarized in Table **1**.

Table 1. Food sources and biogenetic pathway of some phenolic compounds.

Type of Phenolic Compound	Chemistry	Structure	Food Source	Biological Activity	Biogenetic Pathway
Phenolic acids	A phenolic ring and an organic carboxylic acid feature are present in this class of polyphenolic compounds (C6-C1 skeleton) [6].		Generally found in Horse grams, Mushrooms, and dry fruits [7].	Antimicrobial and antioxidant activity [8].	They are derived from L-tyrosine or L-phenylalanine through the Shikimate pathway [8].
Flavonoids	This is the most common class, which has a general structural backbone of C6–C3–C6, with two phenolic C6 units (Ring A and Ring B) [7].		Fruits, herbs, bark, roots, branches, bulbs, tea, and wine are all high in this compound [8].	Reported to have antioxidant, antihypertensive activity and is used in many cardiovascular disorders [9].	They are synthesized by the phenylpropanoid pathway [10].

(Table 1) cont.....

Type of Phenolic Compound	Chemistry	Structure	Food Source	Biological Activity	Biogenetic Pathway
Furanocoumarins	Furanocoumarins have a furan ring connected to a coumarin ring in their chemical structure. The furan ring can be fused in many ways to produce a variety of isomers [11].		Mainly present in citrus fruits like oranges, lemons, mandarins, grapefruits, and limes [12].	They're well known for protecting plants from insects, nematodes, microorganisms, phytophagous herbivores, and rivals [13 - 15].	It is produced from L-phenylalanine through the shikimate pathway [15].
Lignans	Two phenylpropane units are linked by a C-C bond between the central atoms of the respective side chains (position 8 or β), also known as the β-β' bond [16].		Vegetables, grain, nuts, beans, and beverages like tea, coffee, and wine are all rich in this nutrient. Flaxseed contains the most significant amounts of dietary lignans as secoisolariciresinol diglucoside [17].	Anticancer, antioxidant, antihypertensive, antiviral, estrogenic, and insecticidal properties have been documented [18].	They are synthesized by the phenylpropanoid pathway [19].
Stilbenes	Stilbenes are phenylpropanoids with a 1,2-diphenylethylene backbone and belong to a small group of phenylpropanoids [19].		Stilbenes are a type of phenolic metabolite found in grapevine, berries, and peanuts, among various edible plants [20].	Stilbenoids have various biological effects, including neuroprotection, cardioprotection, depigmentation, anti-diabetic properties, anti-inflammatory, and cancer prevention and care [21].	The shikimate pathway's end product, phenylalanine, is a critical link between primary metabolism and secondary metabolic pathways such as phenylpropanoid, flavonoid, and stilbenoid [22].
Hydrolysable Tannins	They are made up of polyhydric alcohol with hydroxyl groups that are partly or wholly esterified with gallic or hexahydroxy diphenic and having long chains of gallic acid coming from the central glucose core [23].		They are found in leguminous seeds, cereals, and, most importantly, in many fruits and vegetables [24, 25].	Tannins have antimicrobial, cardioprotective, and anti-cancer properties, in addition to antioxidant and free radical scavenging properties. They also tend to have a preventive impact against metabolic disturbances and the onset of a variety of oxidative stress-related diseases [26].	A UDP-glucosyltransferase (UGT) action forms an ester bond between gallic acid and glucose to produce β--. β-glucogallin is converted to pentagalloylglucose, which is then converted to gallotannin by several acyltransferases [27, 28].

The different polyphenols have been summarized with their chemistry, structure, biological sources, their biological activity, and their biogenetic pathway.

PHENOLIC ACIDS

There are two kinds of phenolic acids found in polyphenols: hydroxybenzoic acid

and hydroxycinnamic acid. Salicylic acid (Fig. **1**), a hydroxybenzoic acid derived from the bark of willow trees (Salix spp.) [29], was the earliest compound identified to have therapeutic activity. It was chewed in herbal medicine to provide pain and inflammation relief [30].

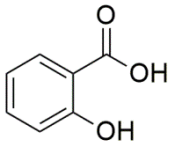


Fig. (1). Salicylic acid.

Salicylic acid is biosynthesized in plants by the shikimic acid pathway, which is a typical intermediate for a number of branched pathways that produce tyrosine, tryptophan, phenylalanine, and a variety of other aromatic compounds. The structure of salicylic acid is:

If we consider SAR, the presence of hydroxyl group at ortho position is important for the pharmacological activity. Shifting of the hydroxyl group at meta or para position abolishes the activity. Substitution of the ring decreases the activity of salicylic acid [31, 32]. The side effects related to the polyphenolic compound are associated with the presence of the carboxylic acid group. Salicylic acid is used in medicinal preparation to cure dandruff, seborrhea, acne, and insect bites [33].

If we consider hydroxy-cinnamic acid (Fig. **2**), which is more common when compared to hydroxyl-benzoic acid, it mainly consists of ferulic acid and caffeic acid [34]. Caffeic acid is predominantly found in different fruits like plum, blueberries, cherries, apples, and kiwi [35]. The structure is shown below:

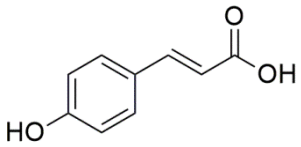


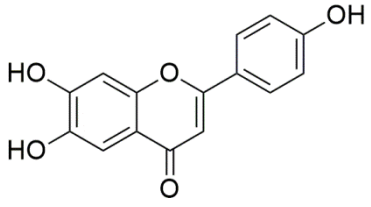
Fig. (2). Hydroxycinnamic acid.

If we consider SAR, hydroxy-cinnamic acid is a highly potent antioxidative agent. The structural modification can be done for more potency [36]. The availability of an unsaturated bond on the side chain is essential for their biological activity. Modifications of the aromatic ring, such as changes in position and number of hydroxyl groups and the addition of an electron-withdrawing group, as well as modifications of the carboxylic group, are essential structural features for antioxidant activity [37, 38].

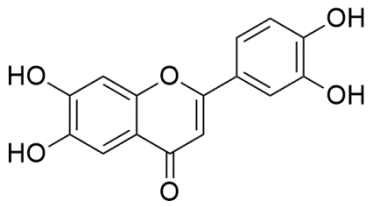
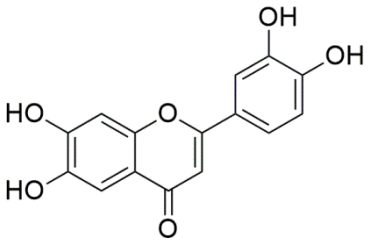
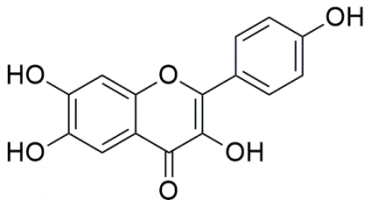
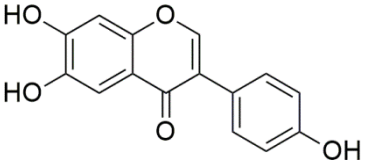
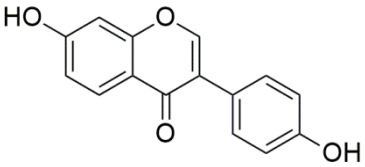
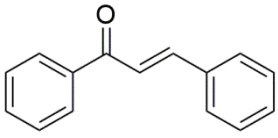
FLAVONOIDS

Flavonoids have been found in over 8000 different varieties and many of them, are responsible for the colours of fruits and flowers. Humans receive them from the consumption of seeds, tea, wine, berries, dark chocolate, wheat, roots, leaves, stems, and flowers. From the literature, it has been found that these are the largest group of polyphenols, which include several thousands of low molecular weight phenolic compounds, belonging to 7 major subgroups ─ flavanols, flavones, flavanols, flavanones, flavanonols, anthocyanidins, and isoflavonoids (Tables **2** & **3**) Among these, flavones, flavanols, and flavanones are the most abundant naturally occurring flavonoids. These molecules are characterized by the presence of flavan nucleus and are known as C6–C3–C6 phenolics [39]. Flavonoids, like carotenoids, are responsible for the coloration of fruits, vegetables, and herbs [40]. The flavonoid parent compound (Fig. **3**) is made up of a fifteen-carbon skeleton that includes two benzene rings and a heterocyclic pyrane ring (C). They are divided into flavones (*e.g.*, apigenin, flavone, and luteolin), flavonols (*e.g.*, myricetin, quercetin, kaempferol, and fisetin), and flavanones (*e.g.*, hesperetin, flavanone and naringenin) [41]. The aglycone is the flavonoid's basic parent structure [42]. An α-pyrone (flavonols and flavanones) or its dihydroderivative (flavonols and flavanones) is a six-membered ring structure condensed with the benzene ring . Flavonoids (2-position) and isoflavonoids (3-position) are distinguished by the position of the benzenoid substituent. Flavonols differ from flavanones in having a hydroxyl group at 3-position and a C2–C3 double bond [43]. Flavonoids are hydroxylated in positions 3, 5, 7, 2, 3′, 4′, and 5′. In nature, methyl ethers and acetyl esters of the alcohol group are known [44].

Table 2. Different types of flavonoids with their structures.

S. no.	Types of Flavonoids	Chemical Structures
1.	**FLAVONES** a. Apiogenin	

(Table 2) cont.....

S. no.	Types of Flavonoids	Chemical Structures
	b. Luteolin	
2.	**FLAVONOLS** a. Quercetin b. Kaempferol	
3.	**ISOFLAVONOLS** a. Genistein b. Daidzein	
4.	**CHALCONES**	
5.	**ANTHOCYANINS**	
6.	**FLAVANONES**	

(Table 2) cont.....

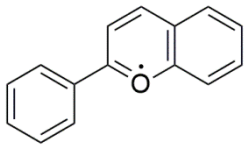
S. no.	Types of Flavonoids	Chemical Structures
7.	**FLAVONONOLS**	

Table 3. Different types of flavonoid have been summarized with their chemistry and biological activity.

S.no.	Sub-Classes of Flavonoids	Chemistry	Food Sources	Biological Activity
1.	Isoflavonoids	They are also called as phytoestrogens. They have 3-phenylchroman backbone [52].	Leguminous plants, such as beans, especially red clover, soybeans, and other legumes, are the most common sources [53].	Isoflavones are nonsteroidal polyphenolic metabolites found in plants that have antioxidant properties [54]. Found to have estrogenic effect from different kinds of literature [55].
2.	Flavones	Flavones have a double bond between C-2 and C-3 and a non-saturated 3-C chain [56].	Flavones are present in leaves, flowers, and fruits as glucosides. Celery, parsley, chamomile, red peppers, ginkgo biloba and mint, are good sources of flavones [57].	The benefits of cardiovascular and neurological disorders have been shown by several studies. Neuroprotective effects in neurons, in culture against oxidative damage, and in models of focal ischemia and parkinsonism have been reported [58].
3.	Flavonols	They have a double bond between positions 2 and 3 of the C ring, as well as a ketonic group at position 4. A hydroxyl group is present in position 5 of the A ring in the majority of flavones found in vegetables and fruits [59].	Apples, broccoli, bananas, brussels sprouts, cabbage, sprouts, green beans, kale, endive, spinach, leeks, olives, carrots, peas, tea, red wine, and tomatoes are also high among them [60].	Reported to have antioxidant action, also indicated in the treatment of Inflammatory bowl diseases [61].

(Table 3) cont.....

S.no.	Sub-Classes of Flavonoids	Chemistry	Food Sources	Biological Activity
4.	Chalcones	Chalcones also called as benzyl acetophenone or benzylidene acetophenone. An aliphatic three-carbon chain connects two aromatic rings in chalcones. Chalcones are -unsaturated ketones made up of two aromatic rings (rings A and B) with various substituents [62].	Chalcones are the most common in citrus fruits, apples, and vegetables such as tomatoes, green sprouts, potatoes, and various plants and spices such as liquorice, according to multiple pieces of evidence [63].	Anticancer, antimicrobial, antitubercular, anti-inflammatory, antioxidant, anti-leishmanial activity are present in chalcones [64].
5.	Anthocyanidins	This type of flavonoid consists of polyhydroxy derivatives of 2-phenylbenzophyryllium [65]. A three-carbon chain connects the two aromatic rings A and B with the phenolic group, forming an oxygenated heterocyclic ring (C ring) [66].	Bilberries, blueberries, cherries, chokeberries, black and red currants, grapes, strawberries, pomegranate, elderberries, and other fruits and vegetables have been reported to contain the flavonoid [67].	Anthocyanins have been used as an anticancer agent, in neurological and coronary disorders, inflammation, diabetes, and bacterial infections. The chelating property of phenolic compounds is also accountable for antioxidant activity [68].
6.	Flavanones	Flavanone is made up of two aromatic rings joined by a carbon bridge, which often forms a heterocyclic ring [69].	Celery, citrus fruits, parsley, rutin, olives, spinaches, and other foods contain flavanones in large amounts [70].	They are helpful in cardiovascular health, vascular relaxation and overall antioxidant and anti-inflammatory activity [71].
7.	Flavonols	These are dihydroflavonols with saturated C3 fragment which make them odorless [72].	These are mainly abundant in citrus fruits [73]	They are fungitoxic compound used in wood preservation [74].

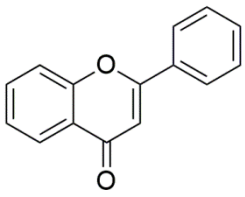


Fig. (3). Parent structure of flavonoid.

Structure Activity Relationship

Substitution at the A or B ring in the flavonoid structure increases phyto-estrogen activity. The existence of the catechol moiety is the most significant factor for high antioxidant activity. In this case, the presence of a C2-C3 double bond is of no significance [45]. In the absence of catechol, the C2-C3 double bond, along with C3-OH and C4 carbonyl, is crucial for antioxidant action [46]. If structure is considered, the total number of OH groups and position of OH at 2nd carbon is very important. The flavonoid is inactive when there is no OH or just one OH present. Isoflavones having OH groups at position 4` on ring B and presence of OH group at 6 and 7 on ring A showed an increase in inhibitory property [47]. Generally, C2 and C3 double bond is very necessary for the antioxidant activity. The different sub-classes of flavonoids can be formed by the substitution or the presence of carbon on ring C on which B ring is attached [48]. The degree of unsaturation and oxidation of C ring is also used to classify different sub-classes of flavonoids [49]. If structure-activity relationship is considered, the molecular form and the capacity of hydrogen atom donation to free radicals is responsible for the antioxidant activity. The presence of phenolic hydrogen and stability of phenoxy free radical and the substitution of phenolic hydroxyl group are responsible for the activity. The presence of 3,4-dihydroxy in case of quercetin, luteolin and catechin makes them highly effective antioxidants [50, 51].

FURANOCOUMARINS

Secondary metabolites found in citrus plants contain furanocoumarins—the fusion of the furan ring with the α-benzopyrone forms the structure. Furan moiety can be in either a 3,2 - or 2,3 -arrangement at the c, f, g, or h bonds of the coumarin; most naturally occurring derivatives belong to the psoralen, allopsoralen, and angelicin group [75]. Coumarin and its derivatives act as anticoagulants and are taken orally. They are insoluble in water; however, the 4-hydroxy substitution gives the molecule weakly acidic properties, making it water-soluble in mildly alkaline environments.

The different most commonly occurring furanocoumarins are:

a. **α-Benzopyrone:** It is found in all aspects of plants, herbs, citrus, spices, the fruits, roots, branches, and leaves. The general structure is given in Fig. (**4**) [76, 77].

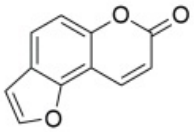


Fig. (4). α-Benzopyrone.

b. **Psoralen:** Psoralen is the parent molecule in a family of furanocoumarins (Fig. **5**). It is found in plants like *Psoralea corylifolia* and *Ficus salicifolia* and acts as a plant metabolite. It is structurally related to coumarin by the addition of a fused furan ring and derivative of 9-methoxy-7*H*-furo [3,2-*g*]chromen-7-one tricyclic ring structures. Cross-linkers, biotinylation complexes, and nucleic acid probes all contain them as photoreactive groups. Psoralens have been used as a photochemotherapy agent for the treatment of psoriasis and vitiligo for many years [78 - 80].

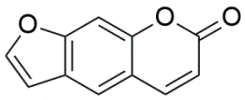


Fig. (5). Psoralen.

c. **Allopsoralen:** It is a novel tetracyclic coumarin derivative produced by the condensation of a fourth cyclohexenylic (5-7) or benzenic (8-10) ring at the furan side with a methoxy (5 and 8) or hydroxy (6 and 9) at ten position (Fig. **6**) [81].

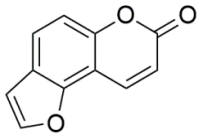


Fig. (6). Allopsoralen.

d. **Angelicin:** Angelicin is the parent compound of naturally occurring angular furanocoumarins. It is made up of benzapyra-2-one fused to a furan moiety at 7,8-position [82]. Plants in the Apiaceae and Fabaceae families, such as *Bituminaria bituminosa*, contain lots of angelicin (Fig. **7**). Angelicin derivatives are used for the treatment of cancer and psoriasis [83] and are also reported to have a tranquillo sedative and anticonvulsant activity [84].

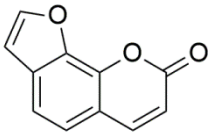


Fig. (7). Angelicin.

LIGNANS

Lignans are the polyphenolic compounds having steroid-like chemical structures, also known as phytoestrogens (Fig. **8**). Heart attack, menopausal complications, osteoporosis, and breast cancer are decreased by lignans, according to a study [85]. Lignans are nothing but phenylpropanoid dimers consisting of two phenyl propane units (C6 and C3) linked by their central C8 carbon and mainly synthesized by phenylpropanoid pathway [86]. Lignans are present in a wide range of foods, including nuts, beans, grains, vegetables, and beverages, including coffee, tea, and wine. Flaxseed has the highest concentrations of dietary lignans [87]. It is well known that lignins and lignans both originate from the C6-C3 units, which indicates that these metabolites are biosynthesized through phenylpropanoid pathway. If the structure of lignans is considered, they contain a basic two or more phenylpropanoid units [88] and the monomers which form lignans. Classical lignans are the molecules that have a molecular linkage between positions β-β′ (also referred to as an 8-8′). If the major structural units are linked in some other ways (non β-β′ linkage), the compounds are known as "neolignans" [89]. There is oxidation at C9 and C9' carbon of the most of the natural lignans. The different lignans are formed by the incorporation of oxygen into the parent structure and on the cyclization process [90].

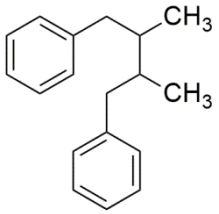


Fig. (8). Lignan.

Lignans have a wide range of structural variations due to the presence of phenoxy free radicals coupling property which is responsible for anti-oxidative action. Lignans also possess antiinflammatory, immunosuppressive activity, and hepatoprotective activity that has been reported in different reviews [91, 92].

Dietary consumption of lignan-rich foods can prevent a few types of cancers due to the presence of bioactive properties (*e.g.*, breast cancer and colon cancer in post-menopausal women). In the case of chronic lifestyle-related disorders, some researches suggest that lignan use is linked to a lower risk of cardiovascular complications [93].

STILBENES

Stilbenes are non-flavonoids that have health-promoting properties. They are phytoalexins, which are produced in plant tissues in response to fungal attack or abiotic stress such as UV irradiation [94]. Stilbenes are polyphenols made up of two phenyl compounds connected by a two-carbon methylene bridge (Fig. **9**) [95]. As per studies, stilbenes are the most common in cowberry, blueberry, lingon berry, and acai berry. Resveratrol is the most well-known stilbene (*trans*-3,4,5-trihydroxystilbene) and found in small quantities in grapes, peanuts, wine, and cranberries. Antioxidative, anticarcinogenic, phytoestrogenic, and cardioprotective activity have all been identified [96]. If structure-activity relationship is considered, the two aromatic rings joined by ethylene moiety present two diastereoisomeric forms, E-1,2-diphenylethylene (trans-configuration) and Z-1,--diphenylethylene (cis-configuration). From the parent structure, several structures are developed by the substitution of substituted hydroxyl-, alkoxy- and glycoside [97]. The structure of stilbene is given here from which the different modifications are conducted for change in the activities. Stilbenes are phenylpropanoids with a 1,2-diphenylethylene backbone. They are the mainly derivatives of the monomeric unit trans-resveratrol (trans-R, 3, 40, 5-trihydroxystilbene), although other type of stilbene structures are also found in plants [98]. The most common stilbene, resveratrol, has been shown to have bacteriostatic, estrogenic, and fungistatic properties, prevents tumors in men and is used as growth stimulants in the breeding of animals. Resveratrol is a phytoncide that alters the qualitative and quantitative structure of micro flora in the gastrointestinal tract, similar to antibiotic growth stimulants did previously [99].

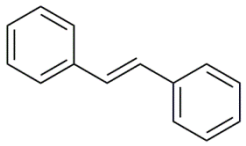


Fig. (9). Stilbenes.

TANNINS

These are the phenolic compounds with astringent properties. They are mainly abundant in coniferous trees and in flowering plant families. Tannins are present in the stems, wood, bark, leaves, and fruit of several plants, mostly in oak species, sumac and myrobalan. They also found in galls, pathological growths caused by insect attacks [100, 101].

Classification of Tannins on the basis of structure:

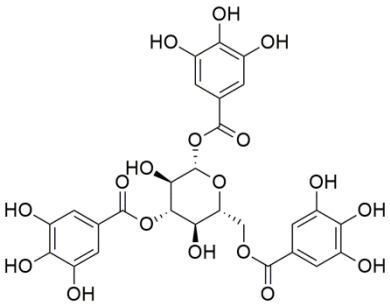
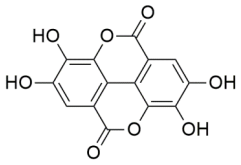
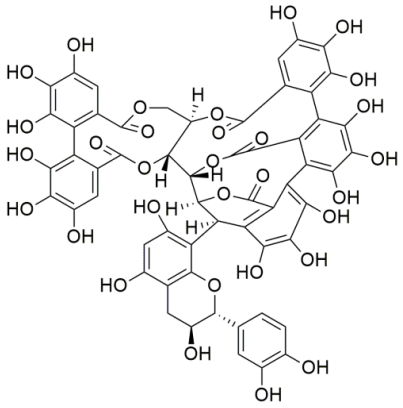
There is no carboxylic group in tannins but is weakly acidic in nature because of the multiplicity of phenolic hydroxyls. The hydroxyl group increases the solublity in water. All regulatory authorities classify it as a nonhazardous substance.

Hydrolysable tannins: In such types of tannins, there is partial or complete esterification of the hydroxyl group by gallic acid [102].

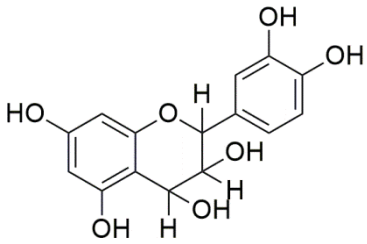
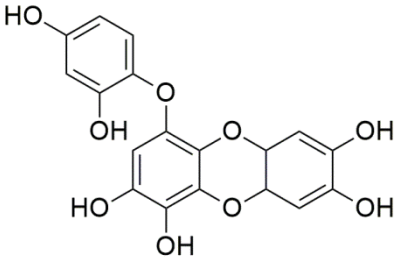
Condensed tannins: These types of tannins are formed by the condensation of phenolic compounds, abundantly found in grapes, pomegranates etc., and have high molecular weights and potential therapeutic activity [103]. They are also known as proanthocyanins. Tannins are non-crystalline substances sparingly soluble in water [104].

Tannins have two to three phenolic hydroxyl groups on a relatively large phenyl ring responsible for these characteristics. Previously, tannins were classified as pyrogallol and catechol type (or catechin) tannins [105]. Two classes were renamed hydrolyzable tannins and condensed tannins as tannin chemistry progressed. The alteration of structure and composition is vital for the pharmacological activity of any target molecule. The previous evidence proved that tannins are high molecular weight compounds due to multiple functional groups in their structure, such as hydroxyls, which provides strong and stable cross-linked association with other molecules, such as carbohydrates or proteins [106]. The tannins are further classified on the basis of chemical composition, which has been given in the tabular form (Table **4**):

Table 4. Types of tannins with their chemistry and biological activities.

S. no.	Types of Tannins	Chemistry	Structure	Biological Activities
1.	GALLOTANNINS	Gallotannins are galloyl-based polymers that bind to polyol-, catechin-, or triterpenoid-units, A core molecule, such as glucose, is surrounded by gallic acid units in gallotannins [107].		Different pieces of evidence proved that due to the presence of short one or more polygalloyl chains, they possess antioxidant activity, anti-inflammatory and are used for the treatment of Alzheimer's disease [108].
2.	ELLAGITANNINS	Ellagitannins are polyphenols, and they are characterized by the presence of one or more hexahydroxydiphenoyl moieties, *i.e*., esterified to a sugar molecule, generally glucose [109]		Ellagitannins have proved to be highly effective as an antioxidant, anti-adipogenic activity, and high potential cancer prevention [109].
3.	COMPLEX TANNINS	They are formed by the combination of ellagitannin and gallotannin and joined through a glycosidic bond to a flavan-3-ol. Eugenigrandin A and Acutissimin A are complex tannins [110].		Acutissimin A, which is the most common example of ellagitannin, is found to have topoisomerase inhibiting activity [110].

(Table 4) cont.....

S. no.	Types of Tannins	Chemistry	Structure	Biological Activities
4.	CONDENSED TANNINS	These are the oligomers of flavan-3-ols, which is linked by c–c bonds and is formed by the linkage of C–4 from a catechin molecule to a C–8 of the other molecule.		The different studies proved that they are used as adhesive materials, used in polyurethane foams also reported as adsorptive agents in heavy metals [111].
5.	PHLOROTANNINS	Structurally, they are 1,3,5-trihydroxybenzene (phloroglucinol). To form high-molecula--weight polymers, the monomers can be connected into the molecule using linear branch linkages. Such types of tannins are classified based on the availability of structural bonds found in their molecules. They are categorized into three main groups: Fucols (C–C bonds), phloroethols (C–O–C bonds), and fucophloroethols (combine C–C with C–O–C bonds) [112].		They are reported to have antidiabetic, anticancer, antioxidant, anti-HIV, antihypertensive, hyalurinidase enzyme inhibition, mettaloprotease enzyme inhibition, antiallergic, and radioprotective properties.

CONCLUSION

In this chapter, all the most abundant polyphenolic compounds with their structure-activity relationship have been discussed. As we are all aware that the molecular structures are directly related to biological activities, the activities can be modified by the structural modifications of covered natural polyphenols. The analysis of the biological effects of a chemical depends on its molecular structure. The researches have proved that polyphenols are the most promising naturally derived chemical compounds found mainly in fruits, beverages, vegetables, and cereals. The different polyphenolic compounds have been summarized in this chapter with their structures, biological sources and their structural modifications. Polyphenols are the most promising natural metabolites, which being propitious compounds for some common health problems of man and possible certain effects of aging are highly celebrated. Different reviews and data have been collected to summarize the different polyphenolic compounds. The study was aimed to

provide a detailed overview of polyphenolic compounds like phenolic acids, flavonoids, furanocoumarins, stilbenes and tannins content, their structure and relationship along with their biological activity. These compounds are used industrially in the development of various materials, fabrics, food, or medicine. Further, deeper research is needed to explore the chemistry of polyphenolic compounds.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest, financial or otherwise.

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CHAPTER 9

Biologically Active Compounds and Structure-Activity Relationship

Sunil H. Ganatra[1,*]

[1] *Department of Chemistry, Govt. Institute of Science, Nagpur, M.S, India*

Abstract: Naturally occurring compounds are found to be the most prominent and effective biological active compounds against various diseases. The majority of drugs approved between 1983 to 1994 are derived from natural products. Still today, the majority of pharmaceutical laboratories are hoping to get new drug candidates from natural resources. The traditional method of drug discovery from naturally occurring compounds has been upgraded by using advanced computer-based drug discovery.

In drug discovery, the initial efforts are to know the relationship between the biological activity of natural compounds and their chemical structures. To be precise, the method of structure-activity relationship aims to recognize the basic structural component responsible for biological activity.

The computational modeling drug discovery using various tools plays a major role in identifying the lead compounds. In this method, three major ways are utilized to understand the structure-activity relationship.

The foremost one is the Quantitative Structure-Activity Relationship (QSAR). In this method, the relationship was established using regression techniques between the 'Predictor Variable (X)' with the potency of the 'Response Variable (Y)'. The predictor variables are molecular descriptors, while the response variables represent the biological activities of the molecules against the selected diseases. If the response variable represents the chemical property, in that case, the model is called as Quantitative Structure-Property Relationship (QSPR).

The second method is called "Inhibition Studies". In this process, the designed chemical entity is docked to the targeted enzyme using docking software. The basic principle of this method is the executive competitive inhibition between the natural inhibitor and the designed chemical entity. The law of thermodynamic is used to understand the best-docked chemical entity by obtaining the value of binding energy (ΔG kcal/mole) due to the complex formation between the chemical moiety and target enzyme.

[*] **Corresponding author Sunil H. Ganatra:** Professor, Department of Chemistry, Govt. Institute of Science, Nagpur, M.S, India; E-mail: sunilganatra@gmail.com

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The third approach is very advanced and more accurate. It is called "The drug discovery using Artificial Neural Network". This is the recent technique adapted by major international pharmaceutical research laboratories. In this method, the neural network is designed and trained to identify the potent chemical compound against a particular disease. The designing of the network can be achieved using the chemical properties of a neuron, and output is related to the biological activity.

This chapter discussed all three methods in detail, along with examples. It also provides the practical procedure to use available computational tools.

The final aim of this chapter is not only to provide the theoretical background of drug discovery using structure-activity relationships but also to provide practical methods.

INTRODUCTION

Naturally occurring compounds are found to be the most prominent and effective biological active compounds against various diseases. Medicines originated from plants and other living organisms were initially used in the crude form [1, 2]. With the progress of the science and isolation techniques, the active components were isolated from natural sources and used as a drug. In the early 19th century, morphine was extracted from opium. Further advancement of techniques provided the method to isolate cocaine, codeine, digitoxin, and quinine [2, 3].

It is well documented that the drugs originated from natural products gives useful information about the possible process for the drug development. It is also reported that most drugs approved between 1983 to 1994 are derived from natural products. The importance of the drug from natural products is still at the highest rate even today, as 11% of the 252 essential drugs are originated from flowering plants. It is also reported that out of 175 cancer drugs, 85 are directly or indirectly originated from natural products.

Still today, the majority of pharmaceutical laboratories hope to get new drug candidates from natural resources. The traditional method of drug discovery from naturally occurring compounds has been upgraded by using advanced computer-based drug discovery. The major techniques are QSAR, In-Silico Docking, Molecular Dynamics, High-throughput Screening, *etc*.

The main philosophy behind computational drug discovery is to identify the structure-activity relationship between a lead compound and a target enzyme. The lead compound, also called a small molecule, has to fit into an enzyme to inhibit it.

The advanced computational chemistry and high-throughput screening help to identify the lead compound in a very short period. This also helps in getting drugs in the market quite early.

THE ORIGIN OF QSAR& QSPR

QSAR stands for Quantitative Structure-Activity Relationship and QSPR stands for Quantitative Structure-Property Relationship. These are predictive methods and uses statistical methodology to evaluate the drug-likeness of the small molecules against a particular target (generally enzyme). These methods are initially put forth by Hansch [4, 5] and then Free [6].

QSPR refers to the physical properties of the molecule, whereas, in the case of QSAR, the molecular properties are related to the biological activity of molecules using the regression analysis.

The mathematics of QSAR models is the relationship of free energy as depicted in the Hammett equation. This equation defines the relationship between dissociation constant and electronic properties of acid or bases [7 - 9].

The equation is defined as;

$$\log \frac{K}{K_o} = \rho \log \frac{K'}{K_o'} \quad \textbf{(1)}$$

In equation 1, a set of substituted aromatic acids are represented by ***K*** and ***K'.*** Unsubstituted acids are represented by $\boldsymbol{K_0}$ and $\boldsymbol{K_0'}$. ρ is the slope of the best fit line for a graph fitted to observed constant values. logK/K0 describes the substituent.

Initially, Hansch tried to formulate the QSAR models based on the Hammett parameter. This model did not provide acceptable results. Then, he accommodates other parameters such as molecular size, lipophilicity, *etc*.

The main aim of the QSAR methodology is to understand the relationship between observed properties and structural features of the molecule. In this case, one lead compound is selected, and by substituting on this leads compound, numerous molecules are grouped. This group of compounds having a common base structure is called a set of molecules. Also, the properties of these molecules are set together.

By considering a set of molecules (having various substituents and properties), a predictive model is developed using statistics. This derived model (an equation) is used to predict the possible biological activity of newly designed or synthesized molecules.

The main strategy is to convert or represent the structure of the molecular descriptors. The descriptors are nothing but the representation of molecular structure in numerical form.

The descriptors can be from simple physical properties like molecular weight or complex forms from partition coefficient, reflective index, *etc*.

Using a defined set of descriptors; a QSAR model can be built. In the QSAR model, the relationship is defined using the regression analysis between the descriptors and the biological activity.

It was Hansch who developed the first QSAR model using a linear relationship between the descriptors and biological activity. Linear models are commonly used. Nowadays, nonlinear regression and algorithmic techniques are also used to define the relationship between descriptors and molecular activities.

The recent advancement in the field of Artificial Intelligence, particularly pattern recognition and machine learning also been used to develop QSAR models [9 - 11]. The development in the QSAR modeling is achieved with the develop ment in the fields of computational algorithms, mathematics, and statistics.

COMPUTATIONAL CHEMISTRY METHODS FOR DRUG DISCOVERY

Computational chemistry, the recent developing science, helps in exploring and evaluating molecular properties. The computational techniques are generally used when it is difficult to evaluate the molecular properties in laboratories. The techniques are also used in collaboration with the experimental data to confirm the possible mathematical modeling designed for the exploration of molecular properties [11].

The computational chemistry includes Molecular modeling, Computer-aided molecular design, Chemical database, and organic synthesis design. The scope is also extended to the Computer-aided drug design.

Molecular modeling is to calculate the properties of molecules in-silico. Several properties like UV Spectra, IR spectra, dipole moments, the heat of formation, *etc*. can be calculated.

Computational chemistry, in a broad sense, can be categorized into Classical mechanics and Quantum mechanics. Molecular mechanics is a method derived from classical mechanics, where it uses the laws of classical physics. The laws are applied to molecular nuclei, where it doesn't consider the electrons.

In the case of Quantum mechanics, the Schrödinger equation is applied to describe the molecule with an explicit treatment of electronic structure. This method is divided into two classes: Ab initio and semi-empirical. Fig. (**1**) explains the branches of computational chemistry methods [10, 11].

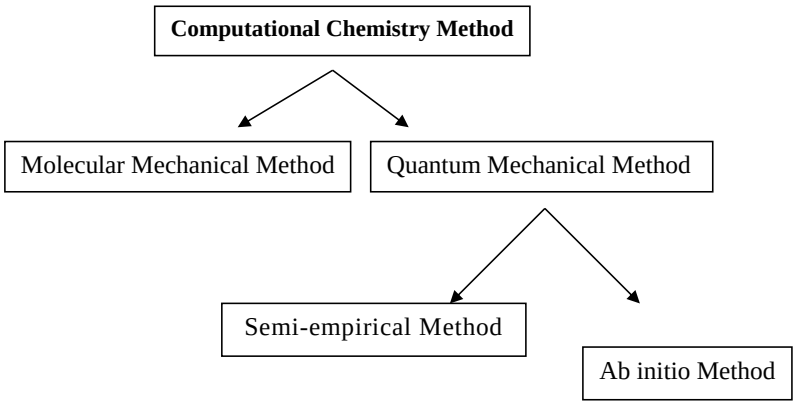


Fig. (1). Computational Chemistry Method [11].

A. Molecular mechanics

Molecular mechanics is a theoretical method to calculate the various properties of molecules, such as dipole moment, the heat of formation, *etc*. In this method, the atoms are assumed as spheres and bonds are like springs. The deformation of the spring is related to the stretch, bend, and twist of the bond as per Hooke's law. The non-bonded atoms interact using various forces like Van der Waals forces of attraction, the static force of attraction, and repulsion forces. The total potential energy is calculated using the following equation.

Potential Energy = Bending Energy + Torsion energy +Stretching Energy +Non-Bonded Interactionenergy.

In the case of structure-based drug discovery, the initial step is to design a 3-D model of a small molecule. Numbers of software are available in the market and

the majority of them use Molecular mechanics for finalizing the 3-D geometry of a molecule. The detailed theory of molecular mechanics is beyond the scope of this book.

B. Ab initio

Ab initio is a theoretical technique, which uses purely theoretical data for evaluating the properties of the system under consideration.

The ab initio calculations are executed using the computational programs to find the exact solution. It starts with the approximations with some magnitude and then using iterative techniques the approximations magnitude finally reaches a very small value. It is observed that for the small molecules, this technique gives good qualitative results with a very small number of iterations. The ab initio calculation uses huge computer memory and time, but due to advancements in the field of computer processors and memory chips, the calculations are faster and cheaper.

C. Semiempirical methods

The semiempirical method is the fastest method to evaluate the potential energy of the molecule. In this method, certain information is approximated or omitted and the error generated due to omission is corrected with parameterization. The parameters are used in curve fitting to bring the obtained results very near to the experimental data.

Semiempirical is the fastest tool to evaluate molecular properties, but sometimes it shows erratic results. It all depends on the selection of parameters of respective molecules. If the selected parameters from the database are of the same molecule which is under study, then the result may be very near to the acceptable limit, else, the obtained results may be of poor quality.

Semiempirical is widely used in organic chemistry for the calculation of geometry optimization or molecular properties. It also provides very good results for organic molecules as there are very few elements used in organic molecules and their parameterization are established with higher accuracy.

STRUCTURE-BASED DRUG DESIGN

Structure-based drug discovery is the new technique. The major problem in classical drug discovery is of time. This hurdle is removed by introducing computer-based drug discovery. Advanced computer programs are used to

understand how small a molecule is interacting with the active site of the target protein. Before learning the concept and procedure of structure-based drug design, it is wise to understand the meaning of certain keywords which are commonly used in the literature. Table **1** shows the list of certain keywords commonly used in the literature regarding structure-based drug design.

Table 1. Basic terms used in structure-based drug discovery [10, 11].

Target Molecule	**Generally the Biomolecule like DNA, Protein, or Specific Enzyme.**
Active site	The pocket of an enzyme where the reaction is taking place. Generally, the lead compound interacts with an enzyme in this pocket.
3-D structure of an enzyme	Digital 3-D structure of enzyme, protein, or DNA. The structure is identified using X-Ray diffraction or NMR techniques. The structure is available from various databanks. 3-D protein structures are deposited at http://www.rcsb.org. Also possible to get it downloaded in various digital formats. A commonly used file format is PDB.
The ligand or Small molecule or drug molecule	A molecule that inhibits the target (DNA, Protein, Enzyme).
Complex	When a small molecule or ligand interacts with the target and making complex. It is also called a ligand-receptor complex or drug-receptor complex.
Lead Compound	It is a chemical compound that shows the biological or drug-likeness property. It initiates the development of new drugs by designing the new chemical compound by substituting the functional groups in the lead molecules.

Biomolecules like DNA, proteins, or enzymes interact with small molecules to carry the functional processes. The functional site of interaction is an active site of the target compound. To study forces responsible for docking into a target site by mimicking the natural ligand is the aim of structure-based drug design [10]. Based on conformations of the ligand and their interaction with the target compound, new chemical compounds can be designed, which may have a better binding ability with the target compound.

All the drug design techniques aim to visualize the designed drug docked into the target macromolecule, also to analyze the forces involved in their interactions. Visualization and analysis can reveal the minute differences in the binding between the two successive members of series of drug compounds and the conformational changes induced in the target molecule as a result of binding [12].

3-D structure of the functional site of the receptor compound can be explored and the topographies of complementary surfaces can be studied to determine the affinity of chemical molecules. Every drug is target-specific and specificity depends upon the physiochemical properties of the drug and the receptor molecule.

The drug-receptor complex is the result of intermolecular forces exerted by the drug molecule.

Based on the architecture of the active site of the enzyme and the study of physio-chemical interactions that stabilize the complex, a new ligand with better binding affinity and shape is designed.

Structure-based drug design has already identified several drugs, which are now in the stages of clinical trials. Some of the worth mentioning inhibitors are thymidylate synthetase as an anti-tuberculosis inhibitor, thrombin-based anti-coagulants, Ace inhibitors, HIV protease inhibitors, *etc*.

A. In-silico drug discover

In-silico drug design is the technique, where receptor biomolecule is inhibited with small molecule using a computer-based model system. Inhibitor-based design depends on the architecture of the active site of the target biomolecule.

In this technique, the 3-D structure of the receptor is used as a target, and a library of small molecules is subjected to inhibit the target using computer software [11]. The score function is calculated using semi-empirical or *ab initio* equations. The score function provides information about the best-suited molecules to inhibit the target compound.

The success of the in-silico drug design is due to the crystallography and NMR techniques, which can elucidate the unknown geometry of the target receptor. Also, several computer-based software which helps in inhibiting small molecules to the target receptor. Commonly used drug discovery computer programs (software) are listed in Table **2**.

Table 2. Software available for drug discovery.

Name	Description	References
AutoDock	Ligand – Protein docking.	[12,13]
Schrodinger	Ligand-receptor docking.	[14,15]
GOLD	Protein-ligand docking.	[16,17]
BioSuite	Genome analyzing and sequence analyzing	[18,19]
Maestro	Molecular modeling analysis	[20,21]
ArgusLab	Molecular docking calculations and molecular modeling package	[22,23]
GRAMM	Protein-protein docking and protein-ligand docking	[24,25]
SYBYL-X Suite	Molecular modeling and ligand based design	[26,27]

(Table 2) cont.....

Name	Description	References
Sanjeevini	Predict protein-ligand binding affinity	[28,29]
PASS	Create and analysis of SAR models	[30,31]

B. Stages Involved in Structure-based Drug Design

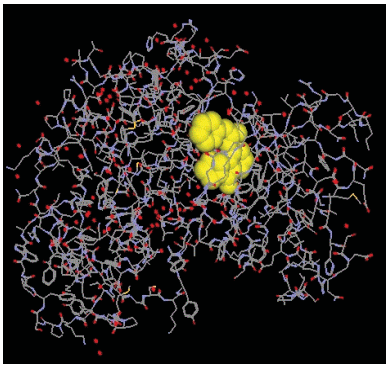
The structure-based drug design is a procedural method. The procedure depends on the software used for the docking. Following are the common steps that need to be executed [32].

The first step is to identify the site of action of the drug on the receptor (biomolecule). The details of the active site like domain structure, secondary and tertiary structural arrangements, and loop architecture give the constitution of the active site. Similarly, the ionic, hydrophobic, and solvent interactions are also understood.3-D structures of biomolecules are available from the online database. A few among them are Protein databank (PDB) [32 - 34], Structural classification of protein (SCOP), Swiss-model, ModBase, *etc*.

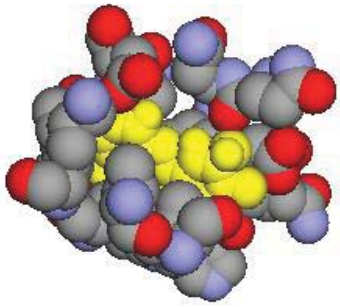
From these databases, the 3-D crystal structure of the biomolecule can be downloaded. Generally, this file is in PDB format (electronic file extension). This file may contain certain information which is required to be corrected before executing the next step. The general procedure is to remove all water molecules and hetero-atoms from this file.

Once the PDB file is corrected, it is advisable to sort out the active site. This is the location or motif where drug molecules will interact. The easiest way is to find out the natural inhibitor in this 3-D file. The location of the natural inhibitor is treated as the active site of the target biomolecule. This task can be executed with the help of drug discovery software. The advanced software automatically searches this location, whereas, in the case of amateur software, a user has to sort it out [35].

Fig. (**2**) shows the 3-D structure of Cyclin Dependent Kinase (CDK4) (PDB Code: 1GII) having 1-(5-oxo-2,3,5,9b-tetrahydro-1h-pyrrolo[2,1- a]isoindol-9-yl)- 3-pyridin-2-yl-urea as a natural inhibitor [36].



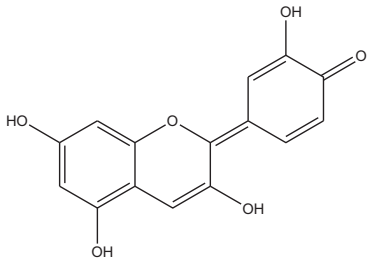
a. 3-D structure of CDK4 (PDB Code: 1GII) inhibited with natural inhibitor



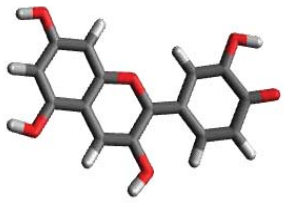
b. Cyanidin ($C_{15}H_{10}O_6$) is docked with CDK4.

Fig. (2). CDK4 enzyme is docked with Cyanidin (Naturally occurring compound) [36].

The second step is to identify a potent pharmacophore or a lead compound that can bind to the active site of the target molecules in competition with a biologically available protein inhibitor (Natural inhibitor). A lead compound can be selected by screening available libraries of compounds or designing compounds using the software. The market is flooded with numerous software helping in the design of new chemical compounds. A few among them are ChemDraw, ChemSketch, *etc*. Fig. (**3**) shows the 2-D and 3-D structure of Cyanidin designed using ChemDraw.



2-D structure of Cyanidin ($C_{15}H_{10}O_6$)



3-D structure of Cyanidin ($C_{15}H_{10}O_6$)

Fig. (3). 2-D and 3-D structure designed using ChemDraw and Chem3D software [36].

The third step is the process of docking of ligand into the active site of a target compound. For this purpose number of software are available. Table **2** shows the list of software that can be used for docking.

The docking is a process where the ligand is subjected to interact with the target biomolecule. The computer algorithm finds the best possible confirmation where the complex of ligand and biomolecule has minimum binding energy.

The essential condition for docking is that the selected ligand should possess the appropriate geometry to fit into the active site with minimal steric interactions. Favorable interactions of the chemical groups between the ligand and the active site of the biomolecule should be achieved [37, 38].

All the docking procedures carry out systematic searches in rotational and translational space and evaluate the electrostatic, hydrophobic, and hydrogen binding energy terms to achieve the best fit of the ligand. The procedures optimally position the ligand into the binding site and update the energy terms. The output of the docking is the binding energy (ΔG) of the ligand-receptor complex. The ligand showing the minimum binding energy is selected to proceed further [38].

To calculate the binding energy, the algorithm uses force field equations and parameters. The obtained binding energy (ΔG) is the total intermolecular interactions, including Van der Waals interaction, H- bonding interaction, electrostatic interaction, and internal static energy of the ligand. The equation is represented in equation number 2 [39 - 41].

$$\Delta G_{bind} = \Delta G_{vdw} + \Delta G_{hydrophobic} + \Delta G_{H\text{-}bond} + \Delta G_{H\text{-}bond(chg)} + \Delta G_{deformation} + \Delta G_0 \quad \text{---(2)}$$

The docking result of Cyanidin as ligand with CDK4 as a receptor is shown in Fig. (**4**). Cyanidin is inhibiting CDK4 in the place of a natural inhibitor. This docking was performed using Autodock 4.0.

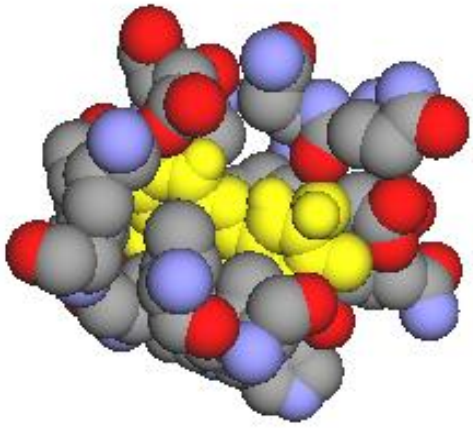


Fig. (4). Cyanidin ($C_{15}H_{10}O_6$) is docked with CDK4 [36].

Table **3** shows the docking results of a few naturally occurring phenol compounds with CDK4 (PDB). The docking was performed using Autodock 4.0 [41]. Non-GA docking results are obtained using non-genetical algorithm whereas the GA docking results are obtained using the genetical algorithm.

Table 3. List of the observed binding energy of phenol-based ligands with 1GII [42].

S. No.	Phytochemical Name	Binding Energy (ΔG) in Kcal/Mol	
		Non-GA Docking	GA Docking
1	Apigenin	-9.96421	-10.5197
2	Baicalein	-10.176	-9.87955
3	Caffeic acid	-9.1941	-9.41513
4	Catechin	-10.1547	-10.4344
5	Chrisyn	-10.4538	-10.4848
6	Cyanidin	-10.0583	-10.7608
7	Daidzein	-9.99772	-11.0058
8	Diosmin	*	-10.5989
9	Ellagic acid	*	-9.54558
10	Emodin	-10.6053	-11.0401
11	Epicatechin	*	-9.82822
12	Epigallocatechin	*	-9.37263
13	Ferulic acid	-8.24349	-8.17937

(Table 3) cont.....

S. No.	Phytochemical Name	Binding Energy (ΔG) in Kcal/Mol	
14	Galangin	-14.5898	-9.37035
15	Genistein	-9.34919	-9.3656
16	Hesperidin	*	-9.32745
17	Hydroxytyrosol	-8.65557	-9.35591
18	Kaempferol	-9.69367	-9.26569
19	Luteolin	-9.74437	-9.85704
20	Myricetin	-9.21467	-10.7346
21	Naringenine	-9.96618	-10.5528
22	Phloretin	-10.9983	-10.65
23	Quarcetin	-9.89271	-8.6555
24	Resveratrol	-11.0243	-10.5651
25	Rosmoric acid	-12.497	-12.011
26	Rottlerin	-10.8003	-13.9986
27	Rutin	*	-9.87545
28	Xanthohumol	-11.3567	-9.81086
* No result.			

DRUG DISCOVERY USING ARTIFICIAL NEURAL NETWORK

An artificial neural network(ANN) is a recent tool used in predicting the biological activities of molecules. ANN uses the available information related to the subject under study and provides the trained network. This trained network is used for the prediction of molecular properties or activities against a selected object.

The working process of ANN is just like the biological nervous system. In a biological system, such as the brain, there is a network of neurons responsible for the flow of information. ANN has also utilized the artificial network of neurons to flow the information [43].

ANN learns by example. It cannot predict without any learning process. Hence the first step in ANN is to train the network with known data. This process is called Network Training.

The training is for the specific application. Once the network is trained, it can be used to predict the properties in the domain of the application for which it is trained.

ANN is utilized to derive meaning from complicated data. The complex trends and patterns can be detected by ANN [44].

Once ANN is trained for a particular application, it can be used to predict the possible results by giving a new situation of interest [45].

Following are a few advantages of ANN

- Adaptive learning: Ability to learn from the given set of data for training
- Self-organization: ANN in process of learning creates its organization or representation of the information.
- Real-time operation: The training of the network and further use of the network can be carried out using a desktop computer. It is also possible to design special electronic hardware for the specific ANN task.

The architecture of Neural Network

A typical neural network has the following parts;

- Input layer
- Hidden Layer
- Output
- Neuron
- Connector

Fig. (**5**) depicts the simplest neural network. This network contains two layers. The first one is the input layer having three neurons. The second layer is the hidden layer contains two neurons. The first layer is also called the input layer. This layer receives the input from the system and delivers it to the hidden layer. In a hidden layer, each neuron receives the information from all input neurons. These inputs are 'weighted'.

Generally, a pre-set threshold value is set, which is used as a reference parameter for the forwarding of information from one layer to another. If the weighted input crosses the threshold value, then the information is passing onto the next layer. The algorithm to pass the information from one layer to other using weighted values may be very simple or may use complex mathematics. It all depends, how users design and define the ANN?

If the weighted input is not crossing the threshold value of a neuron, then the neuron does not send information to the next layer. In mathematical terms, the neuron fires only if X1.W1+X2.W2+X3.W3>Pre-set threshold Value as depicted

in Fig. (**5**). The neural network may be as simple as shown in Fig. (**5**) or may have a quite large number of neurons in each layer. A certain network may have more than one hidden layer and that depends on the complexities of the problem that needs to be solved [44, 45].

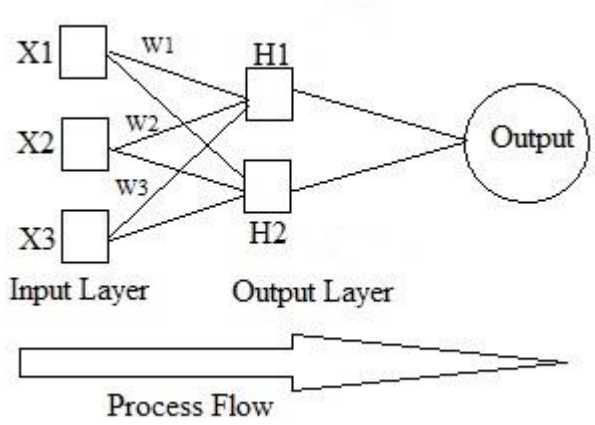


Fig. (5). A typical artificial neural network. [46].

While training the network, the final output is matched with the sample data. If it deviates then the weight of each neuron change using a specific function. This cycle continues until the network produces the desired output. The training of the network ends once the output matches with sample data with allowable standard deviation. The adaptive neural networks can be classified into two major categories depending on the way networks are being trained [47].

Supervised learning: In this method, the output is matched with the desired value. On comparing the obtained output with the desired output, the next step of learning decides. So between each cycle of learning, a watch process is set to understand whether the obtained output is matching with the desired output. The process of learning stops when the obtained output is matching with the desired output. Supervised learning includes error-correction learning, reinforcement learning, and stochastic learning.

Unsupervised learning: In the case of Unsupervised learning, the data are self-organized. The process of organization is based on local information.

In this case, the weight of each neuron is not changed. The point that needs to remember is that the trained network will work for the same domain of problem

with the same type of input and expected output. Any deviation in the input parameter will require another trained network.

ANN experimental technique to map novel drug

The stepwise process of using ANN to map novel drugs is as follows:

- Select the list of existing drugs against a particular disease (For example, list of existing anti-cancer drugs)
- Prepare Molecular Electrostatic Potential of each drug using computer software
- Find out 12 points auto-correlation function
- Apply autocorrelation function to ANN
- Train the network
- Use this train network for the selection of unknown compounds as a novel drug against target disease.

In the case of the Auto-correlation function, molecular properties can be used for network training. The selection of molecular properties can be extracted using QSAR.

Another method is to use Kohonen neural network. This is a pattern recognition neural network. In this case, surface properties are used. For example, charge density can be used as an input pattern.

In this case, the pattern of the surface density of know drugs is supplied to the Kohonen network for training. Once the network is trained, the resultant pattern is used to identify the drug-likeness of the unknown molecule.

In the case of drug discovery, ANN can be used as a tool for predicting the novel drug. The simple process is explained here for anti-cancer drugs [47, 48].

- Select the list of anti-cancer drugs having certain common geometry. For example Alkylating antineoplastic agent.
- List the common properties along with biological activity against cancer cells.
- Apply these properties as a parameter to the backpropagation neural network and generate a trained network.
- Use this trained network for the selection of unknown compounds as an anti-cancer agent.
  In the case of the Kohonen neural network, generate the MEP of each compound.
- Supply this MEP to the Kohonen neural network and generate the common pattern.
- Use this common pattern to screen a new anti-cancer agent (Fig. **6**).

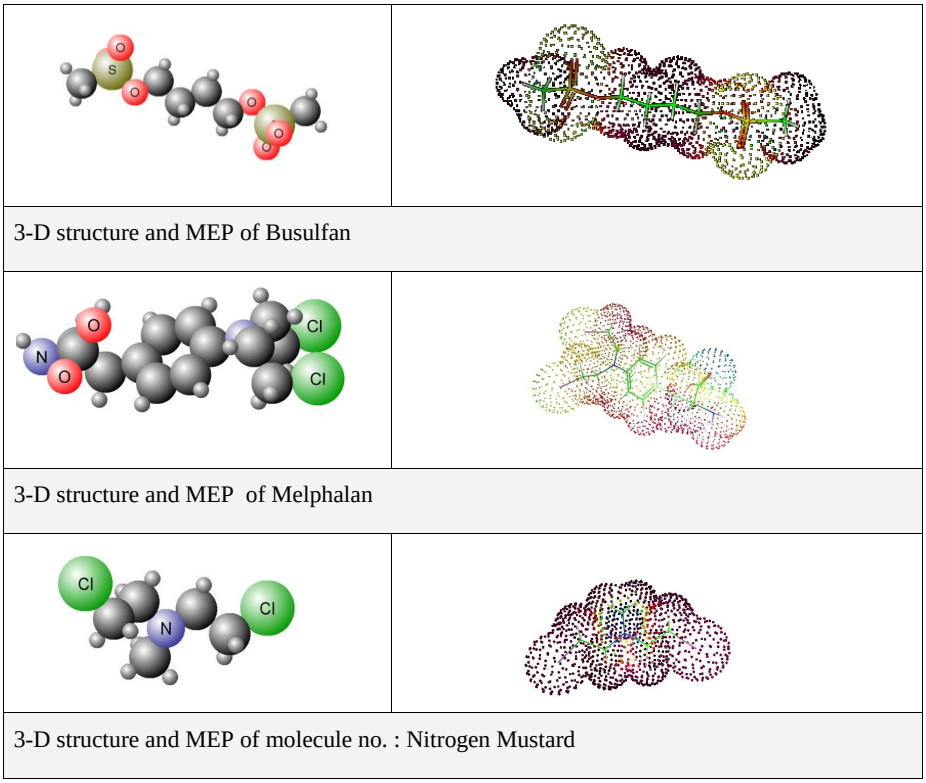


Fig. (6). 3-D structure and Molecular electrostatic potential of anti-cancer alkylating agents [46].

The Kohonen pattern of anti-cancer alkylating agents Busulfan, Melphalan, and Nitrogen Mustard were generated using SONNIA 4.2. Figure 7 shows the individual pattern of each molecule as well as an average pattern of all studied molecules. The average pattern can further be used to predict the anti-cancer activity in new molecules.

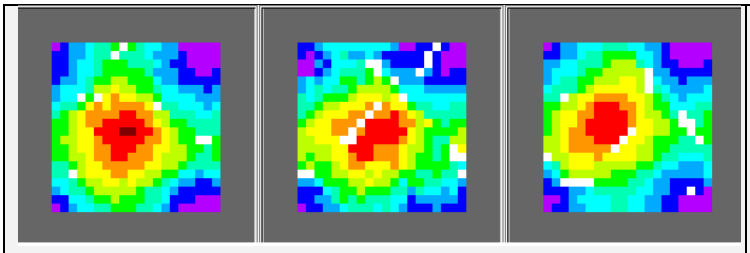
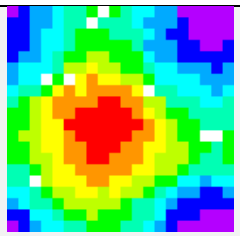
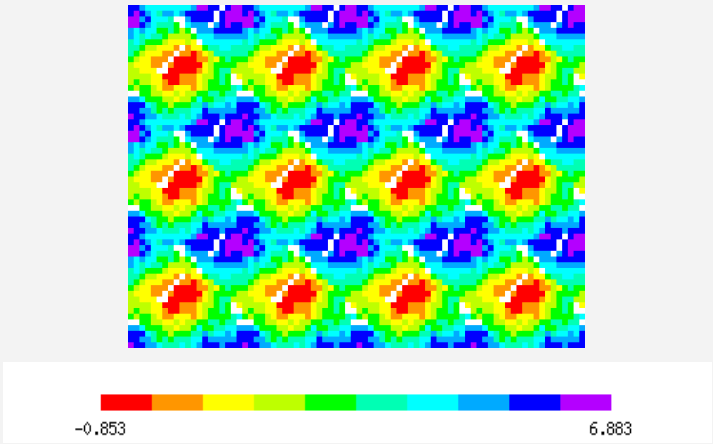
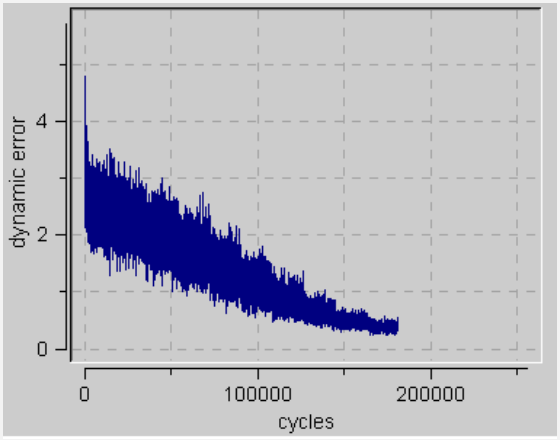
<table>
<tr><td>  </td><td>  </td></tr>
<tr><td>Kohonen Patterns of molecule Busulfan, Nitrogen Mustard and Melphalan</td><td>Average Pattern of anti-cancer alkylating agents drugs molecules</td></tr>
<tr><td> 
</td><td>Multi-layer Kohonen pattern of one of the molecules The pattern is in Multi-layer format and the selection is average hit neurons. The color scheme scale is as follows. The scale depicting the magnitude of MEP over the surface of molecules.</td></tr>
<tr><td> 
</td><td>While training the error decreases as the number of cycles of training increases. Above figure depicting the error graph of one of the series of molecules trained for the Kohonen network.</td></tr>
</table>

Fig. (7). Kohonen patter of the individual and average pattern obtained using Kohonen network [46].

Numbers of computer software are available in the market to perform drug discovery using ANN. A few among them are SONNIA, Neural Designer, Darknet, Keras, *etc*.

Structure plays a vital role in acquiring the drug-likeness properties against a particular target. Knowledge of structure-function relationships provides the easiest path for designing novel drugs. For example, the majority of cancer drugs are originated from natural sources and their basic structure is of Di-terpene or Tri-terpene [49].

Flavonoids are very effective in preventing lipid peroxidation, whereas lipid peroxidation is caused by various diseases such as hepatotoxicity, inflation, atherosclerosis, diabetes, and aging [50].

Naturally occurring compounds play a vital role in managing human health. There is hardly any disease, which cannot be cured using the naturally occurring compound. There are still numerous compounds in nature, which are not explored for their drug-likeness properties. The structure-based drug discovery surely will help in providing unique drugs for each possible disease.

CONCLUSION

The drug discovery process has evolved with the progress of computer sciences. The technology of identifying the lead compound has matured and is widely used in a commercial establishment. The major techniques are Quantitative Structure-Activity Relationship (QSAR), Docking, MD simulation, and Artificial Neural Network.

Nature is the main source of obtaining novel drug molecules for various diseases. Numbers of new drug molecules are obtained from nature. This is possible due to the understanding of the structure-function relationship of the chemical compound obtained from nature.

The progress of computer algorithms helped in developing new state-of-art techniques to screen and identify novel drug molecules. The popular techniques are QSAR, Docking, MD Simulation, Artificial Neural Network (ANN), *etc* . These techniques are very much helpful in identifying the novel drug molecule in a very short time.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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CHAPTER 10

Turmeric Supplementation and Its Valued Clinical Connections

Pankaj Kumar Chaurasia[1,*], Shashi Lata Bharati[2,*], Sunil Kumar[3] and **Ashutosh Mani[4]**

[1] *P.G. Department of Chemistry, L.S. College (A Constituent Unit of B.R.A. Bihar University) Muzaffarpur-842001, Bihar, India*

[2] *Department of Chemistry, North Eastern Regional Institute of Science and Technology, Nirjuli (Itanagar), Arunachal Pradesh-791109, India*

[3] *Department of Chemistry, L.N.T. College (A Constituent Unit of B.R.A. Bihar University) Muzaffarpur-842002, Bihar, India*

[4] *Department of Biotechnology, Motilal Nehru National Institute of Technology Allahabad, Prayagraj-211004, Uttar Pradesh, India*

Abstract: Turmeric (*Curcuma longa*) does not require any introduction for its benefits because it is an extremely renowned spice and cooking material of Indian kitchens. It has a valuable place in Ayurveda for its crude medicinal values. In India, it also has a sacred position in festivals, worships, and wedding ceremonies. For a long time, it is being used as an important ingredient in different Asian dishes and has a significant position in the cooking spices. Except for its valuable uses as a spice, it is known for its role in wound treatment, anti-inflammatory and anti-oxidant, pain relief, anti-cancer, and so on. It is being used for a long time with several expectations of its great health benefits, but there is still no concrete research that proves its heavy potency towards the treatment of any serious disease. Although it is not so potent individually for the treatment of any serious health issues, its supplemental values must be encouraged, and more research is essential to be done on it. This chapter concisely demonstrates the significance of turmeric in the treatment of various health issues and its role in food supplements.

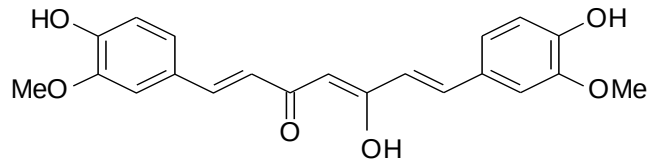
Keywords: Anti-inflammatory, Antioxidant, Arthritis, Curcumin, Indigestion, Spice, Traditional medicine, Turmeric, Wound healing.

[*] **Corresponding authors Pankaj Kumar Chaurasia and Shashi Lata Bharati**: P.G. Department of Chemistry, L.S. College (A Constituent Unit of B.R.A. Bihar University) Muzaffarpur-842001, Bihar, India; and Department of Chemistry, North Eastern Regional Institute of Science and Technology, Nirjuli (Itanagar), Arunachal Pradesh-791109, India; Email: pankaj.chaurasia31@gmail.com and shashilatachem@gmail.com

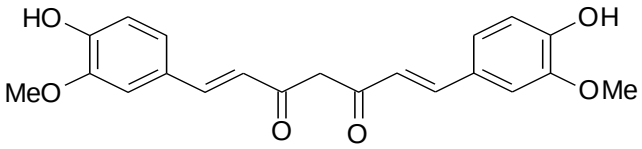
INTRODUCTION

Turmeric does not require any special introduction. It is a renowned name in the field of traditional medication and Ayurveda. It plays an integral part in Indian kitchens for its use as a valuable spice. It is beneficial in curing various human problems and improving human health. Turmeric is famous in Ayurveda for its role in controlling and balancing the Vata, pitta, and kapha, and has useful effects on the blood and plasma of the circulatory system. It is highly helpful in the treatment of cough-related problems as well as in toxins removal. It is known for its good inflammatory properties, wound healing properties, antiseptic and antibacterial properties, arthritis problems, indigestion problems, beneficial for the brains, and so on (https://maharishiayurvedaindia.com/blogs/ayurveda-knowledge-center/countless-benefits-of-turmeric) [1]. Turmeric is related to the Zingiberaceae (ginger family), generally known as *Curcuma longa,* and its roots are used in cooking [2]. It is a perennial, rhizomatous, and herbaceous plant native to the Indian subcontinent and Southeast Asia (https://en.wikipedia. org/wiki/Turmeric) [3].

Turmeric is used in the kitchen for coloring and flavoring the food by drying and grounding its rhizome in the form of yellow-orange powder. It is significantly being used in Ayurveda, Siddha medicine, Traditional Chinese Medicines, Unani [4], and other traditional/folk medications. Turmeric was also known as Indian saffron in Medieval Europe [5]. Curcumin, a biologically and pharmaceutically active molecule of turmeric, is responsible for its beautiful golden yellow color. It generally exists in keto and enol forms and is the main curcuminoid of turmeric (https://en.wikipedia.org/wiki/Curcumin) [3b]. Fig. (**1**) shows the chemical structure of keto and enol form of curcumin, a biologically active component of turmeric [3b].



Curcumin (Enolic form)



Curcumin (Keto form)

Fig. (1). Enol and Keto forms of the biologically active compound 'curcumin'.

Recent Research Updates

Although turmeric is known for its attractive color, its wide use in food for enhancing color and flavor, its nutraceutical virtues, and its use as traditional and folk medications, there are not many scientific proofs, which can prove its strong role in the cure of human problems. However, at a supplemental position, research strongly supports its clinical uses.

A good mechanistic review has been presented by Ahmad *et al*. (2020) [6] on biochemistry, safety, pharmacological activities, and clinical applications of turmeric. They have summarized the scientifically known studies on the aforesaid title. They reviewed the pharmaceutical roles of turmeric as its anti-inflammatory, anti-oxidant, anti-cancer, anti-mutagenic, anti-microbial, anti-obesity, hypolipidemic, cardio-protective, and neuro-protective effects and showed that due to these pharmaceutical roles of turmeric, it is a great spice for future research [6].

Rathore *et al*. (2020) [7] reviewed curcumin and its many benefits for health as well as its different biological activities such as anti-inflammatory, anti-oxidant, anti-arthritis, anti-cancer, wound-healing, anti-bacterial, anti-viral, in depression, anti-diabetic, anti-venom, anti-obesity, anti-asthmatic, and other. Observations of different clinical trials, various roles, and activities of curcumin have been discussed in this review [7].

An informative page on the title "Curcumin is the spice of life when delivered *via* tiny nanoparticles: Treatment for Alzheimer's and genital herpes" shows the

significance of curcumin (www.sciencedaily.com/releases/2020/03/20030513 2144.htm) [8].

Vitali *et al*. (2020) [9] presented a very informative work on curcumin with the title "Curcumin Can Decrease Tissue Inflammation and the Severity of HSV-2 (Herpes Simplex Virus Type 2) Infection in the Female Reproductive Mucosa". They investigated whether curcumin, encapsulated in nanoparticles and delivered by various *in vivo* routes, could minimize inflammation and prevent or reduce HSV-2 infection in the Female Genital Tract. Their result suggested that curcumin nanoparticle delivery in the vaginal tract could reduce local tissue inflammation [9].

Zahedipour *et al*. (2020) [10] wrote a review in order to show the effective role of curcumin in the cure of infections caused by COVID 19, which is acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with considerable mortality worldwide. In this infection, symptoms produced are mostly related to a respiratory system such as the lungs. In this review, they have given an overview of the antiviral effects of curcumin, which can modulate a range of molecular targets, which is the reason behind its possible efficacy for the cure of this pandemic [10].

A review article written by Sharif-Rad *et al* . (2020) [11] deals with the role of turmeric and its main constituent 'curcumin' on health, considering their bioactive effects, safety profiles for food, pharmaceutical, and biotechnological applications. They have an in-depth discussion on curcumin for its food and biotechnological applications with its potential role in health and disease cure has a special emphasis on its biological activities like anti-inflammatory, anti-oxidant, anti-cancer, neuroprotective, hepatoprotective, and cardio-protective effects. They have also covered the multidimensional role of curcumin, agro-industrial procedures to offset its instability and low bioavailability, food attractiveness optimization, upcoming strategies for clinical application, and health concerns [11].

A review has been written by Stohs *et al*. (2020) [12] on highly bioavailable forms of curcumin and promising avenues for curcumin-based research and application in which they have discussed formulations designed to enhance the bioavailability, metabolism of curcumin, relationships between solubility and particle size relative to bioavailability, human pharmacokinetic studies involving formulated curcumin products, the widely used but inappropriate practice of hydrolyzing plasma samples for quantification of blood curcumin, current applications of curcumin and its metabolites, and promising directions for health maintenance and applications [12].

Shanmugarajan *et al*. (2020) [13] performed computational modelling, simulations, and ADMET studies to explore curcuminoids against novel SARS-CoV-2 targets. Bioactive ingredients (curcuminoids) present in *C. longa* are known for their different pharmacological properties, and fourteen curcuminoids were studied with the possibility of their role in SARS-CoV-2 inhibition. They performed a study on their *in-silico* properties towards SARS-CoV-2 target proteins by homology modelling, ADME, drug-likeness, toxicity predictions, docking molecular dynamics simulations, and MM-PBSA free energy estimation. This study shows that surface proteins are key drug target proteins of SARS-Co--2, and probably curcumin blocks essential biologically active drug target residues, thereby attenuating the viral infection.

Fadus *et al*. (2017) [14] wrote a review on tile "Curcumin: An age-old anti-inflammatory and anti-neoplastic agent" in order to demonstrate the various pharmacological roles of curcumin, a biologically active compound of turmeric, which has a valued role in the cure of chronic conditions like **rheumatoid arthritis**, **inflammatory bowel disease**, Alzheimer's, and common malignancies like colon, lung, stomach, skin, and breast cancers. In this review, they showed the scientific information on the medicinal role of curcumin (the "curry spice") and identified the current gap [14]. A review on the mechanism of anti-inflammatory effects of curcumin was written by Jacob *et al*. (2007) [15], in which they very finely highlighted the anti-inflammatory role of curcumin. The beneficial effect of curcumin in sepsis appears to be mediated by the up-regulation of PPAR-γ (peroxisome proliferator-activated receptor-*γ*), leading to the suppression of pro-inflammatory cytokine, TNF-α expression, and release [15].

There are also a number of other research in the field of turmeric and curcumin and their clinical applications, but only a few recent reports have been summarized in this chapter in order to show the potency of turmeric and its constituent curcumin in the medicinal field. For more information and research updates on turmeric and its uses in the pharmaceutical application, the reader can also visit the works of Kim *et al*. (2020) [16] and Kocaadam & **Şanlier** (2017) [17]. There are other different articles that may be useful for readers [18 - 22]. A page showing ten important benefits of turmeric use can also be visited (https://www.healthline.com/nutrition/top-10-evidence-based-health-benefits-of-turmeric) [23].

CONCLUSION

In this way, the aforementioned studies on the pharmaceutical role of turmeric and its biologically active organic molecule 'curcumin' clearly demonstrate the great significance of turmeric in solving various human health issues. Although it is not

a perfect medication, individually, its role as great supplemental food should be encouraged, and scientific research works should also be encouraged in order to search out its major valuable roles in treating the different types of health-related issues as well as in the purification of the human system for saving the human from various problems and enhancing their immunity.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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Pankaj Kumar Chaurasia

Pankaj Kumar Chaurasia, Ph.D. (Editor 1) is presently working as an Assistant Professor in the P.G. Department of Chemistry, L.S. College, B.R.A. Bihar University, Muzaffarpur. He has experience of teaching Post Graduate (PG), Under Graduate (UG) as well as I.Sc students. He has a strong academic as well as research career. He has qualified 'National Eligibility Test (NET)' in 2009 as CSIR-JRF (NET) and was awarded with SRF-NET in 2012. He received his 'Ph.D. degree' in 2014. He has worked as 'Guest Faculty' (2016-2017) in the Department of Chemistry, University of Allahabad, Prayagraj (A Central University of India). He has been awarded 'Research Associateship' by CSIR-New Delhi (India) in 2017 and after it, he worked as CSIR-RA in Motilal Nehru National Institute of Technology (MNNIT), Allahabad/Prayagraaj (India). He is highly engaged in teaching as well as research works. Presently, he is supervising four Ph.D. research scholars. He has more than 50 publications (Books/papers in Journals/ papers as book chapters in edited books) with international journals/publishers of repute. He has expertise in wide research areas viz., biological chemistry, biotechnology, microbiology, enzymology, organometallic chemistry, bioorganic chemistry, and environmental chemistry.

Shashi Lata Bharati

Shashi Lata Bharati, Ph.D. (Editor 2) is presently working as an 'Assistant Professor' in the 'Department of Chemistry, North Eastern Regional Institute of Science and Technology, Nirjuli, Arunachal Pradesh (India). She has guided many M.Sc. project students and presently, she is supervising a Ph.D. research scholar. She has a good academic as well as research career. She was awarded 'UGC-DSA fellowship' for the meritorious students during her Ph.D. program. She obtained her Ph.D. degree in 2012 in 'Chemistry'. She was awarded UGC-post doctoral fellowship for women in 2013 and worked as 'Post-Doctoral Fellow' in the 'Department of Chemistry' of DDU Gorakhpur University, Gorakhpur (India). Along with academic works, she is also interestingly involved in research works. She has guided many M.Sc. project students and also supervised a Ph.D. research scholar. She has 40+ publications (Books, journals papers, and papers as chapters in edited books) in national and international journals/publishers of repute. She has expertise in the field of inorganic chemistry, organometallic chemistry, biological chemistry, environmental, and enzymology.