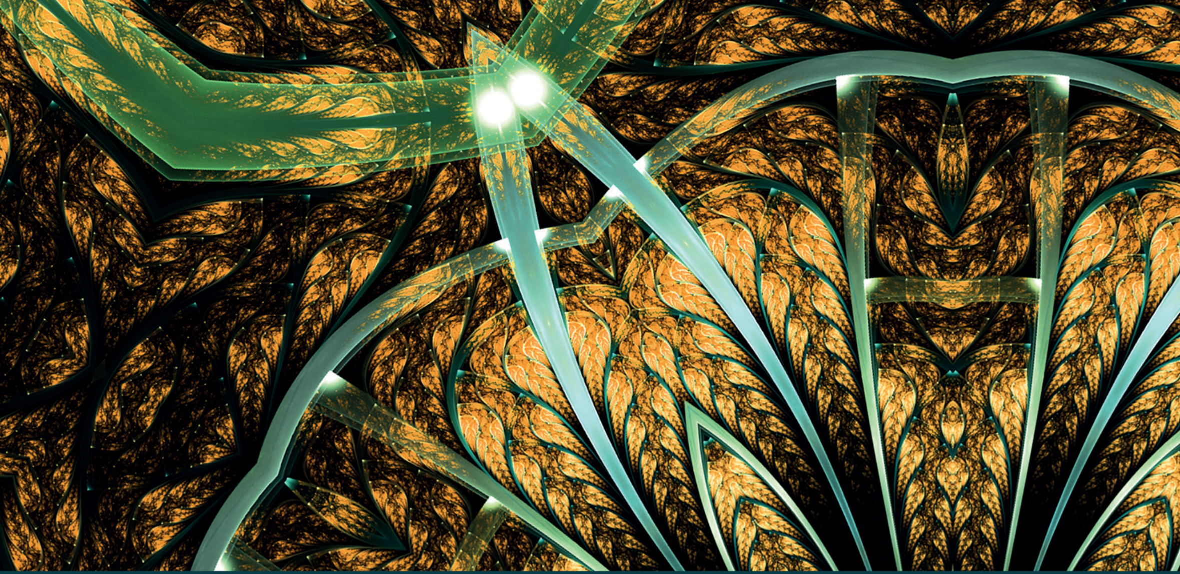

IMMUNITY BOOSTING FUNCTIONAL FOODS TO COMBAT COVID-19

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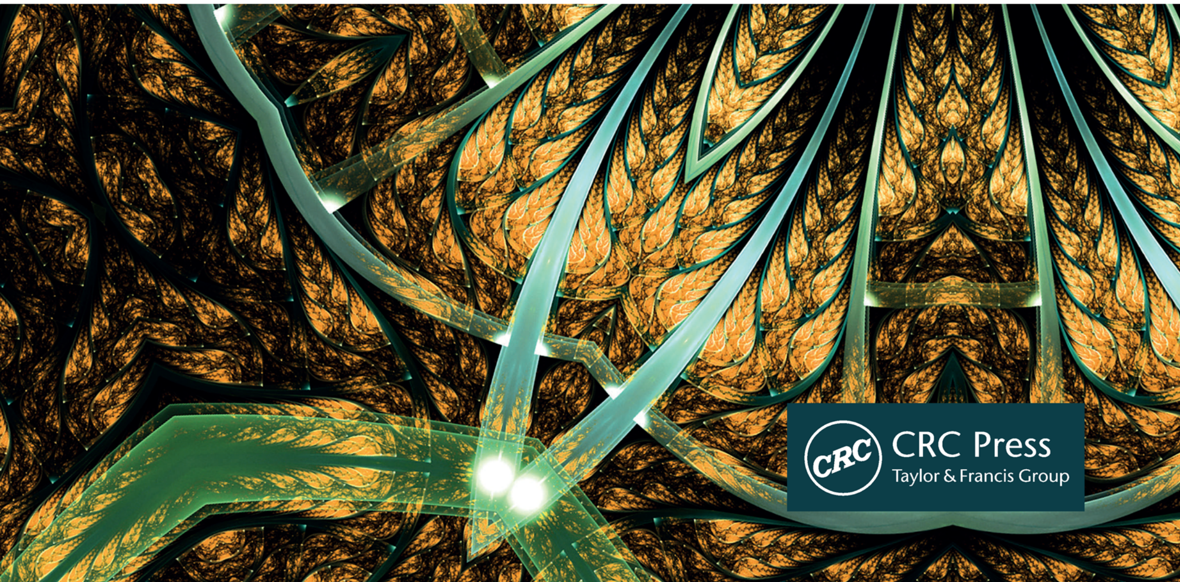

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IMMUNITY BOOSTING FUNCTIONAL FOODS TO COMBAT COVID-19

Throughout the world people are restless to find out the ways that can minimize the risk of present outbreak of COVID-19 pandemic. It is considered that healthy eating habit is one of the remedial ways against this. The people who are weak in immunity are prone to severe attack of COVID-19. Functional foods are those foods which have health beneficial role beyond its basic nutrition. So, functional foods which can improve the immunity of the people,are helpful to combat COVID-19. The book 'Immunity Boosting Functional Foods to Combat COVID-19' contains seventeen chapters which describe immunity boosting effect of some functional foods/food ingredients such as different medicinal plants, herbs, fruits, vegetables, seeds, dairy products, probiotics, vitamins, minerals, etc. The book may be helpful to common people and health professionals as well as scientists, teachers, scholars and students.

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IMMUNITY BOOSTING FUNCTIONAL FOODS TO COMBAT COVID-19

Editor

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Dedicated To

All My Respected Teachers

CONTENTS

PREFACE

We are very much experienced that the disease COVID-19 which is originated from Wohan city of China in December, 2019, has spread all over the world and has made it pandemic. The COVID-19 pandemic has taken several lives, hampered academic system, disturbed the people's way of income generation and declined the world economy. Besides it made huge pressure to the health systems.

It has been reported that to protect against the spread of this disease some precautions may be taken - such as using mask, hand sanitizer, washing hand with soap frequently, not to go outside of home except any essential work etc. However, there is no particular treatment or medicine against this disease. It may be assumed that vaccination may be ultimate solution against this highly contagious disease. But, we have to keep in mind that the virus mutates, and may overcome the vaccine effect. Due to the RNA virus, the antigenic structure is altered frequently and that make difficult to develop a successful vaccine.

On the other hand, it has been considered that physical exercise and healthy eating habit are two effective remedial ways to fight against this disease as both enhances the body immunity. The people who are weak in immunity are prone to attack COVID-19. Functional foods are those foods which have health beneficial role beyond its basic nutrition. In this direction, functional foods which can improve the immunity of the people, are helpful to combat COVID-19. In this book 'Immunity Boosting Functional Foods to Combat COVID-19', several functional foods or food ingredients, their mechanism of immune enhancing properties and use in food products have been discussed through seventeen chapters written by eminent authors.

There are several medicinal plants which have significant role for immunity boosting such as Ashwagandha, Tulsi, Shatavari, Giloy, Aloe vera, Amla, Neem, licorice, garlic, ginger, turmeric, rosemary, black cumin, cinnamon, sage, thyme, fenugreek, peppermint, black pepper, clove etc. Angiotensin-converting enzyme 2 (ACE2) protein acts as receptor for virus's spike protein and gives provision for infection of our body. The ingredients which contain ACE inhibitory peptides, protect to produce ACE2 in our body. COVID-19 has been shown to engage the host cell ACE2 through its spike protein. It was noticed that specific compound of different medicinal plants detaches the binding interface of ACE2.

Fruits like berries and Dragon fruit and vegetables such as mushroom, broccoli also enhance body immunity due to its immunity enhancing bioactive components. It has been reported that green tea has role in immune-modulation that is mediated both through innate and adaptive immune responses. Probiotic bacteria have also been identified to have immunomodulatory role. It play a positive role in host defense mechanisms, which may include regulation of invasive bacterial translocation and the production of specific and non-specific immune responses.

Fermented milk products (as contain lactic acid bacteria and probiotic bacteria) and cheese (due to lactic acid bacteria and renneting) contain ACE inhibitory bioactive peptides. Due to this bioactive peptide, consuming cheese and fermented milk products may protect us from severe attack of corona virus.

It has been noticed that whey protein of the milk and milk product also contains very active ACE inhibitory peptide. Besides, it comprises of different fractions such as β-lactoglobulin, α-lactalbumin, immunoglobulin etc. and they have effective role to immune modulating effects for human body with different mechanisms. In addition to, food components like some vitamins (D, E, C, B6, B9, B12), some minerals (Zn, Se, Mg) have immune enhancing role.

We have to keep in mind that prevention is better than cure, even less expensive. In this direction functional foods may protect our life from the severity of this disease after attack. People have to aware about these functional foods. More researches have to be conducted on the effect of these functional foods against this disease. I hope the book will be helpful to common people and health professionals as well as scientists, teachers, scholars and students.

Apurba Giri
Editor

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This book 'Immunity Boosting Functional Foods to Combat COVID-19' is a collection of papers presented in the International Webinar "Strategies to Boost Immunity by Functional Foods to Combat Covid-19" held on 15th July, 2020. The webinar was organized by the Department of Food Processing in collaboration with Dept. of Nutrition & Research Cell, Mugberia Gangadhar Mahavidyalaya, Bhupatinagar, Purba Medinipur, West Bengal. This book also includes some invited papers related to the topic of the webinar.

Immunity power is an important mechanism of human body to combat external harmful virus, bacteria, fungi, etc. To build our immune system effectively, we need to take food with proper recommended nutritional elements. We know the six basic nutritional elements are carbohydrate, protein, fat, vitamin, minerals and water. All these elements should be in our diet with good proportion. These elements with appropriate proportion in our diet could prevent malnutrition by building proper immune system in human body. Hence, we should take lot of, fresh fruits and vegetables, nuts, seeds, probiotic etc. apart from normal food like rice, bread, pulses, meat. Boosting immune system is now specially, very important issue during this COVID world. At present about 110 million people are affected by novel Corona virus around the globe and death toll reaches to above 2.4 million (20.02.2021). However I think we should maintain ICMR Protocol like using mask, creating social distaining, washing our hands and mouth and Yoga activities for combating this pandemic.

This book will extend the mental horizon of the readers by thoughtful information, because knowledge is a perpetuating and propagating process which needs continuous updating by way of mutual discussions. Hope this book will greatly enrich the interested readers and policy makers of the programme. Also it will be helpful to the researchers around the world.

It is my great pleasure that the Food Processing Department of our college has organized this type of webinar in Collaboration with our Research Cell and Nutrition Department. This book is a joint endeavor of eminent academicians and distinguished scholars to whom we owe our respect and gratitude.

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Dr. Swapan Kumar Misra
Principal
Mugberia Gangadhar Mahavidyalaya

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The book 'Immunity Boosting Functional Foods to Combat COVID-19' is the outcome of the series of lectures delivered by eminent professors, academicians, scientist and young researchers from colleges/ institutes/ universities in the One Day International Webinar on "Strategies to Boost Immunity by Functional Foods to Combat COVID-19" which was organized by Dept. of Food Processing in collaboration with Dept. of Nutrition & Research Cell, Mugberia Gangadhar Mahavidyalaya on 15st July, 2020. Beside this some of the invited articles related to the theme of webinar are included in this book.

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I also express my gratitude to all the eminent contributors. I apologize if I inadvertently missed acknowledging my gratitude to anyone else.

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CHAPTER - 1

POTENTIAL APPLICATIONS OF IMMUNE BOOSTING MEDICINAL PLANTS IN FUNCTIONAL FOODS TO COMBAT COVID-19

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ABSTRACT

The novel corona virus disease COVID-19 which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) became a pandemic causing a huge loss to the lives of the people and to the global economic situation while imposing a significant pressure on the health structures of the nations worldwide. Immunocompromized people are more vulnerable to the infection and are at high risk of death. In the absence of an effective antiviral drug or a vaccine, alternative prophylactic and therapeutic solutions are essentially needed to be used to save the lives of the people from this disaster. The article highlighted the possibilities of utilizing medicinal plants rich in phytochemicals which are having proven immunomodulatory and antiviral activity in developing novel functional foods with acceptable consumer appeal to be used in reducing the risk of SARS CoV-2 infection by strengthening the immune system of the individual and complement the therapeutic measures taken against the disease. Innovative functional foods made by fortification of medicinal plants have a great promise to improve the general health and immensely help the general public against the viral infections such as COVID-19. Nevertheless, more evidences are required through controlled clinical trials to support the safety and efficacy of the functional foods fortified with medicinal plants.

Keywords: Antiviral, Coronavirus, Functional foods, Immune boosting, Medicinal plants, Phytochemicals

INTRODUCTION

Highly contagious novel corona virus disease, COVID-19 which was reported to be originated in the Wuhan city, Hubei Province of China during late 2019, has spread in an unprecedented manner all over the world within a short period of time causing a huge loss, not only to the lives of the people but also to the world economy creating a global crisis. It imposes a significant pressure on the health systems of the countries worldwide. COVID-19 is caused by a RNA virus and was named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (Gorbalenya *et al*., 2020). As of 15th September 2020, a total of 2,95,28,057 confirmed COVID-19 cases were reported while 9,34,230 were succumbed to death affecting 213 countries around the world (www.worldometer.info, 2020). However, actual number of infected people might be higher than the reported since, many in the population shows no symptoms. Radiating spread of this disease throughout the world is due mainly to the increased global travel of the people.

In the absence of a known cure or a treatment, the best way is to find alternative solutions to control this pandemic while gradually getting into the normal life until an effective anti-viral therapy and/or preventive vaccine has successfully been developed. Nevertheless, it is essential to keep in mind that the viruses mutate, hampering and overcoming the drug effect, which is also the case of SARS-CoV-2, the novel coronavirus. It is reported that, SARS-CoV has very high mutation rate (Ahmad *et al*., 2020). Especially for the RNA viruses, the antigenic structure is altered frequently and hence, developing a successful vaccine is a difficult task. Even though a vaccine is successfully developed, it could be less or ineffective when there is a change to the antigenic structure in the existing virus (Mousa, 2017).

Therefore, taking measures to control and prevent the risk of infection is important in managing the current problem of COVID-19. Among the several possible alternatives, taking healthy foods rich in functional ingredients to strengthen the immune system is one of the promising practices that could be recommended because a healthy immune system is vital to protect our body from the invading pathogens including viruses. Some plants especially the medicinal plants contain immunomodulatory phytochemicals which can be incorporated to develop functional foods. Some of the phytochemicals have exhibited broad spectrum antiviral activity for the viruses that shows resistance for the drugs. Those are due to the multifunctional components possess by these plants (Tolo *et al*., 2006). In this context the foods fortified with medicinal plants/their extracts/powders/essential oils which are having promising immunomodulatory and antiviral effects are of significant importance to fight against COVID-19. Chojnacka *et al.* (2020) reported that use of plant derived compounds and plant preparations in functional food development is relatively fast because the raw materials i.e. herbs and plants are of natural origin and are already approved for human consumption worldwide.

With the above introduction, the objective of this paper is to compile the information on different medicinal plants with promising immunomodulatory and antiviral properties in general and on COVID-19 in particular, that are having potential applications in functional food developments with favourable consumer appeal.

SARS-CoV-2 and COVID-19

SARS-CoV-2 the virus responsible for the COVID-19 disease is a RNA virus of the family *coronaviridae* (sub family *Coronavirinae*) and its lineage is similar to the coronaviruses that causes SARS but genetically distinct (Dhama *et al*., 2020). It has a spike like projections on its enveloped surface giving it a crown like appearance and hence the name coronavirus (Kumar *et al*., 2020; Singhal, 2020). Zhou *et al*. (2020) reported that the virus binds via viral structural spike (S) protein with angiotensin-converting enzyme 2 (ACE 2) receptor and invade the host cell primarily through endocytosis. SARS-CoV-2 virus transmitted from person to person by multiple means such as aerosols, droplets and fomites (Wang and Du, 2020) by contacting with the eyes, nose and the mouth. Symptoms of COVID-19 include fever, cough, myalgia or fatigue and less frequently headache, hemoptysis and diarrhea (Huang *et al*., 2020). In a study carried out in UK, Menni *et al*. (2020) reported that loss of taste and smell is also a strong predictor of having been infected with COVID-19. However, the clinical features have a wide range from being no signs or asymptomatic to severe respiratory disorders that need intensive care under hospitalization. Tian (2020) reported that SARS-CoV-2 has shown less severe pathogenesis compared to the SARS-CoV and MERS-CoV, but high transmission competence as evidence by the continuous increase in the confirmed cases worldwide. Further, SARS-CoV-2 has unique characteristics. One such character is around 80% of the affected people shows no symptoms (Day, 2020) and they act as silent carriers and spread the disease. Also there is no guarantee that the patients recovered from the disease are protected from the next time infection (WHO, 2020). Those are the reasons for the high transmission competence of this virus. To date no effective vaccine or antiviral drug is available to treat COVID-19.

Healthy Immune System to Fight Against Diseases

Immune system is a complicated defense system and act to protect the host against invading harmful microorganisms such as bacteria, viruses, fungi, parasites etc. and malignant cells (Calder and Kew, 2002; Venkatalakshmi *et al*., 2016). Therefore, a healthy immune system is an important weapon to fight against pathogens including viruses such as SARS-CoV-2 that causes the COVID-19. However, it is well documented that the immune-competence of a person is affected by many factors such as age (Castelo-Branco and Soveral, 2014; Scepanovic *et al*., 2018), sex (Oertelt-Prigione, 2012), genetic variability (Scepanovic *et al*., 2018), stress (Pruett, 2003), alcohol/drug abuse (Friedman *et al*., 2003), malnutrition (França *et al*., 2009), environmental pollution (Venkatalakshmi *et al*., 2016), lifestyle (Venkatalakshmi *et al*., 2016) etc. With respect to the COVID-19 pandemic, Wu *et al*. (2020) reported that the older age patients had both Acute Respiratory Distress Syndrome (ARDS) and death than the others and one of the main reasons is less rigorous immune system that they possess. Therefore, enhancing immunity is definitely one of the ways medical practitioners all over the world have been using to treat this deadly disease (Balkrishna, 2020). Getting a healthy diet is one of the ways among many others such as having adequate quality sleep, stress management, doing regular physical activity and relaxation practices etc. which help to keep the immune system strong. Panyod *et al*. (2020) mentioned that since treating influenza with large amounts of vitamin C, which is known to boost immunity, has been practiced for decades; it might be an effective nutritional treatment for COVID-19 as well. It has already been reported that, high doses of vitamin C have been administered to the COVID-19 patients in China and some other places in the world and has shown promising results (Balkrishna, 2020).

Medicinal Plants as a Mine of Phytochemicals

Plants are considered as biosynthetic laboratory of phytochemicals (Venkatalakshmi *et al*., 2016) such as alkaloids, flavonoids, glycosides, steroids, polyphenols, polysaccharides, vitamins, tannins, coumarins, gums, terpenes, terpenoides etc. (Okwu, 2004; Mittal *et al*., 2014; Venkatalakshmi *et al*., 2016). Phytochemicals are secondary metabolites that do not essentially needed for the survival of the plant but produced as a response to external stimuli such as infection, changes in the nutrition, climate etc. and accumulated only in certain parts of the plant (Verpoorte *et al*., 1999). They serve as the natural defense system for the host plant (Venkatalakshmi *et al*., 2016). Medicinal plants which are rich in phytochemicals have been used from prehistoric times as natural medicines for prophylactic and therapeutic purposes as a safer alternative (Lin *et al*., 2014; Mittal *et al*., 2014; Ahmad *et al*., 2020). Medicinal plants contain properties or compounds which can be used for therapeutic purposes or those that synthesize metabolites to produce useful drugs. Immune-modulatory and antimicrobial (including antiviral, antibacterial, antifungal, antiprotozoal, anthelmintic) activity are few of the potentials among many others such as anti-oxidant, anti-diabetic, memory enhancing, cholesterol lowering, anticancer, anti diarrheal, anti inflammatory, anti hypertensive, anti allergic, anti asthmatic, anti arthritic, adaptogenic, anti stress etc. possess by phytochemicals present in these plants (Goel *et al*., 2010; Pavaraj *et al.,* 2011; Hemalatha *et al*., 2011; Venkatalakshmi *et al*., 2016; Vinaya *et al*., 2017).

Utilization of Medicinal Plants for the Fortification of Functional Foods

Haslberger *et al*. (2020) in their mini review, referring to WHO expert report on clinical studies on combination treatments for SARS which has immerged earlier, mentioned that functional foods possess a huge possibility for avoiding the mechanisms of viral infection and altering immune responses. The functional food concept was initially introduced by Japanese scientists in 1984, and in Japan, those foods have been marketed as “Foods for Specified Health Use” (FOSHU). Roberfroid (2000) defined functional foods as the foods which are used to enhance certain physiological functions of the body in order to prevent or even to cure diseases. According to Hasler and Brown (2009), functional foods are defined as whole, fortified, enriched or enhanced foods that provide health benefits beyond the provision of essential nutrients, when consumed at efficacious levels as part of a varied diet on a regular basis. López-Varela *et al*. (2011) mentioned that even though natural foods have been considered as functional foods, only the foods which have undergone a methodology is preferred as functional foods. Therefore, the definition of functional food is a debatable issue. However, all the functional foods ultimately provide health benefits further to the basic nutrition that they provide. Even though functional foods are healthy, taste and pleasure are also important for them to be successful in the market, since the majority of the consumers’ leading food choice motive was identified as the taste (Narayana *et al*., 2020; Zezelj *et al*., 2012). Further, it is highlighted that functional foods are foods and not drugs and required to be consumed in normal amounts with the normal diet.

Functional foods developed by incorporating phytochemicals rich medicinal plants, plant parts and extracts play a significant role in the market and are having a huge demand and a potential in this era of COVID-19 than ever before. Addition of herbs and spices which are having medicinal and other functional value to foods are also not new and it has been practiced from ancient times. Nevertheless, novel products, for an example, novel dairy products fortified with such medicinal plants could be developed and they give more value for the money spends by health conscious consumers while helping to protect their lives. A variety of medicinal plants with immunomodulatory and potential antiviral activity have been identified by the scientific community (Agarwal *et al*., 1999; Cinatl *et al*., 2003; Goel *et al*., 2010; Balasubramani *et al*., 2011; Hemalatha *et al*., 2011; Mondal *et al.,* 2011; Pavaraj *et al*., 2011; Jayati *et al*., 2013; Balkrishna, 2020;) which are having potential applications in the functional food industry. They could be recommended to reduce the risk of SARS CoV-2 infection by strengthening the immune system of an individual and complement the therapeutic measures taken against the disease.

Medicinal Plants of Significance for Functional Food Development to Combat COVID-19

Ashwagandha (*Withania somnifera* L.)

Ashwagandha (*Withania somnifera*) has been utilized in traditional medicine for more than 3000 years and the bioactive compounds derived from this valuable plant are used in prevention and treatment of various diseases (Gill *et al*., 2019; Balkrishna, 2020). It has been stated that *W. somnifera* possess many beneficial health properties such as antioxidant (Chaurasia *et al*., 2000), antimicrobial including antiviral (Pant *et al*., 2012), immunomodulatory (El-Boshy *et al*., 2013), anti-inflammatory (Chandra *et al*., 2012), anticancer (Wadhwa *et al*., 2013), adaptogenic, cardio protective (Dhuley, 2000) etc. Reported health benefits are due to the existence of many phytochemical compounds such as steroidal lactones (withanolides, withaferins), steroidal alkaloids, saponins, flavonoids, phenols, carbohydrates, glycosides, phytosterols, terpenoides etc. present in this valuable medicinal herb (Tiwari *et al.,* 2014; Swaminathan and Santhi, 2019). Tiwari *et al.* (2014) reported that steroidal lactones and steroidal alkaloids present in this herb are mainly responsible for the health benefits that it possess.

Pant *et al*. (2012) studied the antiviral activity of *W. somnifera* root extract against Infectious Bursal Disease (IBD) virus replication. They have used cytopathic effect reduction assay for the study and showed that *W. somnifera* has a promising effect against IBD virus. El-Boshy *et al*. (2013) carried out a study to find the effect of *W. somnifera* extract on immunological, hematological and biochemical parameters in guinea pigs against *E. coli* attack. They have shown that *W. somnifera* has the ability to correct immunological, hematological and biochemical alterations caused as response of infection. Molecular docking simulations predicted the therapeutic significance of withanone, one of the active withanolides of *W. somnifera*, which is capable of binding to the substrate binding pockets of SARS-CoV-2-M^{pro}, a highly conserved protein of SARS-CoV-2 (Kumar *et al*., 2020). Further, Balkrishna (2020) also showed that withanone docked well in the binding interface of ACE2-RBD (of SARS-CoV-2) complex and on simulation move slightly towards the center of the interface. Author proposed that such an interaction would block or weaken the COVID-19 entry as well as the infectivity.

The possibilities of using *W. somnifera* in functional food applications have been reported. Anita *et al*. (2017) successfully optimized a cookie formulation with *W. somnifera* leaf powder using response surface methodology. Indu and Awasthi (2008) developed cereal-legume based biscuit fortified with *W. somnifera* root powder and concluded that up to 5% powder can be fortified without affecting organoleptic quality of the biscuit which have high mineral content. Gill *et al*. (2019) reported that a dose of 3-6 mg of leaves and/or roots of *W. somnifera* is recommended to be incorporated in functional food formulations in powder form or as it is. Dairy products also have been developed by incorporating *W. somnifera* (Viswaroopan *et al*., 2015; Singh *et al*., 2018). Still, great opportunities are available to develop innovative functional food products to get the advantage of this valuable herb in disease prevention in this era of COVID-19.

Tulsi/holy basil (*Ocimum sanctum* L.)

Tulsi (*Ocimum sanctum* L.) which is known in Ayurveda as “the queen of herbs” (Singh *et al*., 2010) has a wide array of health benefits (Cohen, 2014). Antimicrobial (including antiviral) (Jayati *et al*., 2013), antioxidant (Yadav and Shukla, 2014), anti-asthmatic (Vinaya *et al*., 2017), anti-carcinogenic (Karthikeyan *et al*., 1999), immunomodulatory (Goel *et al*., 2010; Pavaraj *et al*., 2011; Hemalatha *et al*., 2011; Mondal *et al.,* 2011) are few of the scientifically proven health benefits among many others of*O. sanctum*. These benefits are attributable to the high amount of phenolic compounds and antioxidant properties present in the plant (Wangcharoen and Morasuk, 2007). Borah and Biswas (2018) reported that *O. sanctum* contains various phytochemicals including carbohydrate, tannin, flavonoids, saponins, glycosides, terpenoids, fatty acids and phenols in their leaf extract. In Ayurveda, *O. sanctum* is widely used to treat many health ailments such as infections, skin diseases, cold, cough, malaria fever, hepatic disorders etc. (Hemalatha *et al*., 2011). Daily consumption of this herb is known to prevent diseases and to improve the general health. Further, broad spectrum of antimicrobial activity of *O. sanctum* is important for many applications including food preservation (Cohen, 2014).

Pavaraj *et al.* (2011) used different concentrations of *O. sanctum* extract on common carp (*Cyprinus carpio* L.) fingerlings to study the immunity development against heat damaged bacterial pathogen *Aeromonas hydrophila* as an antigen and found that both specific as well as non-specific immunity was enhanced at 10 ppm level of the extract. Further, the authors mentioned that low concentration of plant extract is sufficient to exhibit an immunostimulant effect and hence its use is cost effective. Goel *et al*. (2010) carried out a study to find out the effect of aqueous extract of *O. sanctum* leaves on interleukin-2 (IL-2) cytokine production *in vitro* and *in vivo* and on routine blood parameters and T& B lymphocytes in peripheral blood. They have shown that aqueous *O. sanctum* leaves extract have a stimulatory effect on T & B lymphocytes particularly on Th1 subset of lymphocytes as indicated by enhancement in IL-2 production confirming its use as a potent immunomodulator. Hemalatha *et al*. (2011) in their study to find out the immunomodulatory activity and Th1/Th2 cytokine response of *O. sanctum* using albino mice concluded that *O. sanctum* is a potential immunomodulator since it possess the ability to alter the NF-κB activity. Significant immunomodulatory role was reported by Mondal *et al.* (2011) who studied the effect of ethanolic extract of *O. sanctum* on healthy volunteer adults using double-blind randomized cross-over trial.

Jayati *et al*. (2013) studied the *in vitro* anti-viral effect of *O. sanctum* leaf extract against the virus causing new castle disease (NCD) in poultry using chicken embryo fibroblast monolayer culture. They have reported that the leaf extract of *O. sanctum* showed a potent antiviral activity against the NCD due to the absence of cytopathic effects in monolayer and lower the haemagglutination assay (HA) titer. RNA dependent RNA polymerase (RDRP) without which viruses cannot survive was targeted using *O. sanctum* phytochemicals by Balkrishna (2020) in his *in-silico* study. Author reported that few phytochemical compounds present in *O. sanctum* hit the catalytic cleft of the RDRP and scutellarein is one of them. Accordingly, author suggested that phytochemicals in *O. sanctum* could inhibit the coronavirus replication and control its growth and spread.

O. sanctum is used traditionally in many formssuchas herbal tea, dried powder, fresh leaf, or mixed with Honey and Ghee (Amarah *et al*., 2017). Further it has shown promising applications in other functional foods as well. Juntachote *et al*. (2006) studied the antioxidant potential of *O. sanctum* on cooked ground pork and showed that dried powder can be used as a possible natural antioxidant in food preservation. Alam *et al*. (2013) developed fibre enriched herbal biscuits using *O. sanctum* leaves and concluded that organoleptically acceptable functional biscuit can be manufactured by incorporating leaves up to a level of 1%. *O. sanctum* fortified cookies and biscuits are already available in the market as well. Even though there is a controversy of using *O. sanctum* with milk, milk based functional foods such as ice cream (Kumar *et al*., 2013), ice lolly (Misra, 2016), yoghurt, milk drink etc. have been successfully developed using it and also commercially available. Enormous opportunity is ahead to develop different functional foods using this herb to satisfy the diversified consumer preferences especially to boost the immunity and to prevent from viral infections.

Giloy (*Tinospora cordifolia* Miers.)

T. cordifolia has been utilized in Ayurveda and traditional medicine since ancient times. The plant has variety of bioactive phytochemical compounds such as alkaloids, glycosides aliphatic compounds, diterpenoid lactones, steroids, polysaccharides, polyphenols etc. in various parts of the plant (Mittal *et al*., 2014; Khan *et al*., 2020). *T. cordifolia* is well recognized for its immunomodulatory effects. Among the bioactive phytochemicals, the compounds such as 11-hydroxymuskatone, N-methyle-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordioside and syringing showed promising results as having immunomodulatory effects (Sharma *et al*., 2012; Mittal *et al*., 2014).

Immunomodulatory potential of *T. cordifolia* against IBD virus was investigated in chicken by Sachan *et al*. (2019). They showed that *T. cordifolia* significantly ($p<0.05$) increased the interferon gamma (IFN-γ), IL-2, IL-4, and IL-1 levels in the peripheral blood mononuclear cells of chicken following infection, which shows the potential of *T. cordifolia* to act as an immunomodulatory and antiviral agent due to the phytochemicals present.

Balkrishna (2020) mentioned that out of the phytochemicals reported in *T. cordifolia*, tinocordiside docked well within the ACE-RBD (of the SARS-CoV-2) complex in their *in-silico* study. Further, the author reported that in the simulated state, tinocordiside showed satisfactory binding poses within the interface of ACE2-RBD with several interacting sites. Hence the author claimed that *T. cordifolia* is a potent medicinal plant to be used for drug discovery against COVID-19 caused by SARS-CoV-2. In another *in-silico* study, Chowdhury (2020) reported that among the phytochemicals considered in *T. cordifolia,* berberine could regulate the function of viral $3CL^{pro}$ or M^{pro} protein which is a key CoV enzyme, thus have the possibility to control viral replication.

Bioactive polyphenol profiling and *in vitro* antioxidant activity of *T. cordifolia* was studied by Khan *et al*. (2020) and they mentioned that this medicinal plant has an excellent potential to be used in functional food formulations.

Licorice (*Glycyrriza glabra* L.)

Licorice (*Glycyrriza glabra*) is an extensively used medicinal plant in Ayurveda and traditional medicine from the time immemorial. It is known as 'the father of the herbal medicines' (Foster *et al*., 2017). *G. glabra* is utilized in traditional medicine to treat a range of health complaints such as respiratory tract problems, digestive system related disorders, epilepsy, paralysis, rheumatism, cancer, malaria etc. (Batiha *et al*., 2020) and it has vast array of biological effects such as anti-inflammatory, anti-allergic, anti-viral, antioxidant etc. (Sawant *et al*., 2016). Wang *et al*. (2015) reported that *G. glabra* contains more than 20 triterpenoides and nearly 300 flavounoides. It contains glycyrrhizin and many other phytochemicals such as flavonoids, saponins, glycosides, tannins, steroids etc. (Sawant *et al*., 2016).

Immunomodulatory activity of aqueous methanolic extract of *G. glabra* was studied by Hussain *et al*. (2017) against *Eimeria* species infection in broiler chickens. They have reported that the treated group showed significantly ($P<0.05$) higher dose dependent cell mediated and humoral response as compared to negative control. In the review on antiviral and antimicrobial activity of *G. glabra,* Wang *et al*. (2015) reported that among the phytochemicals identified glycyrrhizin and glycyrrhetinic acid have been reported to have potent antiviral effect. Reported phytochemicals interfere with the viral activity by many ways such as inhibition of viral gene expression and replication, reduction of adhesion force etc.

Behrad *et al.* (2009) studied the effect of *G. glabra* incorporated yoghurt on probiotic fermentation and *Helicobacter pylori* growth *in-vitro*. They have found that the addition of *G. glabra* did not change the yoghurt fermentation but inhibit the *H. pylori* showing its antimicrobial ability and possibility of utilizing in fermented functional food preparations. *G. glabra* is used in both pharmaceutical and health food sector to flavor the food and beverages and also used in tobacco industry to flavor tobacco products (Sawant *et al*., 2016). Ishimi *et al*. (2019) reported that *G. glabra* is a highly used raw material in health foods in Japanese market.

The safety and effectiveness of *G. glabra* in health foods available in Japanese market was evaluated by Ishimi *et al*. (2019). They have detected glabridine and small amount of glycyrrhizin in those products and have mentioned that even though there is a claim that licorice has a beneficial effect on bone health in postmenopausal women, overdose of the functional foods containing licorice should be avoided by young women because of the estrogenic activity that was identified in some of the related compounds and products. Further, Deutch *et al*. (2019) reported that too much consumption of *G. glabra* will increase the blood pressure and can cause life threatening complications especially in the patients suffering from cardiovascular diseases. Therefore, even though *G. glabra* has many health benefits, overconsumption should be avoided.

Shatavari (*Asparagus racemosus* Willd.)

Shatavari (*Asparagus racemosus*) is a popular vine widely used for its medicinal value. Both leaves and roots are utilized in Ayurveda and other food preparations. Leaves are frequently used in Sri Lanka to make porridge and it is having a pleasant characteristic flavor. Therefore, *A. racemosus* has a huge potential to be used in functional food applications with acceptable consumer appeal.Shevale *et al.* (2015) reported that *A. racemosus* contains many phytochemicals such as alkaloids, glycosides, phenolic compounds, tannins, saponins, steroids, flavonoids and carbohydrates. Thakur *et al*. (2012) reported that among many phytochemicals present in *A. racemosus,* fructooligosaccharides and other polysaccharides are responsible for the immunomodulatory properties that the plant possesses. Gautam *et al*. (2009) studied the effect of standardized *A. racemosus* root aqueous extract on systemic Th1/Th2 immunity of sheep blood cells sensitized mice. They suggested that *A. racemosus* root aqueous extract has cytoprotective, immunorestorative activities with mixed Th1/Th2 response and proposed to be used as vaccine or immunoadjuvant. In a study conducted by Veena *et al*. (2014) highlighted the immunomodulatory potential of *A. racemosus* root extract fortified milk due to the increased phagocytic activity of macrophages *in vitro*.

With the view of utilizing in functional dairy product development, Veena *et al*. (2015) studied how *A. racemosus* root extract interacts with milk proteins and influences the physichochemical and functional properties of milk. They have mentioned that the addition of *A. racemosus* root extract interacted with milk proteins and had an influence on the colour, viscosity, heat stability and rennet coagulation time of fortified milk. The information generated by them is useful in developing *A. racemosus* fortified functional dairy products. Singh *et al*. (2014) optimized functional bread preparation with *A. racemosus* root powder using response surface methodology. They have reported that all the phytochemicals present in the original herb powder except flavounoides were found in the optimized bread which has a favourable consumer acceptance. Rani *et al*. (2020) developed functional biscuit fortified with *A. racemosus* root powder and they have concluded that up to 10% powder can be successfully used without compromising the taste of the biscuits with increased shelf life. In Ayurveda *A. racemosus* has been described as a safe herb for long term use and it is recommended to be used even under pregnancy and lactation (Alok *et al*., 2013).

Garlic (*Allium sativum* L.)

Garlic (*Allium sativum* L.) has been used as a valuable medicinal plant for centuries in traditional medicine and in culinary preparations. It has a high reputation in many traditions as a prophylactic and as well as a therapeutic agent (Bayan *et al*., 2014). *A. sativum* contains organosulfur compounds along with saponins, phenolic compounds and polysaccharides with remarkable biological and pharmacological properties (Tapiero *et al*., 2004; Arreola *et al*., 2015; Shang *et al*., 2019). *A. sativum* possesses a wide array of health benefits such as anti-cancer (Li *et al*., 2018), antibacterial (Strika *et al*., 2016), antiviral (Mehrbod *et al*., 2009), anti-diabetic (Eidi *et al*., 2006), anti-hypertensive (Ashraf *et al*., 2013), cardioprotective (Abdel-Baky and Abdel-Rahman, 2020), hepatoprotective (Ilyas *et al*., 2011), hypolipidemic (Murthy *et al*., 2014), antioxidant (Awan *et al*., 2018) as well as immunomodulatory (Keiss *et al*., 2003) Goêbiowska-Wawrzyniak *et al*., 2004) due primarily to the presence of organosulfur compounds.

Keiss *et al*. (2003) studied the effect of *A. sativum* powder extract on cytokine expression in lipopolysaccharide activated human blood samples. They have shown that *A. sativum* can promote the anti-inflammatory environment by cytokine modulation in human blood that leads to an overall inhibition of NF-κB activity in surrounding tissues. Goêbiowska-Wawrzyniak *et al*. (2004) in a pilot investigation treated the children suffering from recurrent respiratory tract infections and mild cellular immunodeficiency with dry *A. sativum* tablets and shown that there was a significant improvement in T-lymphocyte function as well as the clinical conditions. Further, Donma and Donma (2020) reviewed the capability of the *A. sativum* to maintain the immunohomeostasis in an individual through different ways.Rouf *et al*. (2020) reported that garlic has antiviral activity not only against human and animal but also against plant viral infections. Mehrbod *et al.* (2009) investigated the antiviral activity of *A. sativum* extract against the influenza virus using Madin-Darbey Canine Kidney cell culture and showed the successful inhibitory effect of *A. sativum* extract on the virus penetration and proliferation.

While *A. sativum* is used in many culinary preparations and considered itself as a functional food and also since the phytochemical substances in it have been proposed as promising candidates for immune homeostasis and as an antiviral agent, it could be used as a effective ingredient in functional food development with high consumer appeal to be used in this era of COVID-19. In the current market, garlic fortified functional foods like bakery products such as bread, biscuits, and herbal teas, pickle, sauce etc. are already available and new ways and means in utilization of this valuable medicinal plant should be explored.

Aloe vera

Aloe vera has been utilized in traditional medicine for around 3000 years (Dagne *et al*., 2000). Luta and McAnalley (2005) reported that on dry matter basis *A. vera* gel consists of polysaccharides (55%), sugars (17%), minerals (16%), proteins (7%), lipids (4%) and phenolic compounds (1%). According to Kahramanoglu *et al*. (2019), *A. vera* contains nearly 110 potentially active constituents which belong to 6 different classes. Among them, chromone and anthraquinone and their glycoside derivatives are of significant importance. Immunomodulatory and antiviral potential of *A. vera* was examined and proven by previous studies (Keivan *et al*., 2007; Halder *et al*., 2012). *A. vera* gel as well as the powder prepared from the gel is already extensively utilized in various health foods worldwide. Ahlawat and Khatkar (2011) reported that *A. vera* products are amongst the popular products in the functional foods and supplements market in USA. Even though *A. vera* gel is safe to use, aloin from the yellow exudates is reported to cause DNA damage and cancer (Lachenmeier *et al*. 2005) and therefore, *A. vera* products should be manufactured with utmost care. Apart from used in functional food applications, *A. vera* gel is used in the food applications as an edible coating to preserve fresh produce (Kahramanoglu *et al*., 2019). Postharvest quality of the fresh produce will be protected by application of *A. vera* due to the inhibition/reduction of respiration and transpiration by these fresh produce.

Other Medicinal Plants Having Proven Immonomodulatory and Antiviral Activity with Potential Applications in Functional Foods

Apart from the medicinal plants mentioned above there is a possibility of many others with proven antiviral and immunomodulatory properties such as *Zingiber officinale* (ginger), *Curcuma longa* (turmeric), *Salvia rosmarinus* (rosemary), *Nigella sativa* (black cumin), *Cinnamomum verum* (cinnamon), *Salvia officinalis* (sage), *Thymus vulgaris* (thyme), *Houttuynia cordata,Trigonella foenum-graecum* (fenugreek), *Mentha piperita* (peppermint) etc. to be utilized in functional food applications. Some of them have already been utilized and some, experimented to be fortified in functional foods development. The health benefit of *Zingiber* *officinale* was documented around 2000 years ago (Caroviæ-Stanko *et al*., 2016) and used in many food applications. Some others mentioned above are normally used in culinary preparations as spices. It has been documented that *H. cordata* which is widely used in some countries as a leafy vegetable and *N. sativa* which is widely used as a spice possess anti-SARS activity. Lau *et al*. (2008) studied the effect of aqueous extract of *H. cordata* on immunomodulatory and anti-SARS activity in mouse model. They reported that *H. cordata* act against SARS in 2 different ways, i.e. by activating cell mediated immunity to prevent viral infection and if infected, by slowing down the viral replication. They also documented that *H. cordata* water extractis not toxic to laboratory animals after the oral administration of 16 g/kg. Since *H. cordata* has a fishy smell, there is a possibility to use extracts/powders of this plant with fish and meat based functional foods. Sommer *et al*. (2020) reported that due to the existence of thymoquinone, one of the main phytochemical compounds, *N. sativa* is an effective herb which can be utilized to treat SARS-CoV-2. Thymoquinone might be potent against SARS-CoV-2 by inhibiting viral proliferation, by killing the virus, by killing bacteria associated with pneumonia and by improving the immunity (Sommer *et al*., 2020). *N. sativa* and its essential oil have many functional food applications already (Ramadan, 2007). Since the above mentioned medicinal plants have proven antiviral and immunomodulatory activities, novel functional food products with higher consumer acceptability could be developed for the functional food market to be used by the health conscious consumers worldwide especially in this crisis situation of COVID-19 to improve their overall health and to protect from being infected.

CONCLUSION

Medicinal plants have been used since ancient times in traditional medicine as prophylactic and therapeutic agents for various health ailments. Bioactive phytochemicals derived from those plants have several different scientifically proven health benefits including immunomodulatory and antiviral properties. Optimal cultivation, harvesting, preservation and storage conditions are required to preserve the medicinal value of these medicinal plants. It is also crucial to guarantee the correct plant is used. Rigorous quality assurance measures are needed to be applied to the products not only in the functional food sector but also in any application to guarantee the product quality, safety and efficacy and thereby to ensure consumer health. Quality and quantity of bioactive phytochemicals present in the final functional food should be assured. For this, product claims are needed to be tested. The claims should be verified and certified by regulatory authorities before delivered to the market. Phytochemicals in the medicinal plants when fortified can interact with the food matrix. Therefore, thousands of years of usage cannot be taken as evidence for safety and efficacy of medicinal plants when incorporated with foods. Hence, more evidence is required through controlled clinical trials to support the safety and efficacy of the functional foods fortified with medicinal plants. Studies should also be carried out using specific food substrates under storage and food processing conditions. Functional foods with better consumer appeal developed accordingly, could be utilized as an effective means for the prevention of diseases. They could enhance the immunohomeostasis and protect the body against COVID-19. Functional foods can be recommended to enhance the immunity of the group of people who are unexposed as well as exposed to COVID-19.

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Tulsi-A Potential Immune Boosting Functional Food Ingredient to Combat COVID-19

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