

THE CHEMISTRY INSIDE SPICES & HERBS: RESEARCH AND DEVELOPMENT



Editors:
Pankaj Kumar Chaurasia
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The Chemistry inside Spices & Herbs: Research and Development

(Volume 1)

Edited by

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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.

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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 Fayeze *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.

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CHAPTER 1

Spices Biotechnology: Opportunities and Challenges

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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 studied 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.

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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 nigrum* and *Piper cubense* 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*

CHAPTER 2

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

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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

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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	<i>Escherichia. coli</i> , <i>Salmonella species</i> , <i>Citrobacter</i> , <i>Enterobacter</i> , <i>Pseudomon</i> , <i>Klebsiella</i> , <i>Streptococcus</i> , <i>Bacillus anthrax</i>	[6]
2	Ginger	Gingerol, Zerumbone, Zingerone	<i>Porphyromonas gingivalis</i> , <i>P. endodontalis</i> , <i>Prevotella intermedia</i>	[7]
			<i>Pseudomonas aeruginosa</i> , <i>Salmonella choleraesuis</i> , <i>Bacillus subtilis</i>	[8]
			<i>Bacillus cereus</i> , <i>Staphylococcus aureus</i> , <i>E. coli</i> , <i>Yersinia enterocolitica</i>	[9]
3	Tumeric	Curcuminoid, Turmerone, Curlone	<i>E. coli</i> , <i>S. aureus</i> , <i>Salmonella typhi</i>	[10, 11]
			<i>B. cereus</i> , <i>Bacillus coagulans</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	[12]
4	Thyme	Thymol	<i>B. subtilis</i> , <i>Salmonella enteritidis</i> , <i>P. aeruginosa</i>	[13]
5	Clove	Eugenol	<i>P.aeruginosa</i> , <i>S. aureus</i> , <i>S. choleraesuis</i> , <i>Klebsiella pneumoniae</i>	[13]
6	Cinnamon	Cinnamaldehyde, eugenol, cinnamic acid, cinnamate	<i>P.aeruginosa</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>Bacillus megaterium</i> , <i>K. pneumonia</i> , <i>Enterobacter cloaca</i> , <i>Corynebacterium xerosis</i> , <i>Streptococcus faecalis</i> , <i>S. typhi</i> , <i>Pseudomonas fluorescens</i> , <i>Bacillus licheniformis</i> , <i>Y. enterocolitica</i> , <i>Proteus spp.</i>	[14]
7	Cardamom	1, 8-cineole, α -terpinyl acetate, linalool	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Bacillus pumilus</i>	[15]
8	Pepper	Piperine, terpenes, phenols	<i>S. typhimurium</i> , <i>Bacillus</i> , <i>E. coli</i> , <i>S. aureus</i>	[16]
9	Cumin	Cuminaldehyde, cymene, terpenoids	<i>E. coli</i> , <i>S. aureus</i> , <i>S. faecalis</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>B. megaterium</i> , <i>Brevibacillus brevis</i> , <i>Enterococcus faecalis</i> , <i>Pseudomonas pyocyaneus</i>	[17]
10	Basil	Linalool, estragole, eugenol, 1,8-cineole	<i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>Pasteurella multocida</i>	[18]

CHAPTER 3

Spices and Herbs in the Treatment of Neurobiological Disorders

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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-

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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

CHAPTER 4

Spices and Herbs in Bacterial and Fungal Resistance

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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

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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 spices. 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.

CHAPTER 5

Naturally Isolated Compounds from Spices and Herbs and their Medicinal Uses

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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

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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).

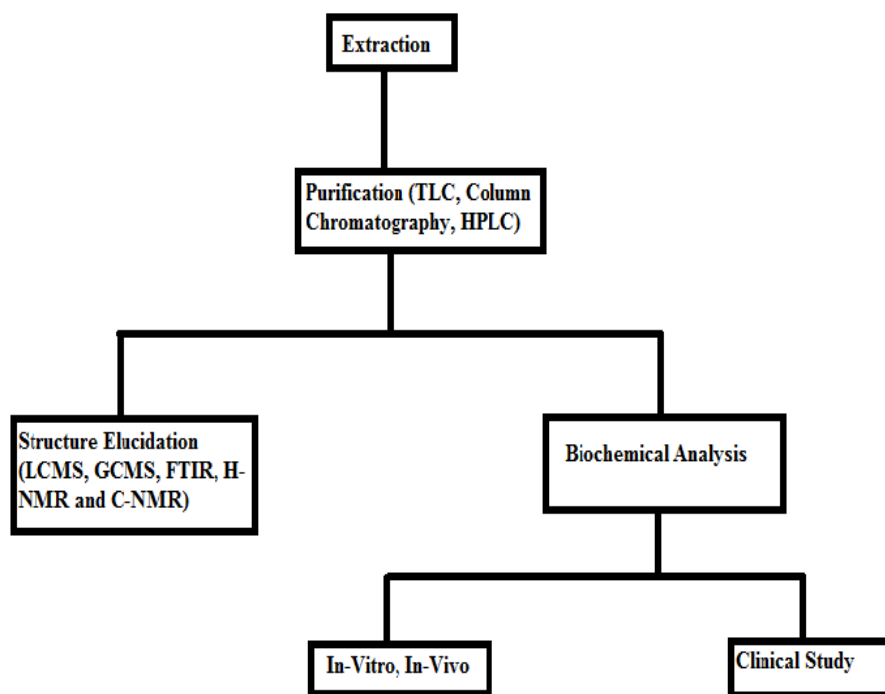


Fig. (1). A brief summary of the general approaches in extraction, isolation, and characterization of a bioactive compound from plant extracts [8].

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 (<i>Dalchini</i>)	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, <i>etc.</i>

CHAPTER 6

Naturally-derived Analgesics and Anti-Inflammatory Agents

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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-I)-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,

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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- κ B, 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.
<i>Acanthus ilicifolius</i> Linn.	<i>In vivo</i> analgesic effect for the chloroform and petroleum ether fractions <i>In vitro</i> antioxidant activity	[8]
<i>Ajuga laxmannii</i> (Murray) Benth.	Inhibition of phagocytosis and decreasing the total leukocytes <i>in vitro</i> <i>In vitro</i> antioxidant activity	[9]
<i>Anadenanthera colubrina</i> var. <i>cebil</i> (Griseb.)	<i>In vivo</i> 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]
<i>Asphodelus microcarpus</i> Salzm. & Viv.	Strong antioxidant capacity Reduction of the <i>in vivo</i> paw and ear edema induced by carrageenan and xylene	[11]
<i>Athyrium multidentatum</i> (Doll.) Ching	Decreased the expression of iNOS and COX-2 enzymes Downregulation of the <i>in vitro</i> and <i>in vivo</i> mRNA expression of IL-6, IL-1 β , and TNF- α	[12]
<i>Backhousia citriodora</i> (Lemon myrtle)	Antioxidant properties Reduction of IL6, TNF- α , and NO levels	[13]

(Table 3) cont....

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

CHAPTER 7

Phenolic Compounds and their Biological and Pharmaceutical Activities

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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

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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 (naphthoquinones), C6-C1-C6 (xanthenes), C6-C2-C6 (stilbenes, resveratrol, anthroquinones), C6-C3-C6 (flavonoids, isoflavonoids, isoflavones, flavanones, anthocyanidins, apigenin, (+)-catechin, (-)-epicatechin, cyanidin, daidzein, delphinidin, erodictoyl, Isorhamnetin, genistin, glycitin, hesperetin, kaempferol, luteolin, malvidin, myricetin, narengenin, pelargonidin, petunidin, peounidin, quercetin), (C6-C3)₂ (lignans, neolignans, lariciresinol, matairesinol, medioresinol, pinoresinol, secoisolariciresinol), (C6-C3-C6)₂ (bioflavonoids), (C6)_n (catechol, melanins), (C6-C3-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, xanthenes, 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.*

CHAPTER 8

Structure-Activity Relationship of Flavonoids: Recent Updates

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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

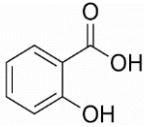
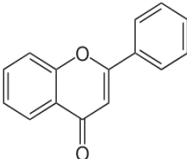
Herbal or medicinal plants have gained exceptional importance around the world. Plant products have been noticed for nutrition, cosmetics preparations, diagnostic agents, and mitigating diseases of human beings. Therefore, a plethora of studies have been done on different plant species, and their effects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

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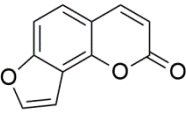
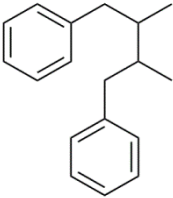
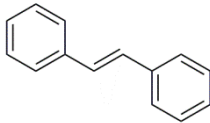
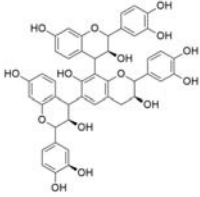
ed. Due to their safety and medicinal efficacy, plant-derived functional foods are of great interest.

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 -glucogallin. 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

Biologically Active Compounds and Structure-Activity Relationship

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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.

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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;

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

In equation 1, a set of substituted aromatic acids are represented by K and K' . Unsubstituted acids are represented by K_o and K_o' . ρ is the slope of the best fit line for a graph fitted to observed constant values. $\log K/K_o$ 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.

CHAPTER 10

Turmeric Supplementation and Its Valued Clinical Connections

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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.

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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://maharishiaurvedaindia.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].

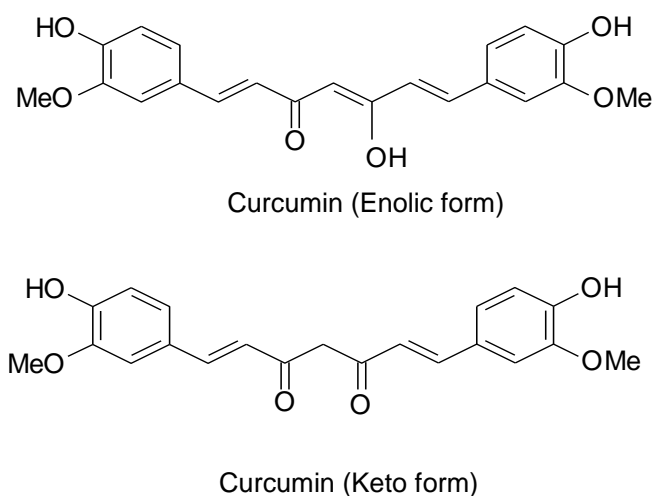


Fig. (1). Enol and Keto forms of the biologically active compound ‘curcumin’.

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

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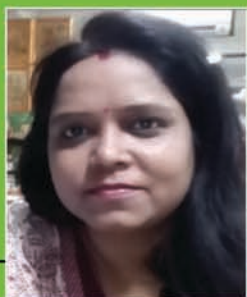
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