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Review Article

Covid-19 Pandemic, Significance of Reimagining Immunity and Relevance of Medicinal Plants to Combat SARS-CoV-2 Infection: A Perspective

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Abstract

The Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, emerges as a pandemic is potentially a lethal disease which cause immense concern globally. The pandemic has generated mayhem throughout the worldwide due to insufficient threat evaluation. The present COVID-19 scenario has come into a precarious stage. SARS-CoV-2 has spread fast compared to other viruses including SARS due to increased globalization as well as pioneer adaptability in every environment. Due to this many agencies, researchers, health care workers are being engaged in different ways to tackle and mitigate the burden before it goes out of hand. Here we have highlighted some aspects of the virus and the disease symptoms of COVID-19. The importance of healthy immune system and reimagining the concept of immunity and the role of medicinal herbs in boosting individual immunity have also been discussed. The significance of Indian traditional medicinal practice in tackling diseases, the antiviral properties of medicinal plants and their relevance to SARS-CoV-2 have been point out. We have also highlighted the potential and the possible benefits the antiviral medicinal plants might have against SARS-CoV-2.

Keywords: COVID-19; SARS-CoV-2; Immunity and Immune Booster; Medicinal Plants

Introduction

The COVID-19 caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has resulted fear throughout the world and raised health distress globally ever since it emerge in December 2019. The viral disease has been acknowledged as a pandemic by World Health Organization (WHO). The outbreak has already claimed lives of many people across the globe. With the ongoing battle to combat this lethal virus, the WHO as well as many other health policy makers around the globe has strategized to disrupt human contacts, separate patients at initial phase, identify so as to reduce the transmission. Many companies and researcher are already engaged hard to find suitable vaccine and drugs. At this time it is extremely essential to comprehend the basic nature of the virus to combat the menace. The SARS-CoV-2 exhibited similar sequences as that of SARS-CoV [1]. However, its transmission capability and diagnosis are quite different. Several drugs are being evaluated very swiftly and also many drugs are in the final stage of clinical trials. At this juncture it is prudent and relevant to emphasize about the role of the body's immune system and immunity to tide over the infection. In this communication we intend to further reimagine the concept of immunity in fighting microbial infections. We will also be highlighting the immune boosting potential of some local herbs. India is a treasure house of many medicinal herbs with potential for treatment of various illnesses [2]. Several Indians ad-

opted the practices of Ayurveda and Siddha in treating many illnesses. In this context, by repurposing the Indian medicinal herbs, more novel treatment strategy can be expected to overcome this viral transmission and the menace. The pandemic having reached the stage of community transmission, it is apt to pay more attention in gathering relevant information on immune system of the individual and how to boost up the immunity of the community in the context of "herd immunity" would be worthwhile to mention. This review put forward the significance of immune system in combating infection and the relevance of medicinal herbs in boosting the immunity. Here it is intended to highlight the usefulness of traditional herbs in fighting against viruses similar to SARS-CoV-2.

Brief outlook of coronavirus and COVID-19

Coronaviruses, which comprise of 39 species falls under the broad category of Riboviria, belongs to the family Coronaviridae, suborder *Cornidovirineae* and order *Nidovirales* [3]. SARS-CoV belongs to the Beta- coronavirus genus and comes in the severe acute respiratory syndrome-related coronavirus species. Very few of these species infects human while majority of them are zoonotic in nature [4]. SARS-CoV-2 comes under the family Coronaviridae having capability to infect human as well as other animals [5]. It belongs to the subgenus Sarbecovirus resembling bat coronavirus, which shares 96.2% sequence homology [6]. The world witnessed the unexpected appearance of COVID-19 in 2019. The origin of the virus is still an ambiguity to the scientific community worldwide. On 11th February 2020 WHO declared the disease cause by the virus as COVID-19 [7,8]. The pathogen has been named as SARS-CoV2 [1]. It is pertinent to point out that SARS-CoV emerged in the year 2002. The virus requires relatively long incubation time of almost two weeks to show disease symptoms. Throughout the course of the infection viral replication takes place in upper and lower portion of respiratory tract, resulting in wound formation [9]. Infected individuals are manifest with general symptoms such as fever, cough, sore throat, dyspnoea and lesion in the lungs [10]. As the disease proceeds pneumonia starts appearing which leads to acute pneumonia and acute respiratory distress syndrome (ARDS rendering the patient to life-support system [11]. Viral replication is the important step for the survival of the virus once it enters human host cells. The survival of the virus in the host body depends on the replication of the viral RNA. SARS-CoV-2 virus replication is comparable to that of SARS-CoV which is a complex process and hence needs a meticulous understanding [12,13].

The transmission pace and infection rate of SARS-CoV-2 showed to be very noteworthy in spite of its similarity compared to SARS-CoV. The ability to mutate may be accountable for such a fast rate of spread and infection thereby making the virus a novel and also unique to SARS-CoV. Apart from the infection of the respiratory system, the COVID-19 also brings about diseases of the nervous system. The betacoronaviruses, such as the SARS-CoV has the ability to attack nervous system to cause neurological problems [14]. Coronaviruses, in the beginning attack peripheral nerves and enter the Central nervous system through the synaptic route as reported in HEV67 and avian bronchitis virus [15]. The neuroinvasive inclination of coronaviruses has been established to be a general attribute of these group viruses. SARS-CoV being similar to SARS-CoV-2, it is very probable that SARS-CoV-2 may possibly show similar prospective.

Reimagining the significance of immunity in the present pandemic

So as to defend from any type of infections including COVID-19, it is important to reinforce our immune system. So it is apt to reimagine and comprehend the concept of immunity. Therefore, an efficient immune system must be able to understand changes happening around and react suitably. There are continuous advances in understanding of the immunity and the immune system. Immunity is the ability of an individual to defend from disease and 'Immune system' comprises the parts in the body such as proteins, special cells, tissues etc. which guards against infections. It provides a vital function to thwart away infections. Immunity is largely categorized as innate and the acquired immunity.

The immune response that an individual possesses by virtue of birth is known as innate immunity. It is also known as the first line of defense since the immune response is initiated immediately or within hours of encountering with an antigen by the person. It is not considered as a permanent body defence mechanism as it is unable to recognize the same pathogen if exposed again in future. Human body defensive barriers such as anatomic, physiologic, endocytic and phagocytic, and inflammatory controls the mechanism of innate immunity. Neutrophils, macrophage, dendritic cells, mast cells, basophils, eosinophils, natural killer (NK) cells and innate lymphoid cells plays an important role in the functioning of innate immunity. The immune response or resistance obtain by an individual through the life time either by confrontation to certain

infections or by vaccination is referred to as acquired/adaptive immunity. The activities of innate immune cells trigger the growth of adaptive immunity. The major role of adaptive immune response is to differentiate 'non-self 'and 'self 'antigens and to develop long lasting immunologic memory that can tear down a specific pathogen in subsequent infections. T-cells, Antigen presenting cells (APCs) and the B-cells comprises the major elements of the adaptive immunity. APCs assist the T-cells in recognizing the specific foreign antigen. The cytotoxic T cells (CD8+ cells) bring about the destruction of the infected cells by foreign agents (such as viruses) and the tumour cells. T-helper cells (CD4+ cells) play an important role in establishing and maximizing the immune response. In contrast to T-cells, B-cells can recognize the foreign bodies directly and produces antibodies such as the Immunoglobulins which interfere during virus proliferation in the acute stage of infection.

Upholding immunity and strong immune system is a major concern especially during microbial infections as in the case of current COVID-19 pandemic. Many questions arise on the need and values of boosting the immunity at this juncture. The 'Immune booster' can be redefine as improving the body's immune system either by vaccination which are the only evidence based approach or by dietary supplements including vitamins, minerals, antioxidants, probiotics, and various functional foods. Food items which comprise of fruits are considered as healthy diets and also vitamins including vitamin C plays major role in boosting immunity. The indecisiveness of vaccine with regard to the fight of the present pandemic makes more sense to look at immune boosters. Generally food items such as cereals, legumes, mushrooms, green leafy vegetables etc. are considered to be effective to maintain healthy immune system. Constant exposure to sunlight, as well as doses of antioxidants from items such as garlic, onion, ginger, pepper, green tea etc. can add on to boost up the immunity. In addition, maintaining good life style, healthy habits, regular work outs, performing yoga, at the same time uphold sound emotion and mental state with sufficient sleep are considered vital for balancing a healthy immunity. Thus in the wake of COVID-19 pandemic, lots of interest and attention has been given in ways to strengthen one's immune system, and so as to build a mechanism of defense against the fatal virus. It is a known fact that immunity cannot be built up in a single day, however the scope is that eating a balanced diet and being physically and psychologically active would render enough to keep ones immune system in good condition. So it is essential to be aware of the usefulness of the plants around us which has capability to enhance the immune system. The relook of the potential of medicinal herbs/plants in the context of the present health crisis may be of prime significance in mitigating the effect of SARS-CoV-2 infection. Some of the traditional herbs/medicinal plants which possess immune boosting potential are being listed in table 1 along with their reported mechanism. It is deemed appropriate to highlight the fact that the caterpillar fungus (*Ophiocordyceps sinensis*) commonly known as keera jhar (yartsa gunbu in Tibetian language) is also obsessed with prospective competence to boost immunity. *O. sinensis* is endemic to the Tibetan plateau and mostly distributed in Tibet, Qinghai, Sichuan, Yunnan and Gansu province in China [16]. It is available in Nepal, Bhutan as well as in high altitude of Indian states such as Uttarakhand, Himachal Pradesh and Sikkim [17]. Previous study highlighted that cordycepin, the active compound found in Yartsa gunbu can inhibit lipopolysaccharide (LPS)-induced inflammation through the suppression of NF-κB in macrophage cells [18]. The effect of cordycepin on immune cells could be a novel target for development of immune modulators. It has been reported that during the 2003 outbreak of severe acute respiratory syndrome in china the Yartsa gunbu's value have established huge attention [19].

Herd immunity is another vital category of immunity which is also known as herd protection because it offers indirect defense to people who are not exposed to the infection when large inhabitants are already immune to the infectious disease. This category of immunity finds significance during vaccination program because those individuals, who cannot be vaccinated, such as the very young and immune-compromised, still tends to be protected against disease. In the context to SARS-CoV-2, herd immunity through ordinary infection is hypothetically possible once the herd immunity attains the threshold; the effectiveness of herd immunity mainly depends on the vigor and length of the immunity obtained. Immunity against SARS-CoV-2 can probably be envisaged into two broad ways. The first instance is the development of an efficient and harmless vaccine followed by mass vaccination program. The second one is the natural immunization of the people around the world with the pathogen over the time. The later is a sort of grave but far-reaching as it entail a huge people infected with the pathogen, and several who would succumb as a result of it. Therefore without a tangible vaccination schedule, ascertaining herd immunity may not be taken in the face value. And moreover there are no proven data as yet to highlight the potential of herd immunity as in the case of COVID-19 pandemic. Hence, it is essential to improve the immune system which is critical in combating against many infectious illnesses.

Common name	Scientific name	Family	Active component	Immune boosting mechanism	Reference
Roselle plant	*Hibiscus sabdariffa*	*Malvaceae*	Organic acids (hibiscus acid, 13-24%, Hydroxycitric acid), anthocyanins, polysaccharides and flavonoids	Immunostimulatory activity by increasing the production of IL-10 and decreasing the production of TNF-α.	[20]
Split gill (kind of Mushroom	*Schizophyllum commune*	*Schizophyllaceae*	Glycomannans	Activation of nuclear factor-kappa (NF-κB) and mitogen-activated protein kinase (MAPK)	[21]
Soya bean	*Glycine max*	*Fabaceae*	Isoflavone glycoside	Increase TNF-α, IL-6 and iNOS Activation of nuclear factor-kappa (NF-κB) and mitogen-activated protein kinase (MAPK)	[22]
Taro	*Colocasia esculenta*	Araceae	Flavonoids, alkaloids, sterols, tannins, phytates, Tarin, a GNA (Galanthus nivalis agglutinin) -related lectin	Enhances Cytokines expression IL-2, IL-1β, INF-γ and TNF-α	[23]
Keera Ghas, Yartsa gunbu (Caterpillar fungus)	Cordyceps sinensis (Synonym-*Ophiocordyceps sinensis*	Ophiocordycipitaceae	Cordycepin (3 -deoxyadenosine), cordycepic acid, Polysaccharides (CP), Ergosterol	Mitogenicity and activation of immune cells, such as lymph proliferation response, NK cell activity, Phytoheamagglutinin (PHA) stimulated interleukin-2 (ILS-2) and TNF-α) production on Human mononuclear cells (HMNC) resulting in production of cytokines.	[16,19,24,25]

Table 1: Traditional herbs/medicinal plants with immune boosting potential.

Further it will be appropriate here to reiterate and highlight some aspects and principles of antiviral immunity which states that the immune system usually controlled many human viral infection successfully, however some emerging viruses tends to overpower the immune system leading to severe morbidity and mortality, other viruses often developed mechanisms to overcome or evade the immune system and persist. In such scenario people with flawed in innate or adaptive immunity exhibit more stern viral infectivity. T-cell immunity is quite essential for control than antibody with severe viral infectivity. Antibody is important to reduce reinfection, particularly at mucosal sites. Immune memory is frequently adequate to thwart away secondary disease, but may not be applicable in all viral infectivity [26].

Significance of Traditional system of Indian medicine

It is deemed that the practice of traditional systems of medicine in India to be one of the oldest therapy in human evolution which occupies major responsibility in battling health care requirements [27]. Ayurveda, Siddha, Unani and Yoga, Naturopathy and Homeopathy comprise the main system of Traditional Indian medicines that are use for alleviating several illnesses [2]. Such traditional systems of remedy are often disregarded in the present scheme of contemporary drug development since their translational prospective have been repeatedly underrated. These medications may be unclear; however there are several applications reported in other medical field [28]. The phytochemical constituents present in plants may exert their function either singly or in amalgamation with other compounds in yielding the desired pharmacological result [29]. Several molecules have been obtained from plants based on the traditional use and later on modulated as medicine for treatment of diseases [30,31]. The investigation of compounds having antiviral efficacy is a continuous endeavor. Medicinal plants provide the raw substance for essential antiviral medicines in place of synthetic one [32]. Medicinal plants have replaced synthetic drugs as life-saving drugs [33] in treatment of many viral diseases. It is a matter of fact that the usages of these medications are obtained through verbal from one generation to other and therefore often tend to lost in due course of time, as there have been no appropriate recordings. Research activities based on these traditional practices concerning the medicinal herbs and plants need to be encouraged

so as to gain edge on their usage in clinical settings for the prevention and treatment of several diseases. Taking into account of the plants with antiviral, anti-inflammatory and antioxidant potential for consideration to analyze for their effectiveness in the treatment of COVID-19 could be useful. Some of the plants with antiviral potentials are being listed in table 2.

Scientific name of the plant	Family	Active component	Antiviral against	Reference
Colocasia esculenta	Araceae	Flavonoids, alkaloids, sterols, tannins, phytates, Tarin, a GNA (Galanthus nivalis agglutinin) -related lectin.	Tarin exhibited anti viral activity against SARS-CoV (SARS CoV, Frankfurt 1 strain) (FIPV, strain 79-1146)	[34,35]
Garcinia indica	Clusiaceae	-	Anti HIV activity: inhibition of HIV-1 Protease and HIV-1Integrase enzyme	[36,37]
Ananus comosus	Bromeliaceae	Bromelain	Anti HIV, Hepatitis C and Human Papilloma Virus	[38,39]
Hibiscus sabdariffa	Malvaceae	Protocatechuic acid (PCA)	HSV-2, Hepatitis A virus (HAV)	[40,41]
Houttuynia cordata.	Saururaceae	Hyperside Norcepharadione B Quercetin 3-rhamnoside (Q3R)	Anti SARS CoV Dengue virus serotype 2 (DEN2) HSV-1, Influenza A WS/33 virus	[42-46]
Bombax ceiba (Synonym -*Bombax malabaricum*)	Bombaceae	Kaempferol-3-O-(6″-O-E-p-coumaroyl)-β-D-glucopyranoside; Mangiferin; Quercetin	Respiratory syncytial virus (RSV)	[47]
Momordica charantia	Cucurbitaceae	Protein - ribosomal inactivating proteins (RIPs) Protein - MAP30	Influenza A (H1N1, H3N2, and H5N1), Hepatitis B virus, Dengue virus HIV, HSV-1, HSV-2	[48,49]
Momordica cochinchinensis	Cucurbitaceae	-	Influenza A virus H3N8	[50]
Alpinia galanga	Zingiberaceae	1'S-1'-acetoxychavicol acetate (ACA)	HIV-1 Influenza virus	[51,52]

Table 2: Some of the plants which possessed antiviral activities.

COVID-19 - the worldwide challenge

COVID-19 has been the most dangerous and emerged as pandemic menace all over the world since its outbreak during December 2019. Researchers and virologist are finding it a challenge to mitigate and find a solution for this lethal disease. One of the facts being, the viral infection has been acknowledged for its maximum frequency of recombination or replication giving rise to rapid creation of its progeny in the host cells. Due to excessive mutation as well as rapid alteration in structure, SARS-CoV-2 poses an obstacle for the analysis of the ailment and subsequent treatment regime. The high rate of mutation rate renders very hard to comprehend the genomic set up and virus interaction with the host [53]. Apart from this the ability of the virus to adapt and survive in various environmental conditions also makes it really difficult for the researchers to understand its nature. It is pertinent to point out that the first outburst of the SARS-CoV-2 happened during winter, where the environmental temperature was around 2°C to 10°C. Many people have been infected by the virus since then and the pathogen carries on existing under diverse environmental circumstances across many countries irrespective of the temperature variations. This makes the prediction of the virus on demographic association very difficult. Again the infected individuals who are asymptomatic

continue to travel or gather in social background infecting more people also posed several challenges for the researchers, government agencies as well as for health workers to mitigate the situation of the pandemic. Throughout the world government agencies are working hard to make to minimize human contact by enforcing countrywide shutdowns in public places. Other steps like social distancing, limit congregations of people minimize social interactions and self quarantined has been implemented so as to reduce the spread of COVID-19.

Concluding Remarks and Perspectives

The current COVID-19 pandemic has again urged and makes the scientific community to relook and discover the origin of coronavirus infections not only in animals but also in human beings. All the government and public health sectors throughout the world have taken preventive measures against the virus. The virus capacities for recombination, mutation, evade host immune system as well as infecting other species may account for its high pace of infectivity. In any kind of infection the body's immune system will initially have to fight against the foreign element or the virus. So, keeping a healthy immune system will definitely have a major role in combating such infection. It is essential to uphold immunity and strong immune system is a major concern especially during microbial infections as in the case of current COVID-19 pandemic. Maintaining healthy immune system will be of greatest advantage in dealing with SARS-CoV-2 infection and boosting the immunity may play important role in overcoming the COVID-19.

Relooking at individual immunity is predominantly relevant feature at this juncture where vaccine indecision plays a menace to the health of individual globally as result of COVID-19. So food supplements with effective immune boosting potential could play a vital role in combating the viral infection. At the same time healthy life style with balanced diets, regular work outs, performing yoga, uphold emotional and psychological strength as well as sufficient rest and sound sleep are vital in maintain immunity to thwart away infections. Hence in the wake of the present pandemic, lots of interest and attention has been given in ways to strengthen one's immune system, so as to build a mechanism of defense against the virus. It is a matter of fact that immunity cannot be built up in a day, however the idea is that a balanced diet and being physically and emotionally dynamic would provide enough to maintain ones immune system in good condition. Therefore, it is necessary to be aware of the usefulness of the plants around us which has the potential to enhance or boost the immune system. The recheck of the potential of medicinal herbs/plants in the context of the present health crisis may be of prime significance in mitigating the effect of SARS-CoV-2 infection. The present communication suggests the significance of the medicinal plants that possessed antiviral potential and have been used for treatment of diseases including respiratory conditions. Thus, thorough investigation in researches based on the medicinal plants might be beneficial in fighting the virus and the COVID-19.

COVID-19 spreads from individual to individual through the discharge of infected persons from nose or mouth. Therefore, it is imperative to remain isolated from infected individual. People having other medical circumstances namely high blood pressure, heart disease, lung disease, cancer or diabetes as well as aged persons tend to develop severe disease compared to others [54,55]. Further we reiterate some of the preventive measures as per the recommendations of WHO [56] to be adopted for safety purpose:

- To wash hands using an alcohol-based hand sanitizer which will kill the virus,
- To avoid touching eyes, nose and mouth when one is in outdoors,
- To remain well-run about the present bug,
- To avoid journey or congregation in crammed locations,
- Woman to breastfeed infants to enhance their immunity.

Countries all over the world are coordinating together in an effort to develop vaccines and drugs to prevent and treat COVID-19 [56]. Researchers must be encouraged dedicatedly to work more so as to develop safe and effective vaccine against COVID-19. While the vaccine awaits it's imperative for all the communities and citizen to unite together to fight against coronavirus by observing social distancing and personal-hygiene.

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The authors declare no conflict of Interest in this reported communication.

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