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Phytochemicals: A promising immunomodulators against COVID-19 infection

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Abstract
COVID-19, a disease induced by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), has been the cause of a worldwide pandemic. In recent days, extensive research works on the development of effective therapeutics against this global health crisis have been reported, but there is still no approved therapy against SARS-CoV-2. This pandemic situation is strongly admiring the acceptance of immunomodulatory drugs as a part of routine diet as well as a drug regimen in the management and treatment of pathogenic infectious diseases. The present review draw attention to the potential traditional herbal medicines which have been used since past few decades as ethno-medicine and have scientifically of significantly report for boosting the human immune system. This article might be a good source of information for the researchers and practitioners working in the related field.

Keywords: COVID-19, SARS-CoV-2, phytochemicals, natural therapeutics, Immunomodulators

Introduction

COVID-19, A novel coronavirus induced pneumonia, has rapidly increased to an epidemic scale and affected whole human population globally (WHO, 2020) [1]. In India, the first case of COVID-19 was traced in Kerala on January 30, 2020 which was an imported case from Wuhan, China (Sahasranaman and Kumar, 2020) [2]. Coronaviruses are large viruses comprising of four genera, namely alpha, beta, gamma, and delta. The beta-coronavirus class includes severe acute respiratory syndrome (SARS) virus (SARS-CoV), Middle East respiratory syndrome (MERS) virus (MERS-CoV), and the COVID-19 causative agent SARS-CoV-2 (Li G. *et al*., 2020) [3]. Although there is an extremely high resemblance between SARS-CoV and the novel SARS-CoV-2, the SARS-CoV-2 is spreading rapidly as compared to the SARS-CoV, which may be explained by structural differences in the S proteins (Rabaan *et al*., 2020) [4]. Although the pathogenesis of COVID-19 is still not clear, patients with COVID-19 show non-specific symptoms ranging from no symptoms (asymptomatic) to severe pneumonia and death. However, the most common symptoms include fever, non-productive cough, dyspnea, myalgia, fatigue, diarrhea, lung damage, normal or decreased leukocyte counts, and radiographic evidence of pneumonia, which are similar to the symptoms of SARS-CoV and MERS-CoV infections (Rothan and Byrareddy, 2020) [5]. Complications include ARDS, acute heart injury, and secondary infections (Guo *et al*., 2020) [6]. The drugs being tested range from repurposed flu treatments to failed ebola drugs, to malaria treatments that were first developed decades ago (Lythgoe and Middleton, 2020) [7]. There is scale-up development of vaccines across the world by many pharmaceutical companies as well as research organizations. Considering the current situation, various treatment modalities have been well-thought-out, including traditional medicine, which has been widely used during the past epidemic outbreaks, including SARS and H1N1 influenza (Luo *et al*., 2020) [8].

The Indian Traditional System of Medicine is one of the oldest systems of medical practice in the world and has played an essential role in providing health care service to human civilization, right from its inception. India has the exclusive distinction of its own recognized traditional medicine; Ayurveda, Yoga, Unani, Siddha, and Homoeopathy (AYUSH) (Adhikari and Paul, 2018) [9]. These systems are based on definite medical philosophies and represent a way of achieving a healthy lifestyle with conventional and established ideas on the prevention of diseases and the promotion of health. The basic treatment approach of all these systems is holistic and the pharmacological modalities are based on natural products of plants, animals, or mineral origin. Given this, there is a resurgence of interest in AYUSH systems, which have helped the nation in the pandemic crisis due to plague, cholera, Spanish flu, etc. in the past. Hence, by repurposing the traditional uses of Indian medicinal plants and formulations, new treatment options can be identified to combat the current deadly pandemic (Ahmed *et al*., 2021) [10]. The present was focused on the potential traditional herbal medicines which have been used since past few decades as ethno-medicine and have scientifically of significantly report for boosting the human immune system.

Immunity

Immunity, the natural body defense mechanism that works against different types of harmful diseases and infection, are of two types: the first one is a short-term mechanism named innate mechanism which is the first-line defense of the body and the another one is an adaptive mechanism which is known for its memory, complexity and diversity (Calder, 2013) [11]. Humoral immune response (works by B lymphocytes) and cell-mediated cytotoxic response (works by T lymphocytes) are two subtypes of the adaptive immune system (Sharma *et al*., 2017) [12]. Antigenpresenting cells (APCs) like dendritic cells (CDs) help to innate immune response (Borish and Steinke 2003) [13]. By intermolecular cross talks, Cytokines, maintain physiological stability in the form of interleukins (ILs), interferons, and chemokines through their secretion in all nucleated cells by the inducible response to injury. Direct interaction of cells like B and T lymphocytes, T helper (Th) cells, natural killer cells and myeloid cells: Neutrophils, Basophils, Macrophage and

Monocytes and secreted synthesis by-products like immunoglobins, colony-stimulating factors and growth factors strongly controlled the immune response of the immune system (Alimonti *et al*., 2003) [14].

COVID-19 and Pathogenesis

COVID-19, an infectious disease caused by the recently identified novel Coronavirus, SARS-CoV-2, was unknown before the outbreak in Wuhan, Hubei Province, China in December 2019 (Chakraborty and Maity, 2020) [15]. Coronaviruses comprise a group of large, enveloped, positive-sensed, single-stranded RNA viruses that damage the respiratory tract of mammals including humans, bats, and other animals, leading to infections in the respiratory tract (Lu *et al*., 2020) [16]. Fever, tiredness and coughing are the most common symptoms of COVID-19. Some patients may have body aches, runny nose, loss of smell and taste, sore throat, diarrhoea and in case of serious illness difficulty in breathing may develop. Aged people and those with underlying medical problems are more prone to develop serious illness (Russell *et al*., 2020; Wang *et al*., 2019) [17, 18]. The pandemic has infected millions of people of more than 200 countries in short period of time and causes death of millions of people worldwide, and declared as Global pandemic by the World Health Organization (WHO). Human-to-human transmission of the virus via respiratory droplets or via contact is accelerating the rate of infection (Chan *et al*., 2019) [19]. According to the analysis of the Confederation of Medical Association of Asia and Oceania (CMAAO), there are huge numbers (30 to 50) of asymptomatic patients for each symptomatic COVID-19 patient. Asymptomatic patient remains either due to very small viral load or due to better immunity strategy. Epidemiological models envisage that a large number of asymptomatic or mildly symptomatic patients will help to build up the herd immunity to control the COVID-19 infection (Long *et al*., 2020) [20].

Similar to SARS-CoV, the SARS-CoV-2 S protein is a significant determinant for the entry of virus entry into host cells using angiotensin converting enzyme 2 (ACE2) receptor; but the binding affinity of virion S glycoprotein and ACE2 is 10-20 folds higher in SARS-CoV-2 as compared to SARS-CoV (Song *et al*., 2018) [21]. In severe cases of COVID-19 infection plasma concentrations of pro-inflammatory cytokines including interleukins (IL-6 and IL-10), tumor necrosis factor (TNF)-α, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1α, and production of IgM and IgG antibody are increased (Yuki *et al*., 2020) [22]. The IgG antibody last for a longer time than IgM antibody and is believed to play a protective role. Recent research reported the activation of pro-inflammatory cytokines such as nuclear factor-κB (NF-κB), interferon regulatory factor 3 (IRF3) and type I Interferons (IFN-α/β) and reduction of CD4+ and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients (Li *et al*., 2020) [23]. In SARS-CoV infection, Cytokine storm, a deadly uncontrolled systemic inflammatory response due to the release of large amounts of pro-inflammatory cytokines and chemokines by immune effector cells leads to acute respiratory distress syndrome (ARDS) and causes the death of many patients (Guo *et al*., 2020) [24]. Remdesivir and Favipiravir, two antiviral drugs are reported to reduce viral load (Pan *et al*., 2020) [25]. Feline coronavirus drug (GC 376) inhibits themain protease of SARS-CoV-2 and blocks virus replication (Vuong *et al*., 2020) [26]. In spite of several ongoing drug trials, there is no clear evidence at present that whether these antiviral drugs can cure COVID-19 infection or not. Keeping this is mind invention of new antiviral drugs for COVID-19 treatment and introduction of immunostimulating materials in regular diet as infection prevention measures will remain at the forefront.

Medicinal Plants

Medicinal herbs are powerful source of potentially bioactive molecules that give rise to potent drugs for the treatment of several health problems. Scientific researches clearly stated that various herbs possess immune-stimulating properties (Khodadadi, 2015) [27]. Different types of herbs have a wide range of phytochemicals like alkaloids, flavonoids, tannins, resins, glycosides, terpenes, saponins, carotenoids, plant sterols and phthalides. Many immunoboosting properties like antioxidants, anti-inflammatory, antitumor, antibacterial, antifungal and antipyretic are potently found in these phytochemicals. Many plants contain antioxidant compounds which are very effective against chronic diseases. Plants which are rich in flavonoids, vitamin C or carotenoids can enhance immunity. The flavonoids rich plants have anti-inflammatory action and boost the activity of lymphocytes and increases phagocytosis which help in interferon production. Above mentioned phytochemicals are potent immune-stimulants and boost immunity (Sharma *et al*., 2017) [28]. It is reported that micronutrients deficiency leads to several health problems including growth retention of physical and immune system (Kipkoriony and Jaja, 2012) [29]. In routine diet, a proper balance of carbohydrates, proteins, fats, vitamins and minerals is very essential to maintain the health of individuals and to prevent illness. Several research reports reveal that amino acids, vitamins and minerals are very essential components of the immune system as they take part in several metabolic reactions in the body including the immune system, increased sensitivity of B-cells and boost cytotoxicity of T-cells towards infected and transformed cells in the body (Cherayil, 2011) [30]. Compared to other conventional immunomodulators, the significance of rasayanas as immunomodulating agents is that they activate the immune function without altering the other basic parameters of the body (Balasubramani *et al*., 2011) [31].

Since the last fifty years the emerging trends of pathogenic infections specially the microbial threat has created a challenge towards the researchers, practitioners, and the Governments of developed and developing countries. Scientists all around the world are trying to discover the most effective antiviral drug to combat SARS CoV-2. Indian herbal medicines with 1000 years' experience in the prevention of pandemic and endemic infectious diseases may have significant role in this COVID pandemic. During the last few decades, many antiviral and immunomodulating polysaccharides such as xylan, acemannan, sulfated fucans, sulphated xylomannan, fucoidans, pectins, glucans, porphyran, glucoarabinan, and arabinoxylan have been identified from Indian medicinal plants; and their therapeutic applications is drawing attention of the researchers all over the world. Plant polysaccharide can inhibit the viral infection through interference with the viral life cycle or by improving the host immune response. Intake of certain immunomodulating plant polysaccharides may

also protect from the virus to a certain extent. This information may be utilised by general public for maintaining immunity in day-to-day life. Keeping in view the potential activity of medicinal plants, the herbal drug manufacturers, and the national and global research organizations should develop necessary strategies for furtherance of preclinical and clinical research on these promising therapeutic leads.

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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