MEDICINAL PLANTS, PHYTOMEDICINES AND TRADITIONAL HERBAL REMEDIES FOR DRUG DISCOVERY AND DEVELOPMENT AGAINST COVID-19

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PREFACE

The pandemic outbreak of coronavirus disease-2019 (COVID-19) has become an increasing threat to public health across the globe. It is an unprecedented infectious disease caused by the newly discovered severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with the widespread occurrence, severe respiratory problems and devastating fatality worldwide. Despite rigorous physical distancing, quarantine, and containment efforts, the incidence of COVID-19 has continued to rise globally. COVID-19 is a severe respiratory malady causing mild symptoms to severe illness and fatal complications (acute respiratory distress syndrome, cardiac arrhythmia, cardiovascular shock, heart attack, kidney or multiple organ failure and even death. The most serious complication is a type of pneumonia attack named 2019 novel coronavirus-infected pneumonia (NCIP). Based on current consensus, COVID-19 has imposed a significant healthcare crisis alongside severely affecting the global economies. Certain therapeutic/ prophylactic interventions that are currently in clinical practice include antiviral or anti-retroviral medications, corticosteroids, immunosuppressants, breathing support such as mechanical ventilation, and blood plasma transfusions (convalescent plasma therapy). Since no specific approved drugs or vaccines are currently available, the discovery and development of potential drugs for the treatment as well as the management of COVID-19 is an urgent need of the hour. The chapters covered in this book would be useful to researchers or scientists to discover and develop new drugs or lead molecules using various plant-based or herbal resources and/or phytochemical bioactive compounds for the treatment as well as management of COVID-19.

The book titled “Medicinal Plants, Phytomedicine and Traditional Herbal Remedies for Drug Discovery and Development against COVID-19” presents drug discovery opportunities from medicinal plants, phytomedicines, and traditional herbal remedies for the prevention as well as treatment of coronavirus disease-2019 (COVID-19). This book comprises chapters on basic aspects of SARS-CoV-2 virology, disease biology, and pathogenesis of COVID-19 including prevention and control measures of SARS-CoV-2-induced respiratory infection with possible drug discoveries from phytomedicines and traditional herbal therapies. This book specially deals with bioactive compounds-based drug discoveries from various medicinal plants of traditional importance and herbal medicines for combating SARS-CoV-2 infections and associated respiratory complications. In addition, possible preventive strategies using natural immune-boosting foods, functional foods, herbal drugs, indigenous spices and alternative medicines are also presented in the book. The discovery of drugs from phytomedicines/ herbal drugs using phytochemical database searching or by in silico repurposing approach is the special attraction of this book. The key features of the book are depicted below:

1. Presents drug discovery scopes and opportunities from medicinal plants, phytomedicine and traditional herbal remedies against COVID-19.

2. Details current advances in the utilities of medicinal plants, herbal drugs and traditional medicines for combating COVID-19.

3. Documents natural immune boosting indigenous herbs/ spices/ functional foods and herbal drugs or traditional antiviral remedies for chemo-prophylactic potential against SARS-CoV-2 infection.

4. Highlights drug repurposing strategies of phytomedicine-derived bioactive compounds or phytochemical databases for drug discovery against COVID-19.

This book is proposed to contain chapters covering various cutting-edge topics on virological research and possible drug discovery updates to deal with SARS-CoV-2 infections and respiratory complications associated with COVID-19. The authors contributing chapters to this book are renowned researchers and/or subject experts from reputed academic and research institutions from different regions of the world. The chapters are integrated properly within a well-structured format in a sequential order to aid flow, consistency and continuity. This book consists of chapters on various topics in various segments of COVID-19 research avenues as enumerated in the content. The book is intended to be useful to drug developers, drug discovery scientists, medicinal chemists, public health scientists, molecular biologists, biochemists, pharmacologists, toxicologists, biologists, immunologists, biotechnologists, industrialists, food technologists, policymakers, students, and educators and many others.

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CHAPTER 1

Phytoconstituents from Mother Nature against SARS-CoV-2/ COVID-19

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Abstract: Coronavirus disease-2019 (COVID-19) is a pandemic disease due to the infectious virus "Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2)". Scientifically validated phytoconstituents sourced from "Mother Nature" are now an area of interest and targeted approach as a worldwide prophylactic measure against SARS-CoV-2. This section focuses on providing a clear understanding of the structure of SARS-CoV-2 as well as verified phytoconstituents from traditional medicine (TM) for addressing the virus with all feasible targets. Target-specific inflammatory pathways triggered by SARS post-infection include NLRP3, Metallopeptidase Domain 17, JAK-STAT, p38-MAPK, endocytosis pathways *e.g*. Clathrin, HMGB1 as well as associated interleukins and cytokines are primarily highlighted, which directly or indirectly trigger the immune system and play a significant role. Selected Indian medicinal herbs and their possible leads are detailed below, with the goal of focusing on specific routes with a high likelihood of preventing pandemics in the future.

Keywords: COVID-19, Coronavirus, Mother Nature, Phytoconstituents, SARS-CoV-2, Traditional Medicine.

INTRODUCTION

SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2) is the virus that causes the COVID-19 pandemic. This zoonotic virus is quite tiny (65-125 nm in diameter), but it affects people all over the world [1]. According to the "International Committee on Taxonomy of Viruses (ICTV)," SARS-CoV-2 belongs to the "Coronaviridae" family, and its genome is made up of a positive-sense single-stranded RNA [(+) ssRNA] virus with a size range of 30 kbs [2 - 5]. Out of the existing two major variants, L (~70%) is more aggressive and infectious compared to S type (~30%) [6]. Coronavirus replicates inside the host

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cell and is responsible for severe health issues, especially for respiratory illness, *e.g*. severe pneumonia [7] further morbidity and also for mortality [8]. SARS-CoV-2 is more severe than other viruses in a similar category [1]. On the 31st of December, 2019, China officially declared instances of pneumonia related to an unknown cause for the first time [9]. From that day onwards, the numbers are increasing at an exponential level. Situations are still very complicated and even after the vaccination program, people are affected by this virus with a new variant, namely, Omicron. After almost 2 years of completion, 271,963,258 confirmed cases are reported from 224 countries, areas, or territories. Therefore far, a total 5,331,019 number of deaths are confirmed globally as per Worldometer- *17 December 2021* at *5.14* am [10].

Antiviral drugs [11] and clinically/FDA-approved vaccines against COVID-19 [12] are the primary and immediate solutions to manage this pandemic condition. Antimicrobial includes antibacterial and antiviral; antibiotic, antimalarial, anthelmintic, human amniotic fluid (hAF), Type 1 Interferons (IFNs), Monoclonal antibody (mAb), Convalescent plasma therapy and mesenchymal stem cells (MSCs), and various vaccination programms are some of the other prospective treatment alternatives that are in use and being researched [11], however other health-associated complications are also diagnosed, which can persist prolong and very difficult to normalize the patient. Not to forget, the recurring frequency of COVID-19 is also very high even after full vaccination with the proper dose recommended by the inventor companies and standard instructions released by WHO. *In silico* computational docking technologies are still being used by researchers to find and locate compounds of virtual ligands from chemical databases that already exist [12, 13]. Considering the pandemic situation and the alternative solutions, researchers are also considering preventive attitudes instead of curative approaches by which people can immunize their body system against this virus. Natural products and traditional systems of medicine could be an alternate source to answer this intricate problem. Plants may be the best source since they grow in Mother Nature's environment and habitat in a variety of extreme climates to survive their existence and nourishment. Some plants with high immunomodulatory properties and the ability to protect against infectious outbreak infection during sensitive seasonal changes must yet be studied scientifically to determine the mechanisms by which they function against this viral outbreak. To obtain an alternative source from Mother Nature and to brighten the dark, one must first comprehend the nature of the virus, its replication, pathophysiology, and implications on the bodily organs. This chapter provides a quick overview of viral structure, structural and nonstructural proteins, pathogenesis, and method of action, with a focus on potential targets for virus suppression and alternative treatments as preventative medicines. The findings from attentive knowledge were extracted using Elsevier Scopus database

information about traditional medicine. Further, Indian medicinal plants recommended by the Government of India were also considered in this study [14]. In all, 20 plants are featured here, and *via* this strategy, the research community and scientists will receive access to information on plants that might be the key to a future solution to the SARS-CoV-2 outbreak.

MATERIALS AND METHODS

SARS-CoV-2 and Phytoconstituents Data Collection

The title "SARS-CoV-2" was searched using Scopus, an online database tool from Elsevier https://www.scopus.com/home.uri with the language limit set to English only. The database was searched for published literature, which was then filtered using the subject matter keywords "phytomedicine/phytoconstituents" from medicinal plants as anti-SARS-CoV-2 treatments [15]. From an Indian perspective, some of the potential medicinal plants compiled by scientists at the National Medicinal Plants Board (NMPB), Department of AYUSH (Acronyms: Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy), Government of India, are also taken into account in this study for naturally boosting the immune system [14].

Information Evaluation

The information is summarized as follows:

Structure of SARS-CoV-2 and it's replication; possible potential targets and also phytoconstituents-alternative as a preventive medicine.

RESULTS

SARS-CoV-2 and Ethnomedicinal Plants

To conclude the study, global publications on pandemic SARS-CoV-2 including medicinal herbs and their phytoconstituents were reviewed and downloaded from the Elsevier Scopus database. Scientists and academicians from various countries, including the United States, India, the United Kingdom, Italy, and China, have been observed to publish the greatest number of articles with their co-authors for the keywords "SARS-CoV-2" in conjunction with "phytochemical, herbs, spices, phytomedicine, phytotherapy, and phytoconstituents."

Medicinal plants that have been utilized in the Indian System of Medicine (ISM) since antiquity [16] and that are prevalent in the list of plants advised combating COVID-related disorders are chosen based on publications, cost-effective affordability, and stress-free availability, and are explained in detail. *i.e.*,

CHAPTER 2

Role of Medicinal Plants and Phytomedicine against COVID-19 Management

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Abstract: COVID-19 has taken the global population by surprise. All around the globe, there have been combined efforts from scientists to find a cure for this disease. Numerous alternative modes of medicine have also been explored for the same. In this chapter, the authors have reviewed the role of medicinal plants and phytomedicine in combating this disease. There is an urgent need to standardise the protocols for conducting clinical experiments on herbal medication for COVID-19 to ensure consistency and batch-to-batch efficacy. Also, literature regarding these studies needs to be categorised and catalogued properly. The scientific community needs to draw from the rich diversity of herbal and medicinal plants to meet this extraordinary challenge.

Keywords: Coronavirus, COVID-19. Phytomedicine, Herbal plants, Medicinal plants, SARS-CoV-2.

INTRODUCTION

There seems no end in sight in the fight against COVID-19 which is causing havoc due to its extraordinary basic reproduction number, high mortality, and dearth of clinically approved drugs and vaccines [1]. Cumulatively, nearly 22,487.60 confirmed cases per million and 485.61 confirmed deaths per million have been reported by June 11, 2021. https://ourworldindata.org/coronavirus-data?country=~OWID_WRL

TRANSMISSION AND LIFE CYCLE OF SARS-CoV-2

The efficient transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified from inoculated donors to simple contact hamsters by direct exposure or *via* aerosols (Fig. **1**) [2].

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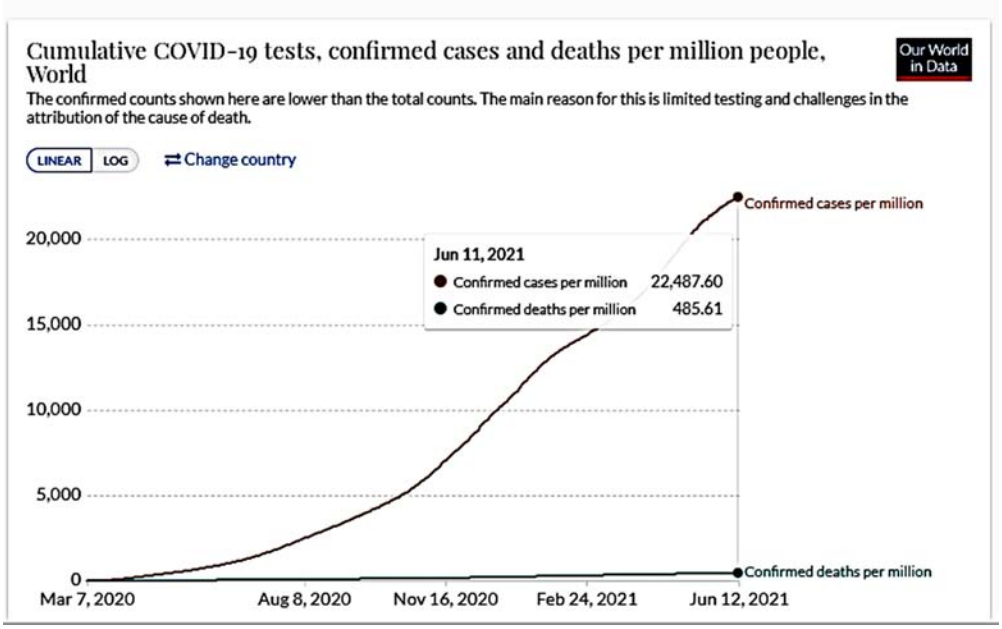

Fig. (1). Confirmed COVID-19 cases and deaths. (Map was reproduced from https://ourworldindata.org/coronavirus-data?country=~OWID_WRL.

Some researchers simulated three transmission approaches in naive human angiotensin-converting enzyme 2 (hACE2) mice and discovered that SARS-Co--2 can be transmitted *via* respiratory droplets and close contact [4]. Various transmission routes for the SARS-CoV-2 virus are:

Contact Transmission: Contact transmission refers to the transmission of pathogens through indirect or direct contact with various mediums. Droplets that contain viruses are settled on the surface of objects, which can contaminate hands. Additionally, the mucous membranes of the mouth, eyes, nose, *etc*. are easily contaminated, leading to eventual infection. In fact, scientists have found indications of SARS-CoV-2 at the top surface of numerous materials and halted strong viability [5, 6]. Although, while disinfection is beneficial for blocking-up the contact route of transmission, it cannot completely do away with the ribonucleic acid (RNA) virus from the surface [7].

Respiratory Droplet Transmission: Respiratory droplet transmission refers to the transmission that results from coughing, talking or sneezing, which are then directly inhaled by susceptible individuals. The diameter of the droplet is >5μm and it cannot last long in the air, which accounts for the contiguous range of droplet transmission [8, 9]. The transmission of respiratory droplets of SARS-

CoV-2 has been proved by various animal experiments. Some researchers provide experimental confirmation of burly transmission of SARS-CoV-2 through hACE2 mice and the respiratory droplets in between ferrets.

Aerosol Transmission: Aerosol transmission refers to the emanated gas in the droplet nuclei or fine particles (whose particle size is <5μm) dangled in the air to form aerosols and can cause infection after inhalation [10]. These aerosols can drift in the air for longer periods of time, potentially penetrating to depths of the lungs, where these may be rested in the alveoli (Fig. **2**) [11].

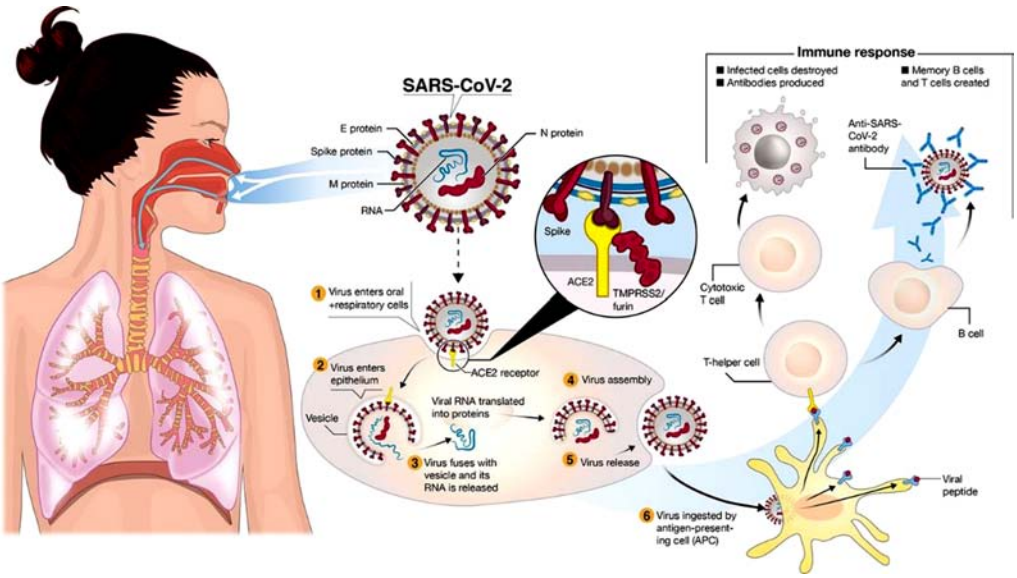

Fig. (2). Transmission of SARS-CoV-2; Taken from [3]; licensed under the Creative Commons Attribution 4.0 International license.

Fecal-Oral Transmission: Recent studies show that SARS-CoV-2 RNA may be distinguished not only in surface samples and air, besides it is also present in fecal specimens, indicating another potential path of SARS-CoV-2 transmission [12, 13]. SARS-CoV-2 might be present in the gastrointestinal track for longer duration than in the respiratory system, proposing that efforts should be made to avert the spread of infection among patients at high risk [14, 15].

LIFE CYCLE OF SARS-CoV-2

Life cycle of SARS-CoV-2 begins with the binding of receptor binding domain (RBD) present in the S1 subdivision of spike protein into angiotensin converting enzyme 2 (ACE2) which is revealed on the superficial side of epithelial cells both

CHAPTER 3

Immune Foods for Fighting Coronavirus Disease-2019 (COVID-19)

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Abstract: Nutritional measures and food components such as micronutrients, macronutrients, and food bioactive compounds, boost the immune system to effectively fight COVID-19. Nutrient deficiencies reduce immune functions against COVID-19, while supplementation of specific nutrients improves the immune system against viral disease. Several macronutrients and micronutrients, including bioactive compounds, prebiotics, and probiotics, have been linked to COVID-19 treatment and prevention. Vitamins D, C, A, E, and B vitamins have been linked with improvement and recovery from COVID-19. Several minerals such as zinc, selenium, iron, copper, magnesium, *etc*. have activities against SARS-CoV-2 and COVID-19. Many studies have shown that bioactive compounds such as resveratrol, astaxanthin, quercetin, docosahexaenoic acid, eicosapentaenoic acid, epigallocatechin-3-gallate, theaflavin, *etc*., have promising actions against SARS-CoV-2 and COVID-19. Foods and food components should be properly utilized to fight COVID-19 and are valuable in drug discovery against COVID-19.

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Keywords: Bioactive compounds against COVID-19, Immune boosting foods against COVID-19, Micronutrients against COVID-19, Macronutrients against COVID-19, Minerals against SARS-CoV-2, Nutritional therapies for COVID treatment, Vitamins against SARS-CoV-2.

INTRODUCTION

The immune system is made up of a network of physiological and biological processes which protect organisms from diseases and help fight the diseases when organisms are exposed to such diseases. The immune system identifies and responds to several pathogens and diseases, including viruses, cancer cells, and parasitic worms, as well as objects like wood splinters, and distinguishes them from the own healthy tissues of the organism. There are two main immune system's subsystems; the innate and the adaptive immune systems. The innate immune system gives preconfigured responses to several stimuli and situations. The adaptive immune system gives tailored responses to every stimulus by learning how to identify the molecules or substances it encountered previously.

Both the innate and adaptive immune systems use cells and molecules for their functions. The immune system takes part in numerous body physiological regulations. The strength and effectiveness of the immune system depend on several factors, including nutritional status, age, lifestyle, type of food consumed regularly, genes, *etc*. The immune system intimately networks with other systems in the body, including the nervous system and the endocrine system [1 - 6]. The immune system plays a significant role in tissue regeneration and repair, embryo development (embryogenesis) [7], and disease prevention or recovery, including the prevention of recovery from viral infections such as coronavirus disease 2019 (COVID-19), influenza, flu, among others [2].

Developing immune-targeted therapeutic measures against COVID-19, a contagious viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in December 2019 in Wuhan, China, is vastly necessary despite the challenge it may present [8]. As COVID-19 has spread worldwide, several immune-targeted measures are required for prevention and quick recovery. Adequate foods and nutrition are a prerequisite for optimal immune system functions. Nutritional measures, such as administering micronutrients, macronutrients, and food-bioactive compounds, have the potential to boost immune functions in fighting COVID-19. Micronutrients' supplementation, such as trace elements and vitamins, and food-bioactive compounds, including polyphenols and carotenoids, have been demonstrated to help the immune system in fighting and recovering from COVID-19 and other viral diseases [9, 10]. Generally, the efficacy of nutrients and food-bioactive compounds in fighting infectious diseases is affected by many factors, such as the

dose, type of pathogen, duration and the timing of supplementation, previous nutritional status of the individual, the target population characteristics, *etc*. Supplementation of nutrients and bioactive compounds should be done under the supervision or advice of a health practitioner, nutritionist, or a dietician.

Overnutrition *(e.g*., overweight) is among the known risk factors for COVID-19 severity. Overnutrition is linked to various diseases, including obesity, cardiovascular diseases, and diabetes mellitus, all of which affect the functions of the immune system. Specific nutrient deficiencies and moderate malnutrition can result in compromised immune responses, which reduces the body's ability to fight some infectious diseases such as COVID-19 [11]. Diets rich in essential fatty acids, such as omega-3 and omega-6 fatty acids, improve healthy immunity; their deficiencies can result in prolonged immune system impairment [12 - 14]. Micronutrients, e.g., vitamin D, are directly linked to immune cells. When T-cells encounter foreign pathogens such as SARS-CoV-2, they extend vitamin D receptors. The receptor is in essence a signalling mechanism that allows the binding of T-cells to the vitamin D active form, the steroid hormone calcitriol. T-cell and vitamin D have a symbiotic relationship. T-cells do not only extend vitamin D receptors, essentially requesting to bind to calcitriol, vitamin D steroid hormone version, T-cells also express the CYP27B1 gene responsible for the conversion of calcidiol, the vitamin D prehormone version, into calcitriol. T-cells can only perform their intended functions after binding to calcitriol. Macrophages, keratinocytes, and dendritic cells are other cells of the immune system known to express the gene CYP27B1 and consequently activate calcidiol into vitamin D [15, 16]. Vitamin D deficiency has been associated with COVID-19 severity in many clinical studies. This chapter covers the foods, nutrients, and food bioactive compounds required to boost the immune system against SARS-CoV-2 (COVID-19). Nutritional immunology studies the nutritional influence on the immune system, along with its protective function. It also covers the likely effects of foods on the management and prevention of the development of infectious diseases, cancer, allergy, chronic diseases, and autoimmune diseases [17]. Nutritional immunology is associated with related topics such as malnutrition, nutritional metabolic disorders, and malabsorption, as well as their immune products [18, 19]. Immune-boosting foods are essential in the fight against COVID-19.

ROLE OF FOODS CONSTITUENTS IN IMMUNE SYSTEM FUNCTIONS

Food, nutrients, and bioactive compounds play a significant role in immune functions. Table **1** shows the common food, nutrients and bioactive compounds which play a role in the immune system against several diseases such as COVID-19.

CHAPTER 4

Plant Sources of Pro and Anti-Inflammatory Mediators against COVID-19

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Abstract: The first and the most vital biotic response of the immune system against stress, oxidation, infection, injury and irritation is inflammation. Reports revealed that the anti-inflammatory effect is mediated by various inflammatory cytokines and non-cytokine mediators *i.e*. tumor necrosis factor alpha-a, nitric oxide, interleukins, interferon gamma-g, and prostaglandin E_2 respectively. Herbal medicine is playing an important role in the treatment of COVID-19. Plant-based foods are rich source of bioactive compounds (phytochemicals) and have a potential anti-inflammatory effect. The purpose of this chapter is to sum up the recent findings of work already done both in vitro and in vivo on the anti-inflammatory effects of plant-based foods. As a source of natural modulators of gene expressions, phytochemicals from plants could be used along with other pharmaceutical formulations as anti-inflammatory drugs. Therefore, the regulation of inflammation by modulating the pro-inflammation and anti-inflammation cytokine expression through different plant-based food also boosts immunity.

Keywords: Cytokines, Cyclooxygenase, Inflammation, Medicinal Plants, Tumor Necrosis Factor Alpha.

INTRODUCTION

The ongoing coronavirus threat that emerged in China has rapidly spread to other countries and has been declared a global health emergency by the World Health

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Organization (WHO). Many nations are diverting their best efforts to the implementation of appropriate preventive and control strategies. The active molecules in fruit, vegetables, herbs, spices or their oils can activate the immune function, as well as promote antioxidant, antiviral, anthelmintic and antibacterial activities. Due to the increased incidence of lifestyle diseases and the numerous side-effects associated with allopathic medicines, there has been considerable interest in developing effective nutrient-based complementary medicines, vitamins and herbal products. These products are also increasingly being formulated out of the growing acceptance that nutraceuticals have definitive merit in the treatment and prevention of COVID-19.

Inflammation is an uncontrolled, complicated biochemical process carried out by both immune cells and non-immune cells [1]. Inflammation can also be defined as the sequential release of pro-inflammatory cytokines [2]. Thus, the inhibition of pro-inflammatory cytokines *i.e*. interleukin (IL)-1, IL-6, IL-12 and tumor necrosis factor-alpha (TNF-a), may prevent inflammatory diseases and inflammatory associated disorders [3]. Inflammation occurs in response to harmful stimuli, *i.e*. tissue injury, oxidative stress, infection, irritation and microbial attack, to maintain homeostasis. The key role of inflammatory reaction is to protect the body from any harm, by the actions of immune cells, *i.e*. macrophages, monocytes and natural killer (NK) cells, upon activation of various molecular signaling pathways.

Macrophages and monocytes are important in inflammatory responses and key sources of pro-inflammatory cytokines and enzymes *i.e*. interleukins (ILs), tumor necrosis factor-a (TNF-a), cyclooxygenase (COX), and nitric oxide synthase (NOS) [4, 5]. The genes that are responsible for the initiation of pro-inflammatory mediators are induced during the inflammation process. The tumor necrosis factor *i.e*. TNF-a and IL-1b are cytokines that act as signaling molecules for immune cells and direct the inflammatory responses [6]. Cyclooxygenase-2 (COX-2) is responsible for the production of pro-inflammatory prostaglandins. That's why it is the main target for many anti-inflammatory and anti-cancer drugs [7, 8]. Nitric oxide (NO) is a free radical that is responsible for many pathophysiological and physiological processes, *i.e*. inflammation and neurotransmission. The formation of nitric oxide is catalyzed by the conversion of L-arginine to NO and L-citrulline. Expression of the inducible isoform of NOS (iNOS) in activated macrophages is responsible for the production of NO during inflammation. It is also important to discuss that nuclear factor-kB (NF-kB) plays a key role in the immune system [9]. NF-kB is well known to regulate the expression of nearly all inflammatory mediators that are involved in inflammation [5]. Nuclear translocation of NF-kB in response to various pro-inflammatory stimuli is associated with the activation

of the inflammatory cascade and therefore, this transcriptional factor is a primary target of many anti-inflammatory therapeutic strategies [10].

A cascade of molecular events in inflammatory cells stimulates the production of inflammatory mediators *i.e*. tumor necrosis factor (TNF)-α and nitric oxide (NO) are cytotoxic to the host cell and pathogens that are responsible for tissue injury. Although inflammation is considered a vital defense mechanism in the human body, responses to inflammatory reactions lead to serious problems when the reactions prolong, *i.e*., chronic inflammatory conditions. Persistent inflammation causes many chronic diseases *i.e*. asthma, multiple sclerosis, cancer and rheumatoid arthritis [11]. So, inflammatory mediators are important to prevent immune cells from tissue injury and also to prevent inflammation-associated disorders. In this context, anti-inflammatory agents are highly recommended and desirable for proper body functioning.

The plant kingdom comprises several plants that have medicinal value due to bioactive compounds. The plant compounds that are responsible for the health-improving effect are known as phytochemicals and they are widely found in various fruits and vegetables (Table **1**). More than 100 natural anti-inflammatory agents have been proven through various clinical experiments [12]. Recently studies have been focused to isolate, screen, identify and commercialize biologically active molecules in the international market. Unfortunately, plant-based herbal medicines are only restricted to certain communities in which such medications were first introduced. In this way, the knowledge regarding the utilization of plants as a medicine and their application is only limited to folk wisdom that excelled through generations. Recently such plant-based medication has received considerable attention from the pharmaceutical and medical industries but up till now only a small fraction of herbal plants have been evaluated. In the past few years, many studies just focus on the meditational properties of higher plants with ethnobotanical histories. This may be due to several reasons (1) interest in plant-based therapies, (2) concern regarding possible side effects of allopathic medicine (3) lower cost of phytotherapy, and (4) many plant-based or herbal medicines successfully substitute allopathic medicines.

No doubt, that bioactive compounds extracted from fruits, vegetables, legumes and medicinal plants are important in the treatment as well as in the prevention of chronic disorders. Bioactive molecules from natural plants are now gaining more attention due to their treatment as anti-cancer, anti-diabetic, anti-carcinogenic, anti-inflammatory, and anti-aging agents [24]. Approximately, 25% of drugs are derived from herbal plants with or without further variation [25] and still many plant-basedbioactive compounds are pharmacologically unexplored. From ancient

CHAPTER 5

Drug Therapies against Acute Respiratory Distress: A Critical Endpoint of COVID-19

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Abstract: Pulmonary diseases have been increasing for decades, which are responsible for the high incidence of morbidity and mortality all over the world. Since the year 2019, the world suffers from coronavirus disease 2019 (COVID-19) which is caused by SARS-CoV-2 and it was classified as a pandemic respiratory disease by the World Health Organization (WHO). The problem of this virus is the lack of a medicine or a specific antivirus drug to combat it, so many approaches have been designed to protect the patients from its symptoms and side effect and also to raise the human innate immunity. Consequently, this chapter will provide an overview of herbs and their derived natural products which have anti-inflammatory, immunomodulatory, and anti-microbial activities which might be beneficial for the discovery of structurally-related compounds that can be candidate therapeutics alleviating the symptoms associated with acute respiratory diseases.

Keywords: Anti-Inflammatory Herbs, COVID-19, Immunomodulatory Herbs, Respiratory Distress.

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INTRODUCTION

Pulmonary diseases rate has been increasing for decades, accounting for the worldwide high rate of morbidity and mortality [1]. Among pulmonary diseases, acute respiratory distress syndrome (ARDS) is a life-threatening severe form of acute respiratory failure with a more than 25% mortality rate [2]. This pulmonary disease is characterized by pulmonary inflammation mediated by several inflammatory mediators [3].

A pneumonia of unknown origin was discovered in Wuhan, China in December 2019, and was later reported by the World Health Organization (WHO) to be an infection caused by a novel Coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was declared a pandemic disease after being exposed to contaminated droplets or surfaces. The clinical spectrum of the infection ranges from mild upper respiratory tract illness that are common among other viral respiratory infections such as fever, dry cough, and dyspnea, to severe acute respiratory syndrome (ARDS) [5, 6]. ARDS is a complex clinical syndrome characterized by acute inflammation, microvascular disruption, severe hypoxemia with acute respiratory failure, shock, multiple organ failure and death as a common outcome [7]. The infection may be accompanied also by other symptoms such as headache, fatigue, lymphopenia and diarrhea [8]. People with underlying medical problems such as chronic respiratory, metabolic or cardiovascular disorders are more likely to experience a life-threatening illness, if they are infected with SARS-CoV-2 [9].

Contemporary approaches to developing drug therapies against COVID-19 have not been productive because of the complex nature and pathogenesis of the disease. Thus, the treatment of this respiratory disorder often involves the use of antibiotics, antivirals, anti-inflammatory therapies, smooth muscle relaxants, anticoagulants and anti-platelets [10, 11]. Current recommendations for the self-management of COVID-19 include rest and self-isolation in early and mild symptoms without underlying conditions. The use of pharmacological therapies is recommended in case of severe symptoms only.

Natural remedies have been used in folk medicine for many years and the scientific evidence for the use of herbal-derived natural products has been increasing considerably in the last years [12 - 16]. Many herbal-derived natural products such as terpenoids, flavonoids and alkaloids have *in vitro* and *in vivo* biological effects as anti-inflammatory, antiviral, antiplatelet, anti-allergic, and antioxidant [15, 16], representing adjunctive pharmacologic therapy that may improve COVID-19 and associated ARDS [17, 18]. In recent years, several

herbal-derived natural products have been tested in experimental models and have been shown to inhibit multiple inflammatory pathways associated with ARDS and COVID-19 at a molecular level. Because plant extracts or their compounds are pleiotropic in nature, they are targeting multiple pathways and have been shown to be relatively safe.

Here, we review natural remedies shown to attenuate lung inflammation and injury as well as herbal-derived natural products in acute respiratory distress and COVID-19. Additionally, we introduce natural products inhibiting SARS-CoV-2 *via* boosting the body's immunity.

CHARACTERISTICS OF HUMAN CORONAVIRUSES AND SARS-CoV-2

Coronaviruses (CoVs) are a group of enveloped, signal-strand positive-sense RNA viruses with club-like spikes on their surface, possessing the largest genome of all RNA viruses [19]. CoVs can infect both birds and mammals [20].

Among human CoVs, four of them cause minor symptoms: Human coronavirus NL63 (HCoV-NL63), Human coronavirus HKU1(HCoV-HKU1), Human coronavirus 229E (HCoV-229E), and Human coronavirus OC43 (HCoV-OC43). Severe symptoms have been documented for Middle East Respiratory Syndrome related Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [21]. SARS-CoV-2, from other human CoVs, has the highest reproductive number [22]. Apart from its responsibility for ARDS, several cases infected with SARS-CoV-2 were reported to have digestive problems suggesting the spreading of the virus also through the oro-fecal route [23].

SARS-CoV-2 infection is initiated via the interaction with angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease, serine 2 (TMPRSS2) on host cell membrane [24, 25]. SARS-CoV-2 can cause respiratory and homeostatic problems, leading to sepsis, by binding to the ACE2 protein on lung and intestinal cells. The mortality of COVID-19 is mainly due to severe cytokine release syndrome, ARDS and immunosuppression [26, 27]. As a preventive line for COVID-19, several vaccines are in pipelines, their efficacy remains arguable yet.

CONTRIBUTION OF THE INFLAMMATORY PATHWAYS TO THE PATHOGENESIS OF ACUTE RESPIRATORY DISTRESS AND COVID-19

The pathogenesis of SARS-CoV-2 infection begins with the entrance of the virus into the host body through various transferrable modes like direct/indirect contact,

CHAPTER 6

Medicinal Spices for the Prevention and Treatment of Coronavirus Disease-2019

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Abstract: By the end of 2019, and by the year 2020, the COVID virus had spread, and in March 2020, the World Health Organization declared COVID 2019 an epidemic that invaded many Arab and foreign countries and claimed many lives. Since ancient times, medicinal plants have played an important role in treating many epidemic diseases. A Cochrane study confirmed that herbal plants have an effective role in treating respirato-

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ry epidemics such as SARS. In China, the National Health Committee explained the role of herbal plants in the treatment of COVID-19 in addition to Western treatment. Studies have shown that nutrition has an effective role in treating the virus, as foods rich in vitamin C are used to treat respiratory viruses. Plant food such as fenugreek, curcumin, cinnamon, and black pepper that are rich in bioactive compounds can be of help in treating COVID.

Keywords: COVID-19, Natural plants, Traditional medicine, Vitamins, Western medicine.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is caused by the SARS-CoV-2 virus, which infects the respiratory system and causes many health risks [1 - 3]. Currently, the entire world is suffering from the COVID-19 infection, a pandemic disease, which pressurized numerous countries to follow lockdown procedures to ensure the safety of their citizens [4]. During this time, every country's government is interacting with their research teams to overcome this problem that is created by the COVID-19 infection. According to Worldometers, by November 11, 2020, the number of cases was 50636124 in the world, whereas in Pakistan, 343189 COVID cases were reported [5]. Apart from all the strategies and treatment plans that were introduced, medicinal plants are being used in the treatment of COVID-19.

In light of the COVID-19 pandemic, scientists have sought to discover an effective vaccine, but this will require more time and study, and that vaccine is likely to have side effects that may not appear except in the long run. Therefore, scientists turned to natural products and herbal plants in an attempt to find an effective treatment for this delinquent virus, and it yields effective fruits in treatment with fading of unwanted side effects of the chemical drug [6]. About 80% of the world's population uses medicinal plants (spices and condiments inclusive) to prevent and manage different ailments [7]. The herbs and spices are important for boosting immunity as shown in many studies.

In this review, some medicinal plants that are proven effective in treating and preventing COVID-19 will be highlighted.

Medicinal Plant Spices and Herbs for COVID-19

Ginger

Ginger, bearing the scientific name *Zingiber officinalis* (Zanjabeel or Adrak), is a fruitful herbaceous plant that grows in tropical areas. It has been used in

alternative medicine in the treatment of many ailments such as blood pressure, diabetes, high blood fat, headaches, colds, cough, and sore throat. Ginger contains many biological compounds, such as bioactive constituents: Zingiberene, Zingerone, Gingerol, Gingerdiol, Shogaol, Paradols, and Curcumene [8]. Ginger has many benefits as it is antibacterial and anti-fungal, anti-diabetic, anti-viral, and anti-inflammatory. It is used as a spice, a flavoring agent having great medicinal importance and it belongs to the family Zingiberaceae [9, 10]. It contains 1-3% weight of volatile oils, which is responsible for its unique flavor and particular aroma. World Health organization (WHO) considers ginger as anti-emetic, cholagogic, and anti-inflammatory. Other pharmacological properties possessed by ginger include antioxidant, antimicrobial, anti-asthma and expectorant, respiratory protective, antipyretic and analgesic properties [11, 12]. 6-Shogaol interferes with the inflammatory cascade, inhibits COX, and releases prostaglandin [13]. Further *in vitro* studies show that 6-gingerol and 6-shogaol present in ginger have antiplatelet aggregation activity [14]. It helps in treatment of chronic diseases due to its anti-inflammatory and immuno-modulatory effects [15]. Six weeks use of ginger reduces the inflammatory cytokine plasma levels of interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) and thus reduces the chance to infection. Such a strategy is followed in COVID-19 treatment [16]. Ginger as an immune booster basically inhibits the human respiratory syncytial virus (HRSV) induced plaque formation on airway epithelium by blocking viral attachment [17]. A fresh ginger in high concentrations activates mucosal cells to secrete IFN-β which is responsible for the reduction in viral progression [18]. Sudanese people take ginger, tea, or coffee as the local treatment for common cold and cough, which is the major symptom of infection with corona virus as it provides protection and quick recovery from the disease [19, 20]. A randomized study trial indicated that it is effective in the treatment of respiratory diseases [21]. Some scientific research has proven that ginger is effective in treating COVID-19 [22].

Garlic

Garlic, botanical name *Allium sativum* (Lahsun), is another most common spice and is used for various diseases due to its great medicinal importance [8]. It contains mostly sulphur-based compounds which are responsible to create their aroma and other constituents are diallyl polysulfides, vinyldithiin, ajoene, S-allyl cysteine, alliin and few non-sulphur compounds like enzymes, saponins and maillard reaction products [23]. It shows remarkable pharmacological properties such as antiinflammatory and antiviral properties which help in curing various types of diseases like cardiovascular, cancer, common cold, influenza virus [24]. It acts as an immunity booster and is effective against viral, bacterial, and fungal organisms. It is highly enriched in antioxidants against free radicals. It shows

CHAPTER 7

Boosting Host Immunity to Combat Coronavirus Disease-2019 (COVID-19)

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Abstract: Despite significant efforts in drug discovery and development, combating Coronavirus Disease (COVID-19) still remains to be an increasingly challenging health problem because of the fact that the recommended current therapies are intended only for the symptomatic treatment and/or prophylaxis of SARS-CoV-2 infections/ COVID-19 patients, but do not cure the disease. In this context, several complementary and alternative, but potential healthcare practices (CAMs) that could effectively boost host immunity are firmly believed to be one of the major medical interventions for the prevention as well as control of COVID-19. In this review, several immunity-boosting measures based upon traditional healthcare practices including traditional herbal remedies, home remedies, and alternative and complementary therapies including yoga and naturopathies to fight against SARS-CoV-2 infections/ COVID-19 have been reviewed.

Keywords: Antiviral Herbs, Boosting Immunity, Coronavirus, Immune Modulators, SARS-CoV-2, Yoga and Naturopathy.

INTRODUCTION

The current pandemic outbreak of coronavirus disease-2019 (COVID-19) has become an increasing disaster to public health across the globe. This infectious disease was first identified as the cause of an outbreak of viral pneumonia in the Wuhan city, China in the late December 2019, and the onset of pneumonia-like symptoms of the disease was first appeared on 1 December 2020 [1]. The World Health Organization (WHO) originally named the new virus as 2019 novel coron-

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avirus (2019-nCoV) on 12 January 2020 and then officially named this infectious disease as coronavirus disease-2019 (COVID-19) on 12 February 2020 [2]. The virus causing the infection was later named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Owing to its high infectivity and mortality rate, the World Health Organization announced COVID-19 to be a pandemic on 11 March 2020 [3]. To date, there have been three documented highly pathogenic and lethal human coronaviruses (hCoVs), namely severe acute respiratory syndrome coronavirus (SARS-CoV), middle-east respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2, because of their dreadful impacts on humans [4]. In 2003, the severe acute respiratory syndrome (SARS) epidemic due to the SARS-CoV infection appeared in humans. Later, middle-east respiratory syndrome (MERS) was also reported to be an epidemic due to the infection caused by MERS-CoV [3, 4]. However, hCoVs refer to a family of enveloped, positive-sense, single-stranded, and highly diverse RNA viruses belonging to the betacoronavirus subfamily of the coronaviridae family causing predominantly respiratory and gastrointestinal infections [4].

Complementary, alternative and traditional practices are considered as potential alternatives to Western medical approaches. Approximately over 80% of the world's population uses Complementary and Alternative Medicines (CAMs) [5]. According to Takeda and Okumura [6], CAM has been well-known since ancient times that traditional herbal practices, including naturopathy and physical exercises, provide tremendous benefits in numerous health implications. CAM modalities are believed to prevent or even cure many diseases such as infectious diseases, cancer and aging CAMs have been proven to be effective in boosting immune response against infectious diseases. Evidence-based research of traditional herbal practices mentioned in Ayurveda has been receiving considerable attention in India and abroad [7]. Apart from preventive or therapeutic potentials, herbal sources could also provide a significant source of immune-boosting materials that are believed to promote health conditions, to raise the body’s normal defence system against infectious disease (particularly against bacterial and viral infections) and also to prevent or cure various life-threatening to rare and common ailments or diseases [8, 9]. It has been suggested that as a CAM, curcumin, a polyphenolic compound extracted from spice and common food colorant called turmeric, can enhance the body’s immune response even if it is taken at low doses. In fact, the beneficial effects of curcumin in improving different infectious diseases are attributed to its ability to modulate the immune system and antioxidant effects as well [10, 11].

COVID-19 is an unprecedented infectious disease caused by the newly discovered SARS-CoV-2 with widespread occurrence, severe respiratory problems and devastating fatality worldwide [12]. Despite rigorous physical distancing,

quarantine and containment efforts globally, the incidence of COVID-19 continues to rise. To date, COVID-19 has afflicted the lives of millions of people across 216 countries and territories [13]. COVID-19 is a severe respiratory malady causing mild symptoms (fever, fatigue, dry cough, sore throat, headache, muscle aches, *etc*.) to severe illness (shortness of breath, chest pain, loss of movement and pneumonia) and fatal complications (acute respiratory distress syndrome (ARDS), cardiac arrhythmia, cardiovascular shock, heart attack, kidney or multiple organ failure and even death). The most serious complication is a type of pneumonia attack named 2019 novel coronavirus-infected pneumonia (NCIP) [14]. The disease affects men more severely than women. The mortality rate among elderly people (over 60 years of age) is much higher than among younger individuals [15]. Moreover, people with certain health conditions (co-morbid state or pre-existing diseases) such as severe heart diseases (coronary artery disease, heart failure or cardiac myopathies), respiratory diseases [chronic obstructive pulmonary disease (COPD), asthma], kidney disease, sickle cell disease, obesity or type 2 diabetes, and immunocompromised people including those receiving cancer chemotherapy have a higher risk of developing the severe disease complications and disease fatality [16 - 18].

As per current consensus, COVID-19 has imposed a significant health care crisis alongside severely affecting the global economies. Several physical precautionary measures that are currently being undertaken to curb the spread of SARS-CoV-2 infection include avoiding exposure to the virus by regular hands washing with soap water or by alcohol-based hand sanitizer, covering nose and mouth or wearing face mask, maintaining physical or social distancing *etc*. Apart from these, certain therapeutic/ prophylactic interventions that are currently in clinical practice include antiviral or anti-retroviral medications, corticosteroids immunosuppressants, breathing support such as mechanical ventilation and blood plasma transfusions (convalescent plasma therapy). Since no specific approved drugs or vaccines that can cure COVID-19 are currently available, the development of potential alternative therapeutic and/or prophylactic regimens is an urgent need of the hour. Exploring the pathogenesis of viral infections and their interactions with the host immune system is certainly necessary for the successful prevention and treatment of the disease. Boosting/ modulating the host immunity adopting traditional and alternatives health care practices/ measures can effectively protect the body against developing viral infections. In this review, certain alternative, but effective health care approaches that could boost effectively host immunity in the prevention of COVID-19 are summarized herein (Fig. **1**). Our objective was to create general awareness among readers, researchers and general public about various alternative health care strategies that could be adopted for the prophylactic management of COVID-19.

CHAPTER 8

Functional Foods, Herbal Supplements and Nutraceuticals in the Management of Coronavirus Disease-2019 (COVID-19)

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Abstract: Coronavirus disease 2019 (COVID-19) is a unique disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has caused mortalities throughout the world. This unique coronavirus is extremely contagious and has no effective therapy or particular medications. It caused increased worldwide mortality and lockdown. The Food and Drug Administration (FDA) has permitted the use of COVID-19 vaccination in this emergency situation. However, there are concerns regarding the new COVID-19 vaccine's safety, effectiveness, and long-term protection. A deteriorated immune system is an eminent risk factor for viral influenza infections. Many individuals all around the world are interested in herbal nutraceuticals to preserve their health and strengthen their immune systems. The use of dietary supplements, herbal medications, and foods with protective benefits, such as functional foods, improves the immune system's ability to avoid and control pathogenic viral infections.

Keywords: Antioxidative effects, COVID-19 management, Immunological functions, Immunomodulators, Nutraceuticals, Plant-derived compounds, Probiotics, Probiotics.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a deadly disease brought about by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), a virus belonging to the coronavirus family. Since December 2019, the disease has

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changed the world in terms of food, living and travelling habits owing to its highly contagious nature [1]. Individuals living with conditions such as diabetes type 2 mellitus, chronic obstructive pulmonary disease, obesity, serious cardiovascular or cerebrovascular diseases, haemoglobin disorder, chronic kidney disease, weakened immune system and cancer are at a greater risk of fatality from the disease than normal persons.

Impaired immune regulation plays an indispensable role in its pathogenesis leading to grave conditions of COVID-19 cases. These cases need to be under control in COVID-19 as severe cases of the illness necessitate intensive care, hospitalization, ventilators or else may result in death. Despite recent reports of substantial research towards the development of viable therapies to combat this global health issue, there is still no licensed medication for SARS-CoV-2. People are looking for strategies to protect themselves from the COVID-19 virus through prevention [1].

EPIDEMIOLOGY OF COVID-19

Coronaviruses are important diseases in both humans and animals [1]. Human coronaviruses are members of the Coronaviridae family, which is divided into two subfamilies: Orthocoronavirinae and Torovirinae. They were first discovered in the 1960s. There are four genera of coronaviruses in the Orthocoronavirinae family: alpha, beta, gamma, and delta coronaviruses. Coronaviruses can be found in all four genera of birds and mammals, including bats. The first CoVs found that caused sickness in poultry and people were avian infectious bronchitis viruses (IBV). Following the discovery of IBVs, numerous more major CoVs related to human illnesses, such as SARS-CoV, MERS-CoV, and SARS-CoV-2, were found. Because of the scale of the outbreak and the quick transmission of diseases, the seventh human CoV (SARS-CoV-2) has arisen as the most important CoVs [2].

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, Hubei Province, China. It swiftly swept across China, resulting in an epidemic and a worldwide pandemic. In February 2020, the World Health Organization termed the condition COVID-19, which stands for coronavirus disease 2019. COVID-19 is caused by the virus' severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as 2019-nCoV. SARS-CoV-2 (COVID-19) has been transmitted from person to person. Infected people's droplets, fomites, and aerosols usually disseminate through the respiratory tract. A healthy person can become infected with the virus by touching contaminated surfaces and then touching their nose, eye, or mouth without washing their hands [3].

COVID-19 patients experience severe forms of the disease, including decreased basophil, eosinophil, and monocyte percentages, increased neutrophil to lymphocyte percentages, respiratory failure, acute respiratory distress syndrome, multiple organ failure, and also death. Several years of work resulted in the creation of a vaccine, which is currently accessible as the only key to prevent the COVID-19 pandemic and eradicate this disease [4].

DIETARY IMMUNOMODULATORS IN COVID-19 MANAGEMENT

A dietary supplement is a supplement that contains high quantities of vitamins and minerals to supplement the nutrients we get from our food. Genetic factors and dietary choices have the greatest impact on the immune system. Appropriate and balanced nutrition should be emphasized for COVID-19 management in order to improve immune systems and avoid or overcome it with minimal damage. Consumption of antioxidant-rich, vitamin- and mineral-rich vegetables and fruits, as well as protein-rich dietary sources, must be increased. To boost body resistance, people should combine dietary supplements with a healthy, well-balanced diet [5]. Supplements, vegetable and fruit eating, spices, nuts, and nutraceuticals are recommended due to their high level of micronutrients, dietary fibre, and bioactive components [5]. Antioxidant and immunomodulatory properties of plant-based meals are enhanced, and gut-beneficial microorganisms that aid the immune system are increased. Water, minerals like iron, zinc, magnesium, selenium, and copper along with micronutrients like vitamins A, C, D, E, and all kinds of B, combined with a healthier lifestyle, can help to promote health and conquer infection. Several researchers have looked into the effects of potent antioxidant plants and their compounds, such as glycyrrhizin, silvestrol, gingerol, allicin, nimbolide, myricetin, quercetin, on viral infections, including COVID-19. These plant-based diets are critical in improving people's immunity in COVID-19 management [6]. The versatility of secondary metabolites may provide novel antibiotics to tackle Multi-Drug Resistant microbes too.

FUNCTIONAL FOODS, HERBAL SUPPLEMENTS AND NUTRACEUTICALS IN DISEASES MANAGEMENT

Functional foods are an integral element of a healthy eating and nutritional routine [5]. Natural or processed foods containing effective, non-toxic biologically active substances that can regulate physiological functions are referred to as functional foods. Functional food components include phenolic acids, carotenoids, polyphenols, flavonoids, phytoestrogens, phytosterols, isocyanates, soluble dietary fibres, symbiotics, probiotics, and prebiotics [5]. These nutrients are important for maintaining good health and avoiding chronic disorders. Respiratory disorders such as asthma, as well as numerous infectious diseases,

CHAPTER 9

Aromatic Plants, Essential oils, Carminatives, Tea Plants and Expectorant Herbs for the Management of COVID-19

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Abstract: SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) leads to coronavirus disorder (COVID-19). It was detected in Wuhan City, China, in December 2019 and extended to different provinces in China. The drug discovery strategy that holds the thrust of the COVID-19 pandemic is the existing trial of broad-spectrum antiviral drugs. However, molecular docking combined with chemical synthesis assists in discovering various synthetic agents, above one-third of FDA (Food and Drug Administration)- are naturally occurring products as approved drugs. Natural derivative products from different sources of fungus, plant and marine have been abundant in nutrition/ phytochemicals to prevent various disease discoveries for many diseases' prevention. There are scarcely any country that is left intact by the coronavirus outbreak. Only the considerable well-known health threat still now requires it to be managed as early as possible. To date, there is no development of drugs or vaccines that have been proven clinically against COVID-19. Various secondary phytoconstituents with antiviral activities have been extracted from medicinal herbs. Different research works have been demonstrated all over the globe to find antiviral medication effectiveness against SARS-CoV-2 in COVID-19 pandemic. The best preventive measures against COVID-19 infections would be searching for the molecules responsible for modifying or disturbing any pathways related to the virus replication cycle. Natural compounds are capable of altering or inhibiting the configuration of the structural protein of (spike glycoprotein), non-structural proteins (3-chymotrypsin-like protease, papain-like protease, helicase, and RdRP) and accessory proteins encoded by the SARS-CoV-2 genome that are required to be investigated.

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Hence, various natural products and herbal extracts may prove as potent therapeutics in treating the symptoms related to SARS-CoV-2 infection. In this context, we will present some traditional plants/herbs that are found effective against viral activities and reduce the contamination risk by Coronavirus and cure some symptoms of COVID-19, mainly respiratory problems.

Keywords: Aromatic plants, COVID-19, Expectorant plants, Herbal tea, Management of SARS CoV2, Spices.

INTRODUCTION

COVID-19, more frequently suggested as Novel Coronavirus, is related to respiratory diseases in humans. It was announced as an epidemic and pandemic worldwide by the WHO (World Health Organization) in the first quarter of 2020 [1]. According to some of the latest data and other following websites, there are presently over and above 1.3 million population contagious by the Novel Coronavirus over the globe, with nearly 75 thousand mortality rate reported from various regions of the world [2]. Till then, India was allocated out of the list comfortably from the rest of the infected nations by significant boundaries, but current events assist its hike to 27th position, which is a matter of concern. The morbidity rate is below 3%, preferable to the world's ~5.5% morbidity rate. However, the transmission model is gradually leading to an exponential inclination towards the immense loss of survivability and infrastructure. Different countries are focusing on India at present as a World Leader, and still WHO recognized that the world is looking nearly to Indian approaches to hold this epidemic outbreak [3]. India accounts for a global one-fifth global population and thus is the second most significant nation globally. SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) causes coronavirus disorder (COVID-19). It was detected in Wuhan city, China, in December 2019 and extended to different provinces in China. Then the World Health Organization (WHO), on May 8th, 2020, reported 3,759,967 coronavirus positive cases, and the death count globally attributed to novel Coronavirus reached 259,474 [4]. Till now, more than 212 nations and territories have confirmed SARS- CoV-2 related contagious cases. Then WHO announced on January 30th, 2020, the COVID-19 as a Public Health Emergency of Global Concern. In India, the positive case of SARS-CoV2 was observed on January 30th, 2020 in Kerala. Eventually, there was a remarkable rise in the number of COVID-19 instances [5].

As previously introduced, SARS-CoV-2 is the causal organism of COVID-19 that belongs to the Coronaviridae family. It has close resemblance to other β-CoVs, the virion SARS-CoV-2 with a ~3 kb genome size. It also consists of a nucleocapsid containing genomic RNA, and nucleocapsid (N) protein is phosphorylate [6]. The nucleocapsid is encased in a phospholipid bilayer. Two

spike proteins of different types embed it: spike glycoprotein dapper in all CoVs present and the hemagglutinin-esterase allocated entirely in some CoVs. The spike (S) protein performs a pivotal character receptors binding and is the main lead for identifying transmission capacity and host tropism. The viral envelope (E) and the matrix protein (M) are also allocated in the viral envelope [7].

The drug discovery strategy that holds the thrust of the COVID-19 pandemic is the existing trial of broad-spectrum antiviral drugs. In addition, it has been employed to treat other different viral contagions. Application on cytopathy, plaque formation, and virus production in pseudotyped and live CoVs to observe the drug's effect was performed through some standard tests [8], by utilizing the drug discovery approach, which encompasses interferon α, β and γ, ribavirin, arbidol, along with cyclophilin inhibitors [9]. Additionally, to examine the broad spectrum of present antiviral drugs, another approach of anti-SARS-CoV-2 drug discovery would be the screening of chemical libraries, which includes a better deal of existing databases or compounds with the transcriptional signatures in diverse cell lines [10].

A notable exception reported is the anti-HIV protease inhibitor lopinavir-ritonavir, to be potent for SARS-CoV in models of non-human primates and non-randomized clinical trials. Additionally, Nelfinavir, a particular anti- HIV protease drug, has been detected to hold SARS-CoV sound inhibition, evocating a potent candidate for COVID-19 target [11]. Numerous agents have been chosen as therapeutic alternatives in clinical trials for SARS-CoV-2 (Table **1**).

Table 1. Different therapeutic agents for SARS-CoV2 and its mechanism of action.

Therapeutic Drugs	Mechanism of Action
Darunavir	Second generation protease inhibitor
Aciclovir	Nucleoside analog
Amprenavir	Protease inhibitor (HIV)
Amantadine	Interferes with transmembrane M2 protein
Faldaprevir	HCV protease inhibitor
Galidesivir	Protease inhibitor- Adenine analog
Indinavir	HIV protease specific inhibitor
Nelfinavir	Protease inhibitor
Remdesivir	Prodrug-active nucleoside analog C- adenosine triphosphate-(Ebola)
Tenofovir	Acyclic nucleoside analog adenosine monophosphate
Zanamivir	Neuraminidase inhibitor
Umifenovir	Hemagglutinin inhibitor (influenza)

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