INFECTIOUS DISEASES

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Herbal Medicine: Back to the Future

(Volume 6)

Infectious Diseases

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PREFACE

Herbal Medicine: Back to the Future presents expert reviews on the applications of herbal medicines (including Ayurveda, Traditional Chinese Medicines, and alternative therapies) for health benefits. This series of volumes was initiated under the co- Editorship and guidance of late Prof. Ferid Murad who passed away recently. His monumental contributions to science, particularly the role of nitric oxide in health snd well being, will always be remembered. He is greatly missed.

This volume demonstrates the use of sophisticated methods to explore traditional medicine while providing readers with a glimpse into the future of herbal medicine. The book should prove to be a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information regarding natural product chemistry and the pharmacology of natural materials in the treatment of infectious diseases. The chapters are written by eminent experts in the field.

Leitão *et al.*, in Chapter 1, highlights the possible application of compounds isolated from Siparuna species as antiviral agents. In Chapter 2, Vadia *et al.*, emphasise the use of Indian spices and explore their key antimicrobial components for their antibacterial activity and modes of action. Chaughule and Barve in the next chapter discuss the role of herbal medicines in the treatment of infectious diseases. Singh *et al.*, in Chapter 4, focus on the traditional approach to treating infections. In the last chapter of the book, Nawaz *et al.* explore the therapeutic potential of medicinal plants for rheumatoid arthritis. Some important plants that show antioxidant and anti-inflammatory properties against rheumatoid arthritis are discussed in this chapter.

We hope that the readers involved in the study of infectious diseases will again find these reviews valuable and thought-provoking so that they may promote further research on herbal medicines and alternative therapies.

We are grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), and Ms. Asma Ahmed (Senior Manager Publications), at Bentham Science Publishers for the publication of this book.

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CHAPTER 1

Brazilian *Siparuna* Species as a Source of Antiviral Agents

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Abstract: Influenza is an acute viral infection of the respiratory tract caused by the *Alphainfluenzavirus* whose subtypes were responsible for historical pandemics. Recently, the coronavirus SARS-CoV-2 has also affected the world, causing acute respiratory syndrome, thus rendering the search for anti-influenza and anti-SARS-CoV-2 compounds an urgent task. Plants of the genus *Siparuna* are used in Brazilian folk medicine for treating colds, fever, headaches, and rheumatic pain as well as gastrointestinal disorders. *S. apiosyce* ("Limão Bravo") is mentioned in the first Brazilian Pharmacopeia due to its importance as an ingredient in syrup and cough drops. Alkaloids, methylated and glycosylated flavonoids stand out as secondary metabolites described for these species, being also well described in the literature for their antiviral activity. During our investigation of Brazilian plants active against viral infections, the anti-influenza activity of five Amazonian *Siparuna* (*S. cristata*, *S. decipiens*, *S. glycycarpa*, *S. reginae* and *S. sarmentosa*) were investigated, showing the *n*-butanol extracts of *S. glycycarpa* and *S. sarmentosa* as the most active. Dereplication of these extracts pointed alkaloids, *O*- and *C*-glycosylated flavonoids as well as dihydrochalcones and a procyanidin dimer as potential active metabolites. On the other hand, the dichloromethane extract from *S. cristata* containing methylated flavonoids was able to inhibit the *in vitro* replication of SARS-CoV-2, where it was shown that retusin and kumatakenin presented a higher selectivity index than lopinavir/ritonavir and chloroquine controls. Further *in-silico* studies showed the potential interaction between these flavonoids and the virus proteases 3CLpro and PLpro. Here we highlight the possible application of compounds isolated from *Siparuna* species as antiviral agents.

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Keywords: Alkaloids, Flavonoids, Influenza A(H1N1), Kumatakenin, Retusin, SARS-CoV-2, Siparunaceae.

1. INTRODUCTION

Several chronic and acute diseases in both humans and animals may be caused by viral infections such as dengue, influenza, measles, severe acute respiratory syndrome (SARS), and West Nile virus outbreaks [1]. Several viral diseases *e.g.* acquired immunodeficiency and respiratory syndromes, as well as hepatitis are still associated with high morbidity and mortality rates in humans around the world, despite all the progress made by Medicine in the last years [2]. The lack of effective therapies and/or vaccines for several viral infections, allied to the fast emergence of new drug-resistant viruses has made the need for new and effective chemotherapeutic agents an urgent one to treat viral diseases [3].

Natural products from plants or other organisms offer a large array of structurally diverse chemical compounds that could serve as antivirals, some of which have been shown to have great potential as drug candidates in preclinical and clinical trials. Many potentially useful medicinal plants and herbs are yet to be evaluated for further applications as therapeutic agents against diverse virus families [3 - 5].

In this context, we can highlight the Siparunaceae family, represented by two genera: *Glossocalyx* Benth and *Siparuna* Aublet. *Glossocalyx,* with 70 species is native to West Africa and occurs in shady primary forests and along roadsides. *Siparuna* is composed of 72 species occurring from Mexico to the north of South America, Bolivia, and Paraguay and is recognized in the field by its citrus smell. In general, shrubs are dioecious plants that occur in Central America and the Andes, while monoecious plants are large trees (about 15 species) that occur in the Amazon basin [6, 7]. So far, *Siparuna* is the genus with the largest number of reported studies, and a comprehensive review of its chemistry and biological activities was recently published [8].

Species of *Siparuna* occur in tropical and subtropical regions of the Southern hemisphere, with Brazil being considered a center of diversity for harboring these species in all its biomes. Plants of this genus are used in folk and traditional indigenous medicines in both South and Central America for treating colds, fever, headache, and rheumatic pain as well as gastrointestinal disorders [7, 9, 10]. The heated bark of *S. sessiliflora* and *S. thecaphora* is used to accelerate the healing of herpes sores, while the leaves of *S. guajalitensis* and *S. schimpffii* are used in tea preparation to help with fatigue [7].

Siparuna brasiliensis (synonymy: *S. apiosyce*) is a popular medicine in Brazil where it is usually called “limão bravo” and “negramina”. A monograph on this

plant species was included in the first Brazilian Pharmacopoeia (1926), due to its importance as an ingredient in syrup and cough drops sold by pharmaceutical companies in the past [10]. Given these facts, *Siparuna* species may be a potential source of antiviral compounds [8, 11, 12].

2. BRAZILIAN *SIPARUNA* SPECIES

2.1. Occurrence

Approximately 47 species of the genus *Siparuna* occur in the Brazilian territory, distributed in five different biomes: the Amazon, Caatinga, Pantanal, the Atlantic Forest and Cerrado. The epicenter of occurrence is in the Amazon region, where the genus comprises the great majority of species as shrubs and small trees (Fig. **1**) [7, 13].

Fig. (1). *Siparuna* plants: **(A)** *S. brasiliensis*, **(B)** *S. thecaphora*, **(C)** *S. guianensis*, **(D)** *S. decipiens*, **(E)** *S. reginae*, **(F)** *S. pauciflora*, **(G)** *S. grandiflora*, **(H)** *S. lepidota* and **(I)** *S. echinata.* Source: https://www.gbif.org/species/4893899

2.2. An Overview on the Chemistry of *Siparuna*

Among the classes of secondary metabolites present in nature, free and glycosylated flavonoids with kaempferol and quercetin aglycones, aporphine and benzylisoquinoline alkaloids, and terpenoids have been previously reported in the genus *Siparuna* (Table **1,** Fig. **2**) [7 - 10]. The composition of the essential oils of many *Siparuna* species has been the aim of several studies reported in the literature as can be seen in Table **2**, showing that mono and sesquiterpenes are the major identified compounds, occurring either as hydrocarbons of common structural types (*e.g.* elemene, caryophyllene, cubebene, copaene, germacrene *etc* series) or as alcohol derivatives of these skeletal types. The flavonoid 3,7,4'-tri-*O*-methyl-kaempferol (Fig. **2**) from leaves and bark of *S. apiosyce* (*S. brasiliensis*), was the first report of an *O*-methyl flavonoid aglycone in the genus *Siparuna* [9], followed by the report of the same compound in *S. gigantotepala* [14] and *S. guianensis* [15], as well as other *O*-methylated aglycones in *S. cristata*

CHAPTER 2

Antimicrobial and Antifungal Potential of Indian Spices

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Abstract: Infectious diseases caused by pathogens and food poisoning induced by spoilage bacteria pose a global hazard to human health. Microbial resistance has harmed the efficacy of various antimicrobial drugs, which are now used to extend the shelf life, raise the safety of food products in the food business, and suppress disease-causing germs in medicine. As a result, new antimicrobial agents that can overcome resistance must be developed. Many spices, including clove, oregano, thyme, cinnamon, and cumin, were found to have significant antibacterial and antifungal activity against food spoilage bacteria like *Bacillus subtilis* and *Pseudomonas fluorescens*, pathogens like *Staphylococcus aureus* and *Vibrio parahaemolyticus*, harmful fungi like *Aspergillus flavus*, and even antibiotic-resistant microorganisms like methicillin. In addition to their flavor and aroma features, many spices and herbs used today are recognized for their antimicrobial and therapeutic properties. Plant extracts from cinnamon, clove, garlic, mustard, onion, and oregano were sensitive to most foodborne bacterial pathogens studied. The essential oil portion of spices and herbs contains many antibacterial chemicals. Antimicrobial compounds in spices were more responsive to Gram-positive bacteria than those in spices were to Gram-negative bacteria. The degree of sensitivity differed depending on the strain and climatic variables. Spices that stimulate acid generation in starting cultures can have a direct effect on the rate of fermentation. Spices contain antimicrobial compounds such as phenols, alcohols, aldehydes, ketones, ethers, and hydrocarbons. In the current chapter, Indian spices and their key antimicrobial components are explored for their antibacterial activity and ways of action.

Keywords: Antimicrobial, Indian spices, Inhibition of biofilm formation, Inhibition of the bacterial enzyme, Inhibition of DNA-RNA synthesis, Mechanism of action, Receptor modifier, Suppression of cell walls.

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1. INTRODUCTION

Spice history is the history of humanity and empires that rose and fell through the commerce of exotic spices from faraway locations and transformed our society's basic foundations in an intoxicating way. The spices trade of cinnamon and black pepper developed in South Asia and the Middle East by at least 2000 BC. The Egyptians utilized mummification plants and helped promote global trade in their thirst for exotic spices and herbs. The word "spice" is the old French word "spice" that has become "epice" and originates from the Latin root spec, which means the noun "appearance." In China, Korea, and India, by 1000 BCE, herbal medical systems could be identified. Spice is the main substance used for flavoring, coloring, or preserving foodstuff. Spices differ from the herbs used for flavoring or as garnishes, which are the plants' leaves, blossoms, or stems. Spices may sometimes made into a powder for ease of use. Spices are vital in numerous places, from the culinary and medical uses of homes. Each country produces some spice, as India is blessed with various climates. It is hardly surprising that spices are widely used to cook in India. Spices are considered particularly useful not just in India but also in certain other countries. Spices are obtained from all parts of the plant, like root, flower, flower bud, bark, leaves, stem, fruits, seed, *etc*., but herbs are considered to be obtained only from non-woody materials. There are 80 different varieties of spices grown worldwide, and roughly 50 of them are grown in India, making it a major producer of spices. Many medical enterprises, including those in the fields of cosmetics, pharmaceuticals, and aromatic fragrances, rely on spices [1]. Besides providing color and taste, spices offer endless health benefits. Spices safeguard the population's health against acute, chronic, and non-communicable diseases. The favorable benefits to human health have been thoroughly examined in numerous nations [2]. But until recently, in the Western world, the interest in spices has increased [3, 4]. Most of the positive health effects of herbs and spices towards preventing or ameliorating chronic diseases such as cancer, cardiovascular disease, arthritis, and neurodegeneration appear to be mediated through the direct action of their constituent phytochemicals (particularly polyphenols or polyphenol breakdown products) targeting specific receptors or enzymes involved in various anti-inflammatory pathways or immune responses [2]. In India, the traditional medicine -Ayurveda- places a strong stress on diet and the prevention of disease. Turmeric for jaundice, basil for heart protection, mace for stomach infections, cinnamon for circulation, and ginger, the global medicine, for nausea and indigestion are some examples of how plants and spices are used in ayurveda for health benefits. Trade between ancient Rome, China, and India, known as the "house of spices," dates back centuries. Indian spices are the most well-liked in the world today because of their exquisite flavor, aroma, and medicinal properties. The largest domestic spice market in the world is one that India contributes to. In India, where they have

historically been grown on small farms, spices have lately begun to emphasize organic farming. India is the world's greatest spicy producer, user, and exporter; the country produces around 75 of the 109 kinds classified by the ISO and accounts for half of the worldwide spice trafficking. A “Masala Dabba” is one of the necessities in an Indian kitchen. The cups (usually 5 or 7) are normally small, with spices used in everyday cookery. Whether it is a soupy South Indian Rasam, Gujarati Dhokla snack, Bengal Mishti Doi sumptuously serves desserts, or Kashmiri Kahwa traditional tea, spices are common in diverse areas around the country. As opposed to other farm goods, spices are often pricey. Indian spices are quite popular worldwide. In June 2020, spice exports grew 23 percent compared with that of the same month last year. At a value of around 37 billion Indian Rupees, the United States was the top importer of Indian spices. India imports certain spices, such as Asefotieda or Hing, even as one of the largest spices suppliers. Hing has been introduced from neighboring nations, such as Afghanistan, Iran, and Uzbekistan, as the main component in traditional kitchens. Recently, India began to grow this spice, which will be another feather in the country's cape if it succeeds. In the financial year 2019, a total of US$ 2.80 billion was exported from the country, 1.10 million tonnes of pure spices and spice products, whereas in financial year 18, worth US$ 2.78 billion, represented a growth of 7% in volume. The top 10 Indian spice importing companies in the 19th century were the United States, China, Vietnam, Hong Kong, Bangladesh, Thailand, the United Kingdom, the United States, Malaysia, and Sri Lanka. During the financial year 2019, Chilies, Mint products, Pickles and Oleoresins, Curcumin, pepper, Cardamom-Pulver, other spices like Tamarind and Asafoetida, and Cassia and Garlic were the top 10 exported spices and spice products. India's export of chili during the financial year 2019 amounted to 468,500, 180,300 tonnes of cumin export, 133,600 tonnes of turmeric export, and 860 tonnes of cardamom. The overall export of spices for April 2020 was 3,55 billion dollars and 348,32 million dollars in February 2021. Ginger exports showed the biggest growth in the financial year 2020 (through December 2019), at 19.410 tonnes (47 percent), followed by cardamom at 1.060 tonnes (31 percent) and cumin at 7.350 tonnes (14 percent).

Indian cuisine uses a lot of these herbs and spices to add flavor, and large amounts can be eaten in a single dinner. These herbs and spices may also offer good antioxidants, vitamins, and minerals, including iron and calcium. An adult in India is thought to be able to consume up to 4 g of turmeric per day, which could provide 80–200 milligrams of the bioactive compound curcumin per day. According to reports, some Indians consume up to 50 g of garlic per week [5]. Some research shows that traditional food (containing Asian spices) is important to the body and helps boost immunity. Bay leaf is derived from a shrub (Laurel). It is frequently used as a spice in the Mediterranean lands and is considered a

CHAPTER 3

Role of Herbal Medicines in the Treatment of Infectious Diseases

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Abstract: Herbal medicines have helped to cure illness because the practice has continued for generations. Multiple alkaloids/compounds that occur naturally (as against single extracts) exhibit synergistic action and do not show antidote action. This naturally occurring combination of compounds exhibits antiviral, antibacterial, antiprotozoal, and antioxidant actions. The cases related to viral, protozoal, and bacterial infections were selected. Patients with amoebiasis, *e-coli*, gastrointestinal infection, skin and urinary tract infections were treated using herbal drugs. Diagnoses were confirmed with investigations. Repeated investigations were carried out to confirm the improvement.

Most herbal medicines do not exhibit serious side effects and are safe to prescribe, showing greater acceptability. Thus, due to their cost effectiveness, these medicines are in great demand for primary health care for better cultural acceptability and minimal side effects.

Cases varying from COVID 19 to gastrointestinal infection, viral diseases, and skin and wound infections are being treated effectively with herbal drugs.

Keywords: Aegle Folia, Aspidosperma, Alkaloids, Bryonia alba, COVID 19, Eupatorium perfoliatum, Herbal medicines, Holarrhena Antidysenterica, Infectious diseases, *In vitro* studies, Justicia.

1. INTRODUCTION

The use of herbal medicines for the treatment of various health challenges continues to expand rapidly across the world with many people now resorting to these products for improved healthcare.

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There is a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries, with these herbal remedies being available not only in drug stores but also in food stores. Herbal medicinal products are the primary healthcare source for the large population living in developing countries. India has a rich traditional system of medicine. Therapeutic treatments like Ayurveda, Unani, Homeopathy, Sidha, *etc* use mostly herbs. Natural herbal products are being used for the development of modern drugs and dietary supplements to food and beverages. Thus, traditional medicines to have provided a good level of confidence in safety and efficacy as the medicines have been used for thousands of years. There is a growing interest in natural products as a source of new chemical entities for the development of modern drugs and the use of natural products as dietary supplements, ingredients for food and beverages, Phyto cosmetics, and other herbal products.

Herbal medicine is a botanical product that can be used in extract or dilution form. The usage increases when conventional medicine is ineffective because of the growing drug resistance. Large numbers of plant species are used by the Indian herbal industry. These medicines are the synthesis of the therapeutic experiences of generations of practicing physicians. Multiple alkaloids/compounds that occur naturally (as against single extracts) show synergistic action and do not show antidote action. The naturally occurring combinations of compounds exhibit antiviral, antibacterial, antiprotozoal, and antioxidant actions. The cases related to viral, protozoal, and bacterial infections were selected. Patients with amoebiasis, *e-coli*, gastrointestinal infection, skin and urinary tract infections were treated using herbal drugs. Diagnoses were confirmed with investigations. Repeated investigations were carried out to confirm the improvement. Drug and plant review of herbal medicines used is also described in the text.

Since people are more worried about using conventional medicines due to their growing drug resistance, they continue to use traditional herbal medicines for good healthcare. Many hundreds of plants worldwide are used in traditional medicine for the treatment of bacterial infections. Some of these have also been subjected to *in vitro* screening but the efficacy of such herbal medicines has seldom been rigorously tested in controlled clinical trials. Bacterial infection is another source of problem for mankind. Though conventional medicines have effective antibiotic therapy for bacterial infection, they have drug resistance problems. Hence, many known plants are used globally for the treatment of bacterial infections. Thus, healthcare practitioners must be aware of herbal antibiotics. The present study is undertaken to assess critically those antibacterial herbal medicines that have been subjected to controlled clinical trials.

1.1. Pharmacology

Pharmacology can be defined as the therapy of the interaction of biologically active agents with living systems [1] and is further divided into two main areas pharmacodynamics and pharmacokinetics. Pharmacodynamics looks at the effects of an agent at active sites in the body. In contrast, pharmacokinetics is concerned with the medicinal effect on the body. For the therapeutic study, the aim is to examine the pharmacology of key chemical groups in plants as individual herbs under phytochemistry. Nutrients such as vitamins, minerals, and so on are largely responsible for the pharmacological activity of plants.

1.2. Secondary Metabolites

Primary metabolites participate in nutrition and essential metabolic processes inside the plant, whereas secondary metabolites influence ecological interactions between the plant and its environment. Based on their biosynthetic origins, plant secondary metabolites can be divided into three major groups: terpenoids, alkaloids, phenylpropanoid, and allied phenolic compounds [2]. All terpenoids, including the primary metabolites, are derived from the five-carbon precursor isopentenyl diphosphate. Alkaloids are biosynthesized from amino acids and phenolic compounds by either the shikimic acid pathway or the malonate/acetate pathway [2]. Two large groups of secondary plant metabolites can be distinguished in terms of their biological/therapeutic activities, as suggested by Efferth and Koch [3].

1.3. Herbal Medicines and Conventional Drugs

Though conventional drugs or their precursors are derived from plants, there is a fundamental difference between administering a pure chemical and the same chemical in a plant matrix. The homeopathic practitioner uses drugs in complex formulations, whereas a conventional physician prescribes a single agent. It does seem logical that, just as our foods are chemically complex, so should be our medicines. There are, however, several phytotherapy examples from the literature of how an advantage might arise from chemical complexity, and some of these are discussed below.

Synergy is an effect seen by a combination of substances that is greater than would have been expected from a consideration of individual contributions [4]. It is an important hypothesis in herbal pharmacology in the context of the advantage of chemical complexity. If the action of a chemical mixture is greater than the arithmetical sum of the actions of the mixture's components, the entire action is greater than the sum of the individual parts which can be considered as a cooperative or facilitating effect between the components for a specific outcome

CHAPTER 4

Herbal Medicine: Traditional Approach to Treat Infections

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Abstract: Infectious diseases are a major cause of morbidity and mortality at a worldwide level. While common cold, encephalitis, meningitis and gastroenteritis are mostly triggered by viruses, cholera, diphtheria, dysentery, tuberculosis, typhoid and pneumonia infections are caused by various bacteria, whereas valley fever, histoplasmosis, candidiasis, ringworm and eye infections are generated by several fungi. Also, ectoparasites like mites, lice, ticks and fleas can be responsible for some infections by attaching to the skin. However, after the onset of COVID-19, which mostly presents as a respiratory disease, a top interest has been put on virus research. Many studies have shown that phytochemicals exert a plethora of biological effects, among them, their antimicrobial action through different mechanisms has been highly underlined. Indeed, they are able to damage the bacterial cell membrane and suppress diverse virulence factors, including inhibition of the activity of various enzymes and toxins and biofilm formation. This chapter summarizes the impact of certain phytochemicals, for example, flavonoids, polyphenols, saponins, steroids, tannins, terpenoids, and alkaloids, as naturally-occurring bioactive compounds present in plants, in several infectious diseases.

Some herbal medicines containing flavonoids form complexes with cell walls of bacteria, protein and extracellular components and are important and effective antimicrobial compounds. Herbal medicines contain terpenoids involved in weakening microorganism cell wall and membranous tissue dissolution, thus inhibiting the growth of infections. Saponins found in herbal medicines cause microbes enzyme leakage from the cell, whereas Steroid in antimicrobial drugs is responsible for liposome leakage from the lipid bilayer membrane. Based on the evidences, the antimicrobial activity of the medicinal plant *Veronica biloba* was found against *E.coli*, *S.aureus*, and *Aspergillus fumigatus* pathogens. The common herbs tarragon and thyme both contain caffeic acid, which is effective against viruses, bacteria, and fungi. Organosulphur compounds such as allicin, isothiocynate and ajoene have shown antibacterial activity against both gram-positive and gram-negative bacteria. Catechins, the most reduced

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form of the C_3 unit in flavonoid compounds, deserve special mention due to their occurrence in green teas. It was noticed that teas also exerted antimicrobial activity against *Vibrio cholerae*, *S. mutans*, *shigella* and other microorganisms. This chapter focuses on all aspects of infectious diseases and herbal medicines, including chemical constituents and their therapeutic effects.

Keywords: Alkaloids, Antimicrobial, Bacteria, Fungi, Flavoinoids, Saponins, Infectious Diseases, Phytochemicals, Terpenoids, Virus.

1. INTRODUCTION

Out of many several challenges to human health, infectious diseases have a profound effect on the life of humans. All types of infections have different features when compared to other diseases [1]. Primary traits are their unpredictability and probable distinctive effect on the world population, like the pandemic of bubonic-pneumonic plague in the 14th century [2, 3], the influenza pandemic in 1918 [4, 5] and the current pandemic of COVID-19 [6], among others. Infections are generally acute and explicit in nature. The onset of any infectious disease can be instantaneous and distinctive. Furthermore, without any therapeutic intervention, this acute illness shows all or none phenomenon means rapid death and unconstrained recovery. Another unique feature of these infectious diseases is transmission to others. Although the modes of transmission are somewhat less, the most common are inoculation, air and water-mediated transmission. These are well-established and simple to understand, both preclinically and clinically. Majorly, infectious sickness is induced by one pathogen compared to other life-style related diseases induced by multiple co-factors [1]. Infectious diseases can be prevented by general-disease control measures (*e.g.,* hand-washing and sanitization, disinfection by chemicals and vector control) and specific measures (*e.g.,* anti-microbial drug treatment or vaccination).

Although prevention has become more effective, history has depicted that some infectious diseases, especially those that have a wide world impact and for which there is no major non-human source and reservoir, can be eradicated, like poliomyelitis, which has been obliterated from the western hemisphere [7] and smallpox, has been completely removed from the whole world [8]. One more distinctive feature of these pathogens is the marvelous adaptability of replication and mutational changes, which gives them an evolutionary benefit against the aim of their demolition. These adaptations induce the need for the development of new vaccine antigens, *e.g.,* the influenza vaccine, which is updated annually.

2. HERBAL MEDICINAL PLANTS/HERBS COUNTERACTING INFECTIOUS DISEASES

Recently, the popularity of herbal therapy has been increasing day by day, both in developing and developed countries. The research on pharmacological activity, risk/benefit ratio, active phytoconstituents and medicinal values are ongoing worldwide. Research on various aspects of medicinal plants is being executed in Rwanda, Maltese islands, Eastern Africa, Nigeria, Cuba, India, China, European countries, and other countries of the world [9 - 20]. As a precious store of natural medicines, these are attaining much recognition due to their increasing demand and their merits over other treatment systems, including allopathy. These have multiple health advantages and depict much usefulness in complementary systems of medicines as effective therapeutic interventions. These medicinal herbs also play a role in improving and maintaining the general status of health. These medicinal plants provide a cheaper, safer and easily available source of medicines [19, 21, 22].

2.1. Medicinal Plants Used To Treat Bacterial Infections

Several developing as well as developed countries, including India, depend on medicinal plants to treat bacterial infections. These plants include Amla, Heeng, Ashwagandha, Giloy, Arjuna, Turmeric, Ginger, Garlic, Shatawari, Kiwi-fruit, pipali, tea-tree, Neem, Guduchi, Palashlata, Kokilaksha, *etc*. [18 - 20, 23 - 32]. These have many benefits in treating superficial wounds and other ailments caused by bacteria. Some of the best examples are given in Table **1**.

Table 1. Plants/herbs, common name, active phytoconstituents and anti-bacterial activity.

S. No.	Scientific Name	Common Name	Active Phytoconstituents and Mechanism of Action	Extracts Used/ Dose Used	Antibacterial Potential Against	References
1.	***Aloe barbadensis (asphodelaceae)***	Aloevera, Ghrita kumari, Star cactus, Barbados, Guarpatha	**Pyrocatechol:** Act by denaturing proteins and disrupting cell membranes. **Cinnamic acid** inhibits glucose uptake and ATP production in the resting cells of bacteria. **P-coumaric acid:** Increase lag phase of microorganisms. **Ascorbic acid:** Interfering with cell membranes, enzymatic activity and genetic mechanisms.	Aqueous, ethanolic and methanolic extracts	*Pseudomonas, aeruginosa, M. tuberculosis, S. aureus, E. coli, S. typhi, Corynebacterium/ in vitro* study	[33 - 35]

CHAPTER 5

Exploring the Therapeutic Potential of Medicinal Plants for Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis is a chronic autoimmune disease that affects the small joints of the feet and hands, causing polyarticular inflammation. Uncontrolled synovial tissue is the most prominent symptom of this disease. If left untreated, it can result in significant impairment, adversely impacting the patient's quality of life and elevating death risk. Genetic, environmental, and epigenetic variables are all important in the etiology of this disease. The risk of developing rheumatoid arthritis is not age-related, people over the age of 40, particularly women, are significantly more likely to get the disease than men. There are a variety of therapies that are provided based on the severity of the ailment. However, all of these therapeutic techniques have negative effects as well as significant prices. More than 80% of the population in the world is now believed to use medicinal plants to maintain their health. Plants are the most abundant source of antimicrobial agents, and extracts of numerous edible plant species, herbs, and spices have long been used to preserve food due to the presence of potentially powerful antibacterial components. Not only minerals and primary metabolites are found in medicinal plants, but also a wide range of possible chemical compounds that aid in the adsorption and neutralization of free radicals. Some of the plants that show antioxidant and anti-inflammatory properties against rheumatoid arthritis are discussed in this chapter.

Keywords: Autoimmune Response, Inflammatory Diseases, Medicinal Plants, Pathophysiology, Rheumatoid Arthritis, Therapeutic Significance.

1. AN INTRODUCTION TO RHEUMATOID ARTHRITIS

Rheumatoid Arthritis (RA) is a disease that is characterized by inflammation of the lining of joints called synovium. It is a symmetrical form of arthritis and may affect multiple joints. Approximately 0.5 to 1% adult population across the globe is affected by it [1]. The disease usually affects the hand and foot joints and takes a chronic manifestation pathway, if not diagnosed and treated early on. The pat-

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ients usually complain of swelling, joint pain, and stiffness. The symptoms overlap with other diseases as well, therefore specific testing and expert clinical consultation is required for accurate diagnosis. The earlier the disease is diagnosed, the better it is to manage. This is because the drugs get a chance to prevent and halt joint damage. If the disease progresses, cartilage loss and bone erosion occur which can be detected radiologically. One of the most important risk factors associated with joint destruction is the presence of autoantibodies [2].

2. CAUSES OF RHEUMATOID ARTHRITIS

Rheumatoid Arthritis is a multifactorial disease, and its onset may be the result of genetic, epigenetic as well as environmental factors. Various whole genome sequencing studies have revealed numerous loci that may increase the risk of RA [3].

2.1. The Interplay of Genes

Multiple genetic loci have been identified in association with the manifestation of this disease. Some of these loci are studied in association with other autoimmune diseases as well. However, inheritance of HLA haplotypes is the most significant genetic predisposition uncovered so far. The HLA-DRB1 alleles code for specific molecules that bear a shared motif of five amino acids. This motif is called the shared epitope (SE). The presence of these alleles causes predisposition to anti-citrullinated protein antibody ACPA-positive RA. Whereas, ACPA-negative version of the disease has been linked to non-SE bearing HLA alleles. One of the examples is HLA-DR3 allele [3].

2.2. Autoimmune Responses Elicited by Posttranslational Modifications of Proteins

When arginine gets post-translationally modified by peptidylarginine deiminase enzymes, citrulline is produced. This process called citrullination is dependent on calcium. Autoantibodies known as anti-citrullinated protein antibodies (ACPAs) are formed against proteins that are citrullinated. These autoantibodies are made by plasma cells in joints that are affected by rheumatoid arthritis. Since, in an inflammatory environment, citrullination of protein takes place, and consequently, ACPAs are generated. An RA synovium may contain various citrullinated proteins. However, the key citrullinated protein found in an RA joint is fibrin [4].

The diagnostic specificity of these autoantibodies is found to be 90 to 95% and they can be identified in 70 to 90% of all patients who are affected with RA [5].

2.3. Involvement of Rheumatoid Factors

Rheumatoid factor (RF) is another major kind of autoantibody that is detected in the serum of patients suffering from RA. It is formed against the Fc part of antibody IgG in humans. It was incorporated in 1987 ACR (American College of Rheumatology) classification criteria for RA. However, ACPA are considered to be comparatively more specific. Several studies have revealed higher disease activity caused as a result of the synergistic effect of RF and ACPA [6].

2.4. Environmental Factors

Tobacco smoke has been associated with increased risk of RA development. Mainly, smoking amplifies the risk of RF or ACPA- positive RA. It causes citrullination of proteins in the lungs. Another interesting observation made by scientists is that tobacco only increases the risk of disease when it is inhaled by the individual. Chewing tobacco does not increase the risk of diseases.

RA development has also been associated with the presence of other inhaled pollutants. These include traffic pollution, nitrogen dioxide (NO_2), silica dust, textile dust and agricultural pesticides.

Another factor constantly associated with the causation of RA is periodontitis. It is a chronic infection of the gums. The risk was almost doubled for incident RA in severe form of this disease that is characterized by the presence of an edentulous state.

Furthermore, a chunk of scientific research has been directed towards finding out the relationship between hormones and RA since RA is known to prevail more in women than in men. In a nutshell, numerous studies conclude that factors that are associated with a decline of estrogen hormone can be termed as risk factors. On the other hand, those that are connected to high exposure to estrogens can be categorized as protective factors [7].

3. PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

The disease onset is due to a combination of genetic and environmental factors. Once initiated, a series of pathological immunological changes snowball into the chronic form of the disease with lethal clinical manifestation.

Endothelial cells play a key part in the inflammatory process initiation [8]. The synovial membrane gets infiltrated by monocytes, T and B cells and neovascularization occurs. Macrophage-like cells and fibroblast-like cells multiply in the synovium. This causes synovial lining to proliferate. As a result, “pannus” is formed. Pannus refers to the expanded synovium. The periarticular

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Atta-ur-Rahman, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.

Ka Bian

Dr. Bian's research has been focused on NO / cGMP signaling. Through the research on human adult and/or embryonic and cancer stem cells, Dr. Bian has proposed that NO/ cGMP signaling exerts its pathologic effects with two major mechanisms: Up-stream iNOS centered pathway is involved in the enhanced pro-inflammatory status that is key element for cellular damage and cancer micro-environment formation. Down-stream sGC / cGMP mediated pathway is responsible to proliferation, differentiation and self-renewal of stem/cancer cells. Dr. Bian is expanding the research into the area of cancer metastasis and therapeutic resistance since deciphering the role of NO-sGC signaling would facilitate development of strategies to interfere with malignant and metastasis processes.