



Review Article

Immunity boosters in COVID-19: Reality or myth?

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ABSTRACT

COVID-19 pandemic has posed an unprecedented threat to human beings. The emergence of pathogens always had been a threat as the designing and verification of treatment strategies and vaccines take time. In such a scenario, the use of strategies, formulations, or chemicals to improve immunity can provide protection, at least partially. The use of some traditional or folk medicinal preparations and other supplements derived from plants are among the most common agents used for keeping immunity tidy and tough. They are used by many with the belief that being herbal in origin these agents are safe. These formulations/preparations are regarded as “Immunity Boosters.” Revolving information and advertisements in bulk and the strategies of “the attention economy” also propagate this belief. The term “Immunity Booster” is a misnomer for these agents and is scientifically not approved. However, the benefits of these herbal formulations cannot be denied. Few of these herbal formulations have benefits in preventive and therapeutic management infections including those of SARS-CoV-2. Due to lifestyle, diet habits, deficiencies and neuropsychological stress, the immunity of a large fraction of the population is not optimal. Uncertainty and fear prevalent in the time of pandemic also negatively affect the immunity threshold. Many phytochemicals have been proven to aid in maintaining the threshold of immune response to an optimal level in subjects with compromised states of immunity. The immunomodulatory potential of these traditional herbal formulations also offers advantages when used along with standard operating procedures in COVID-19. Proposed formulations and their components also have disadvantageous effects and must be used under supervision with scientific methods. Excessive use of these agents may not only affect the organ and tissues deleteriously, but it can also invite immunopathology. Experimental verification of benefits being offered by these herbal agents will aid in their rightful exploitation in the therapy of human ailments including COVID-19.

Keywords: COVID-19, Herbal formulation, Traditional medicine, Immunity booster, Immunomodulation

INTRODUCTION

In the time of the COVID-19 pandemic, the maximum possible efforts are being made throughout the globe to counter the detrimental and undesired consequences associated with SARS-COV-2 infection.^[1,2] A strengthened immune system is always sought as a protective measure against infectious disorders. A large number of strategies or recommendations are being forwarded and spread through various means even by many authoritative organizations. There proposed beneficial role is largely based on traditional knowledge, and/or beliefs. In a large collection, it becomes hard as well as confusing to utilize these strategies.

Forces around the world are working together to their optimal level to design the cure and preventive measures against this deadly pandemic of COVID-19. Several therapeutic agents

have been identified to be useful in the therapeutic regimens against SARS-CoV-2 infection-associated pathology. However, still, the specific treatment of COVID-19 is absent and no proven effective treatment exists.^[3] Guidelines provided by regulatory authorities around the world under the supervision of experts are being followed for the treatment of COVID-19 patients. Most of these guidelines comprise symptomatic treatment and providing supportive care using already known agents proved to be effective against associated pathological manifestations.^[3] The role of the immune system has been marked in the manifestation of pathological consequences in COVID-19 patients.^[4,5]

In the absence of any proven medication and treatment strategies, preventive measures hold a large promise in combating the rapid spread of this pandemic. Various attempts around the world are currently in practice including social distancing, use of protective gears, frequent hand washing, and sanitization. Moreover, authorities also recommend the inclusion of herbal preparations to fortify the immune system ready against any possible encounter.^[5-10] These boosters include the well-characterized and proven compounds as well as the concoction, mixtures, and preparations recommended in traditional medicinal practices (Ayurveda, Traditional Chinese medicine, Unani, Siddha, etc.). Expected herbal boosters also include those which are being memorized without any written and proven formulation but practiced in families, clans, or endemically distributed societies. Restricted daily leisure activities due to lockdown and perceived fear also detrimentally affect the immune system. This also warrants the firming of immunity.^[6,11] Various means including social- and multi-media platforms are utilized for the spread of information about immunity-boosting. Due to various limitations associated, too much unconfirmed information is also spread. Individuals are now curious about such information; and pouring information in large amounts creates an “Infodemic.”^[12] The effectiveness of these so-called immunoboosters must be critically appraised. Further, it should also be appraised that whether “immunoboosting” is helpful or not against the contract of infection or subsequent pathological manifestations.

IMMUNITY AND COVID-19

In a normal course of a typical viral infection, the clinical presentations and their resolutions correlate with immune response. The infection to the cells triggers the pathogen-associated molecular patterns (PAMPs) recognition by pattern recognition receptors (PRR). This recognition of infection is one of the many measures taken of innate immunity and this drives the production of the interferon (IFN; Type I and III).^[13] An elevated level of IFNs causes the cease in viral replication and subsequent infection of neighbor cells. Contributions of various chemokines (CCL-

2 and CCL-7) and cytokines (Interleukin [IL]-1, IL-6, and IL-18, etc.) are also significant in the inhibition of viral propagation either directly or indirectly.^[4,13] Recruitment and activation of the cells of innate immunity including neutrophils, macrophages, and dendritic cells follow to eliminate the infected and damaged cells. Throughout the action, response shifts toward the adaptive arm having activation of lymphocyte for specific targeting. The activation of the adaptive immune response also represses the innate arm to prevent nonspecific damage to the infected tissue. However, the balance is always maintained in a normal course.^[13,14] A homeostatic balance in a tissue-specific manner is determined by various factors unique to the organ, infectious agent, and cellular, and physiological parameters.^[4]

Various strategies are always operative to prevent the bad consequences of immune responses through multiple checkpoint systems.^[15] The coordinated mechanisms at cellular and intracellular levels operate and brakes are executed when the virus is eliminated and no further immune response is required. These mechanisms include the regulation of stimulants level either soluble (cytokines or chemokines) or cell surface-bound (costimulatory ligand and or receptors). The skewed balance of activating signals and inhibitory signals also plays a critical role.^[4,15] The absence of PAMPs, as well as danger signals (and damage-associated molecular patterns [DAMPs] also), prevents no further activation of an unnecessary immune response. Intrinsic check mechanisms including the inability to divide, the short life span of immune cells, and activation-associated induction of cell death mechanisms provide an additional safeguard. The cellular and molecular interactions, the magnitude of response, and timely activity of different components of immunity along with check mechanisms ensure the required activity with no or minimal collateral damages to infected tissue/organ. The degree of deviation from the normal course of immune response is expected to cause few or many detrimental effects. These deviations occur based on present immune status which is influenced by the physiology of the host, nutrition, genetic makeup, etc. Few types of infectious agents also correlate with such undesired deviations. The role of neuropsychological well-being on qualitative and quantitative traits cannot be ruled out.^[6,8,18]

The primary organs affected by SARS-CoV-2 are lungs and cause respiratory illnesses including shortness of breathing, pneumonia-like symptoms, and acute respiratory distress syndrome.^[2,4] With the subsequent progression, the disease leads to a sharp fall in oxygen saturation level (SpO₂), and patients with severe symptoms need external oxygen support or even ventilation.^[2] The ill effects associated with COVID-19 are not only limited to respiratory organs, they are found to be spread systemically over various organs and tissues of infected patients.^[2,17] Major harmful

consequences on organs/systems other than lungs are cardiovascular, gastrointestinal, disseminated intravascular coagulation, and renal and liver function anomalies.^[2,4,5,17] Neurological consequences are also being reported in patients affected with SARS-CoV-2 infection.^[11,18] Moreover, evidence of the psychiatric and psychological symptoms in COVID-19 patients is also getting heightened.^[7,11,18] Various physiological links and underlying mechanisms for systemic spread to distant organs, pathological manifestations, and neuropsychiatric presentations are given and confirmed through numerous laboratory, preclinical as well as clinical investigations.^[4,7,11,17]

The clinical manifestations of SARS-CoV-2 indicate the overriding of the immune response during COVID-19. The balance outcome of the wrestle of the host's immune system versus infection in COVID-19 may tilt in favor of the invader. The impaired recognition of SARS-CoV-2 through their PAMPs and subsequent insufficient IFN production can be linked with an initial shortcoming in the elimination of the pathogen. The skewed ratio toward DAMPs and their continuous augmented presence favors the activation of myeloid cells supporting the adaptive arm of the immune response.^[4] The abundant innate immune response through myeloid cell activation, driven, and sustained by excessive DAMPs level, prevents the insufficient adaptive immune response. This not only prevents the activation but also brings lymphocytopenia, characterized by a decrease in the number of lymphocytes.^[13] The prolonged elevated level of various cytokines of proinflammatory nature tips the differentiation toward myeloid cells and can be linked as a cause with lymphocytopenia in COVID-19.^[4] Such deviations from the normal course of the immune response are seen in severe patients. The dysregulations brought up in severe COVID-19 patients also include the delayed and impaired IFN response, exhaustion of lymphocyte, downregulated surface expression of MHC molecules, decreased presentation abilities of antigen-presenting cells, and inappropriate cytokine levels (augmented level of proinflammatory cytokines). The improper activation and imbalanced levels of stimulants/regulators, responsible for shaping the immune response against the host and uncontrolled immune response aid in the tissue damage at the site of infection. Moreover, both the local and systemic abundance of activated myeloid cells poses the cytokine release syndrome, also known as "cytokine storm."^[4,5,14,19] Local anatomic damages pave the path for systemic spread of infection with SARS-CoV-2. Along with the infection spread, cytokine storms along with unregulated immune response cause systemic damages to multiple other organs.^[4,11,17,18]

INFLUENCES IN IMMUNITY AND COVID-19?

A number of factors include individual genetic makeup, nutrition, and aging influence immune response to virus infection. Other factors such as environmental and

comorbidities also influence the immune function against the pathogen. Although the immune system is always active, during infection the activity is increased leading to enhanced metabolism which requires various substrates from the diet.^[20] The role of micronutrients (trace elements and vitamins) and macronutrients has been clinically shown to augment the reduced immune response during infection.^[21] Therefore, at the time of infection patient need to take the proper amount of both macro- and micro-nutrient that enables the immune system sufficient to fight against infection. The deficiency of nutrients during infection may lead to weaken immune response and support the growth of the pathogen.

Age-related "Immunosenescence" affects both innate, and adaptive immune responses and results in an abnormal inflammatory response and immune dysfunction.^[22-27] The decrease in immunity due to aging makes the individual more susceptible to infection and clinical.^[16,25]

Genetic susceptibility is another important factor that influences the immune system and therefore response against the pathogen. Due to this factor, when varying range and magnitude of symptoms are being reported, a significant fraction of young adults experienced very severe symptoms of COVID-19 and while others had milder symptoms. Some of the differences can be explained by aging and underlying health issues but the major contribution of genetic makeup cannot be overlooked which outlines the immunity to protects the individual during infection. Major associations have been shown to ABO blood group antigen, ACE, and TMPRSS expression.^[27]

The COVID-19 takes the advantage of bleaks present in the regulatory machinery for immune response to progress through advanced stages. The significant damages to the various anatomical components of organs occur due to the gust originated distantly during the initial stage of infection. Taken together it can be expected that if the preexistent immunity is apt against the establishment of viral infection at the earliest steps, no or minimal detriment will occur. Therefore, it becomes imperative to critically arbiter the immunity against COVID-19 and the ways to strengthen it.

IMMUNITY BOOSTERS: DO THEY EXIST?

The most effective way to improve the preventive ability of the body against infections is vaccination. This strategy is supported by scientific evidences.^[28] The strategies other than natural antigenic encounters or vaccinations used for boosting (stimulating/strengthening) the immune responses are loosely termed as "Immunity Boosting." As established and detailed in the previous section, the immune system has components at cellular and molecular levels along with well-organized regulatory mechanisms. The deficiency in any of the components causes immunodeficiency, usually reflected

early during childhood. Natural encounter and vaccination both activate the immune response (in an antigen-specific manner) which gets relapsed in due course, however, the few antigen-specific lymphocytes outlive as memory cells.^[15,18] In a healthy adult, the immune response is well decorated with the artillery required in combat against invaders. However, there may be some deficit in components (like growth factors/cofactors/minerals) essential to maintain homeostasis. These deficiencies can be negated using supplementation. These supplementations do not have any added benefits to the health if taken unnecessary or in an additional amount.^[28,29] The additional amount of these supplements are mostly devoid of any injurious consequences; however, the doses used in the experimental analysis were not of very large levels.

The magnitude of immunity, or simply the ability to counter anomalous conditions, is designed by the genetic makeup of the host.^[30,31] This also determines the optimal peak level, the threshold to prevent the establishment, and consequences of any pathological condition including those in infections. However, there are a large number of factors that architect the components of immunity (cell, organs, molecules, microenvironment, level of expression, etc.). The final product (the immune system) may fall short in matching the design (determined by genetic makeup) or may have some defects.^[31] The causes of these shortcomings include nutritional factors, lifestyle, physiological and anatomical dynamics, and exposure to toxins during developmental phases. Even after the construction of components of the immune system in adults, its proper functionality requires maintenance and consumables (nutrients and factors). The various temporal factors such as stress, malnutrition, imbalanced diet, and other trauma are shown to avert the optimal functionality of the immune system.^[6,7,11] The use of supplementation will be providing the necessary sustenance to the immunity to achieve the optimal level in these conditions.^[15,28,29] Due to the current age lifestyle, food habits, and exposure to toxic substances (level of pollution); physiological parameters show deviations from normal ranges. Neuropsychiatric and psychological well-being is also essential for achieving optimal immune response.^[6,16] In such circumstances, the use of substances and/or practices that directly or through their effects complement the deficit and/or deviations may be of significant help. However, using the term “Immunity Boosters” for these is misleading and scientifically debatable.^[28,29] However, due to their effectiveness, at an insignificant level, no or minimal toxicity at the doses being prescribed, and being a food component, many individuals use these boosters.^[29] A perceived fear of getting infected also drives the use of the substances and practices. The use of these substances or practices can be seen more frequently in a time of the rapid spread of incurable/harsh diseases.^[8,28] During seasonal changes,

and in individuals believed to have low or compromised immunity, uses of these practices are relatively abundant. The benefits of these “additions” cannot be uniform due to differences in genetic makeup and physiological levels.^[30-32] Unverified prescriptions about strategies are continuously pouring through various means of information in the “infosphere” leading to an outburst of information, known as Infodemic.^[12,28] Due to lack of knowledge, excessive advertisements, and practices of “the attention economy,” a large segment of the population believe in the efficacy of these additions or supplementation as “Immunity Boosters.” However, it will be noteworthy that, many of the practices of traditional medicine are not yet scientifically verified in this line, but their efficacy in optimizing the immune response cannot be ruled out. Moreover, few scientific investigations confirm their efficacy in bettering the immune response, at least on few parameters, in some of the pathophysiological conditions.^[9,10,33,34] However, determination of the qualitative and quantitative consequences of any intervention on “Immunome” through “Immunomics” analysis is recommended for effective clinical development of any strategy.^[35] Although, scientific consent for strategies other than vaccinations as “immunity boosters” is absent, societal acceptance for the term prevail over it.^[28] Many scientific investigations and concept notes also use this terminology which may be in order to better connect with readers, to mark an impact, or showing their uniqueness.^[8-10,28,36] The benefits of such practices, in the current world with individuals having a varying degree of an immune response,^[37] cannot be ruled out. However, a scientific basis must be used in the selection and practice of these strategies on a personalized level considering the distinctive heritable and non-heritable factors influencing the qualitative and quantitative course of an immune response.

CONCEPT OF HERBAL IMMUNITY BOOSTERS

A large number of therapeutic compounds are derived from plants.^[38] Exploring the potential of various strategies to identify the compounds from plant origin, their ability in therapeutic regimens against diverse health ailments, and their production strategies are still underway.^[39] Compounds derived from plants have been shown to display a range of immunomodulatory activities.^[5,9,10,33,34,40] A diverse range of immunomodulatory activities both of stimulatory and inhibitory nature are evident through experimental investigations.^[36,40] The immune-modulatory potentials of herbal compounds in various pathologies including those of infectious as well as malignant origins are evident.^[5,36,38,40]

Bioactivity of plant-based medications exploits the use of pure isolated chemicals, extracts of one plant/plant part, or mixture (concoction/powder) derived from the different origins in a predetermined ratio. The use

of extracts and combinations is common in traditional medicinal practices such as Ayurveda and Traditional Chinese medicine. However, nowadays prescriptions of herbal preparations are also frequent among modern medical practitioners. Immunopotentiating or alleviating ability of herbal compounds or their mixtures (“Divya-Peedantak-Kwath,” “Divya-Swasari-Kwath,” “Divya-Swasari-Vati,” “Cyavanaprāśa,” etc.) were demonstrated by various investigations in hosts or experimental models of pathologies with state of immunosuppression.^[5,41-46] Published evidences support the significant efficacy of the herbal preparations in pathological conditions involving inappropriate (insufficient or hyper-active) immune responses. Although modulations of physiological parameters have been shown after the intake of herbal drugs/preparations in healthy individuals, most of the evidence came from the investigations on pathological conditions. One of the investigations found that the consumption of Ayurvedic preparation “Cyavanaprāśa” significantly decreases the illness episodes in healthy children.^[47] Another investigation demonstrated that the expression profile of cytokines gets altered by herbal syrup “Polinacea[®]” in healthy subjects.^[48] These investigations have shown the ability of herbal preparation in protection against infections and or upsurge in phenotypic cellular function. However, it cannot be ruled out that these preparations may purely have the immunomodulatory ability and or replenishing the essential requisites to show optimal immune response. Interestingly, maintaining the ability of the immune system by herbal preparations to achieve its functional threshold is mostly regarded as herbal “immunity boosting.” Moreover, evidence also indicates that polyherbal formulations named “Immu-21” have a boost in the responsiveness of immune cells to activating stimuli.^[49] A similar upsurge in the responsiveness of immune cells was also reported in human patients/animal models of pathological conditions.^[5,42,44,45] The relatively augmented responsiveness suggests that herbal preparations may provide attentiveness to the immune cells which may take a short time or low stimulus to achieve an optimal immune response. This partially mimics the immunity-boosting abilities of natural infection or vaccination, although pieces of evidence are very less in number in this line. Further, this preparedness of immune cells is not of antigen-specific manner. However, the establishment of a pre-activated (proinflammatory) or primed state of the immune system in herbal preparation exposed individuals may be underlying this heightened response to activation stimuli.

In the current age lifestyle, the upsets in immune responsiveness are common.^[50,51] The major lifestyle-associated ailments linked with non-optimal immune response and disease susceptibility is obesity.^[50,51] The effectiveness of herbal compounds or preparations in reinstating immune responsiveness in many pathological

conditions is well established.^[38,40-46,55] The beneficial role of herbal preparations in suppressed state of immunity; and the frequent occurrence of low immunity state in current age due to various lifestyle factors exist simultaneously. As per the probability game theory, then it becomes more apparent to have a support of herbal preparation favoring the optimal immune response when needed. Such complementation of deficits in immunity prevalent in a major segment of the current population reflects as “immunity boosting.” However, the genetic, epigenetic, as well as non-genetic influences governing the magnitude and direction of boosting by herbal preparations also exist.^[31] As per the principles of the Indian traditional medicinal practice, Ayurveda, formulations must be prescribed based on the nature (*Prakriti*) of individuals.^[52] Similar approaches to personalized medicine are common in traditional medicinal practices such as traditional Chinese medicine.^[53] Even in presence of such forms of personalized medicine prescription strategies, due to lack of knowledge, negligence, and traditional belief, herbal preparations are being prescribed indiscriminately or consumed even without prescription. The doses being consumed are well within the limit of tolerance to cause any detrimental effect after short-term use. Long-term use of these preparations without any requirement may have unfavorable consequences. Long-term continuous modulation of immunity is also expected to deliver a disparaging outcome. However, well-tolerated, side effects of mild nature along with health benefits in a large fraction of users make these herbal preparations regarded as “immunity booster.” The market strategies based on economic benefits also propagate this concept through excessive and sometimes misleading advertisements.^[28,29]

GOOD AND BAD SIDES OF IMMUNE-STIMULATION

Appropriate activation of the immune system is required to eliminate the pathogens followed by its relapse. The inappropriate immune response is mostly associated with deleterious consequences on the host. The immunodeficiency precipitates due to the lack of components of the immune system and has an insufficient immune response. The hyper or continuous immune activation is regarded as hypersensitivity and poses unrequired combat leading to self-damage. In a few cases, immunity tends to attack the components of the host causing the state of autoimmunity. Collectively, any deviation in either side of immunity homeostasis is bad for the host.

A large number of supplementations provide support to the immune system to exhibit the close to optimal immune response through complementing the deficits prevailing in immunity components in a large fraction of the population. Complementing the deficit of immunity components is mostly harmless unless the supplements/

preparations don't have any direct side effects on their own. Many of the supplements having immunostimulatory potential directly activate the components of innate immunity. They may also have the priming effect on cells of the immune system for a rapid and heightened response on activating stimulation. However, activating the immune system without necessities can have detrimental consequences.^[15,54] An intense activation of immune reaction for a prolonged period is possible with continuous intake of the so-called boosters with immunostimulatory activity. Few pathological manifestations also occur due to prolonged, yet uncontrolled, activation of immune components.^[4,14,15,19,54] As the physical and psychological well-being correlates with the immune and endocrine system (*Psychoneuroendocrine-immune*: PNEI system), the consequences of prolonging activation of immune response affect the distal physiological as well as anatomical moieties.^[5-8,11,16-18,54] Such undesired imports may cause some permanent damages to the host.

In a normal course of the immune response, activation of the innate arm of immunity is followed by the activation of adaptive immunity through the creation of a favorable microenvironment by the former for later.^[15,54] Many components of booster preparation mimic the PAMPs and trigger the stimulation of innate cells through PRR. Continuous intake of booster formulations sustains the elevated level of these PAMPs like factors that preserve the high innate immunity response.^[5,55] Many of these formations do not show any toxicity against a variety of cells directly, the elevated immune response may provide a means for damaging consequences on multiple organs for long-term use.^[55,56] Although toxicities studies *in vitro* settings confirm their safety and tolerability, the unscrupulous impact cannot be denied for *in vivo* use of these formulations.^[57] Liver injuries are one of the common consequences of inappropriate use of medicines of complementary and alternative practices.^[58,59] A comprehensive review of herbs used in traditional medicine and their toxicities urges for the data bank to better prevention of such toxicities.^[60] Immunomodulation in response to the intake of herbal medicine can have the underlying routes for causing toxicities to the organs like the liver.^[58] A continuous stimulus provided by innate immune cells triggering not required adaptive immunity may also contribute to negative consequences.^[58] Activation of innate immunity occurs in an antigen non-specific manner and the presence of clones of adaptive immune cells are selected by the presence of a specific antigen.^[15] However, the prolonged elevated stimulus by supplements herbal formulations drive a breach in the regulatory events and favor the activation of adaptive immunity in a non-specific manner.^[58] The activation of many clones with varied antigenic specificity may also cause indirect damage due to cytotoxic response as well may lead to autoimmunity.^[58,61]

A careful evaluation of published findings and exploring the possibilities, immunostimulation through supplements or herbal medications will have consequences either of beneficial or detrimental nature. The essential stimulation to improve the ailments or deficits associated with the immune system will be aiding in maintaining the homeostasis of health. A superfluous stimulation brought up by external means of herbal or any other formulation will exert disadvantageous outcomes. A varying degree of beneficial and harmful consequences may be attributed to the personalized differences at hereditary and non-hereditary levels. A careful decision on the use of these boosters with scientific methods will be of immense help to avert the undesired consequences while exploiting the extraordinary potential of complementary and alternative medications.

IMMUNITY BOOSTERS AGAINST COVID-19: ARE THEY FOR REAL?

The crucial involvement of immune response, at temporal, qualitative, and quantitative scales governs the out-of-a-chance encounter with SARS-CoV-2.^[1,2,4,13] The heterogeneity among spatial distribution at anatomical levels observed in patients with low, mild, or severe symptoms roots in the immunological difference at the individual level as well as the magnitude of the immune response during the earliest steps of infection.^[14,19] Severe symptoms with undesired COVID-19 outcomes were observed in individuals having other preexisting conditions/pathologies (like preexisting respiratory illness, diabetes, hypertensive disorders, etc.). Individuals with limited physical activity and or mineral/vitamin deficiencies are prone to contract with COVID-19 with a severe degree of symptoms.^[8,11,17,50,62] All of these pathologies or lifestyle disorders affect the magnitude of the immune response through the PNEI axis.^[6,8] In the absence of any specific medication, symptomatic reliefs become the standard operating procedure for treatment.^[3] The understanding also precipitates that keeping the immunity tidy and tough will be able to prevent the contraction with SARS-CoV-2.

The herbal preparations are found effective in the clinical management of COVID-19.^[63-65] Legislations around the world have different policies and legalities in conducting the clinical trials of herbal/traditional medicine preparations.^[66] However, cases of a purified or derivative chemical compound differ from those of crude, mixture, or concoction nature.^[65,66] Apart from this, various approaches have been implemented for appraising the potential of these phytochemicals or formulations in the therapeutic management of COVID-19.^[2,3,9,33,44,66] The previously known benefits of these herbal drugs or formulations provide an advantage for their use in the management of symptoms.^[3,5,9,33] The *in silico* predictive tools also offered rapid screenings of pure phytochemicals

or constituents present in the formulations.^[9,10,67,68] Despite predicting interactions with SARS-CoV-2 proteases, network pharmacology approaches also contributed to better envisage the therapeutic benefits of herbal preparations in COVID-19 management.^[10,69-71] The experimental pieces of evidence of protection from SARS-CoV-2 infection and COVID-19-associated severe symptoms are originated from *in vitro* investigations on experimental cell culture models or transgenic animal models treated with herbal preparations such as “Giloy Ghanvati,” “Withanone,” “Shufeng Jiedu capsule,” “Yidu,” “HanShiYi formula,” “Lianhua Quigwen,” and “Huoxiang Zhengqi”.^[72-74] A large number of evaluations were done with the animal of cell culture disease model of symptoms associated with COVID-19. Many of these studies reported moderate to significant benefits when used alone or in addition to standard operating procedures.^[73,74] The inclusion of herbal preparations in treatment guidelines is frequent in countries where these traditional medicine practices are common such as India, China, Bangladesh, and African countries.

The benefits of herbal preparations such as “Giloy Ghanvati,” “Swasari Ras,” “Ashwagandha,” “Tulsi Ghanvati,” “Curcumin,” and “Lianhuaqingwen” in the improvement of immunological parameters were found in many investigations.^[63-65] Based on preexisting knowledge about the effects of phytochemicals or preparations, immunomodulatory activity of these was already proposed.^[5,8,9,75] Moreover, the protective potential of herbal formulations was already predicted.^[5,76] Using observational studies, traditional medicine preparation “Huoxiang Zhengqi Oral Liquid,” and “Jinhao Jieme Granules” were also claimed to prevent the contraction of infection.^[77,78] However, experimental evidences are absent and few of the studies were based on recording COVID-19-associated symptoms, not through the standard method of diagnosis. Clinical benefits of herbal drugs in COVID-19 management indicate the promises of other yet unexplored or scientifically unverified plant-based drugs and preparations.

Experimental and predictive approaches identify the immune regulation by herbal preparation in COVID-19.^[10,69,71,78,79] The modulation of immune components, majorly cell phenotype and circulatory cytokine levels, were reported in human patients affected with COVID-19.^[44,63-65] A decline in the marker of inflammation including CRP with a decreased level of pro-inflammatory cytokine as observed in these investigations indicates the ability of herbal preparations in rectifying the immune response in COVID-19. Therefore, immunological benefits of these plant-derived drugs or herbal preparation cannot be denied.

Measures to contain the SARS-CoV-2 transmission cause a distortion in the lifestyle of a large fraction of the population. The restricted outdoor activities and sunshine exposure, modified diet habits, and low physical

activities are also expected to affect the immunity level of individuals.^[8,11,17] A lower level of immunity in such a scenario will make the individuals more prone to infections including SARS-CoV-2.^[11] Nutritional deficiencies and deprivation from leisure activities contribute to psychological disturbances causing modulated PNEI axis and lowering of immunity.^[6,8,11,16,54] Moreover, perceived fear of infection due to “Infodemic” causes anxiety and depression. The economic loss at the occupational front and uncertainty about the future also contribute to anxiogenic and depressogenic consequences in the era of the COVID-19 pandemic. Collectively these reduce the threshold of immune response from their optimal. Aids provided by any strategies will strengthen the immunity to combat any possible contraction of the pathogen. As the herbal preparations are mostly safe and well tolerable at prescribed doses, the use of these will be a suitable choice.^[5,8,9] Use of any new formulation previously not being used for immune strengthening may deliver harmful consequences. The strengthening/aiding of immunity through these safe immunomodulatory formulations of herbal origin will be of help to some extent against COVID-19. This maintenance of immunity will prevent contraction with other infectious agents also.

CONCLUSION

An optimal immune response is a key to a healthy life in a world full of diverse emerging pathogens. A large number of factors are responsible for the deviation of immunity and its response from its optimum. The factors include lifestyle, nutrition, physical, and psychological well-being, exposure to toxic substances, and other genetic and epigenetic factors. Various strategies to aid in the responsiveness of the immune system to its optimum can be of health benefit. Such strategies strengthening the immunity to achieve optimal threshold are generally regarded as immunity boosting. The only scientifically proven way for Immunity boosting is vaccination, which provides the memory to combat the subsequent natural encounter with the pathogen rapidly and robustly. As any specific medication is not yet proven effective against COVID-19 and the availability of vaccines is not ample, the curiosity for strategies protecting COVID-19 increased. Excessive advertisement on various platforms, the spread of unverified claims, and “the attention economy” build up the societal concept of immunity boosting. Many herbal formulations already proven to aid in maintaining immunity to its optimum pose provide benefits even in COVID-19. Herbal preparations formulated from food items are generally regarded as safe. However, a word of caution must be followed as unrestricted consumption may cause detrimental effects rather than providing benefits. Many herbal preparations are advised even by regulatory authorities throughout the globe based on previous pieces

of evidence of benefits in symptoms associated with COVID-19. An experimental and clinical evaluation of these herbal compounds and preparation on immunity against COVID-19 will provide a strong and more scientific base for their exploitation in therapeutic management.

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