



## AN OVERVIEW ON ROLE OF ETHNOMEDICINE IN BOOSTING HUMAN IMMUNITY TO COMBAT VARIOUS VIRAL DISEASES

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## ABSTRACT

Some of the medicinal plants valued in Ayurvedic Rasayana for their therapeutic potential have seen scientifically investigated with promising results. Several plant-based principles have been isolated with a potential immunomodulatory activity that can explain and justify their use in traditional medicine in the past and can form the basis for further research in the future as well. Hence, the present review of the literature study was planned to document common and easily accessible functional food plants that can modulate the immune system and are biologically active against several medical problems arising from respiratory tract infections and in addition this review will serve as a guideline to the general public to include important medicinal food plants in their daily diet for strengthening and improving their immune system and overall health. Based on the knowledge from this review of the literature study we hypothesize that plants may help individuals to overcome the infection by (i) modulating the body's immune system (ii) generating antiviral activity against the infection (iii) reducing other respiratory problems. A substantial number of plant extracts and phytochemicals have been explored for their antiviral property. Herbal preparations owing to their holistic approach strengthen the body's immune system, which in turn may help the body fight against invading infectious viruses. In this review of the literature study, we documented twenty functional food plants with immunomodulatory and antiviral properties that have been reported to induce the immune system in several ways. These mainly include liquorice (*Glycyrrhiza glabra* L.), garlic (*Allium sativum* L.), tea (*Camellia sinensis* [L.] Kuntze), ginger (*Zingiber officinale* Roscoe), turmeric (*Curcuma longa* L.), pomegranate

(*Punica granatum* L.), black pepper (*Piper nigrum* L.) and several others. Thus, the practice of ethnomedicine plays a pivotal role in boosting human humanity to combat various viral diseases and will also help human beings to protect against the current Covid-19 like pandemic situation.

**Keywords:** Ethnomedicine, Immunomodulatory, Antiviral, Onion, turmeric, Zinger, Garlic, Tea, Black pepper.

## INTRODUCTION

Throughout history, mankind has been accompanied by infectious diseases that have, in one way or another, raised the question of its survival. Almost all the time, mutations in strains of influenza A viruses lead to the emergence of infectious diseases with new symptoms and consequences. Avian flu, swine flu and other zoonotic influenza virus infections in humans lead to diseases ranging from mild upper respiratory tract infections to severe pneumonia, acute respiratory failure syndrome and death.<sup>1</sup> Each of them is initially regarded as a pandemic, but as soon as a treatment medication and a vaccine are developed, it is considered a regular seasonal flu. The coronavirus that led to the COVID-19 pandemic is similar to the pathogen SARS-CoV (a viral respiratory disease of zoonotic origin) that caused the epidemic of 2003. A drug for atypical pneumonia that has passed clinical trials is yet to be developed. In 2020, humanity is being forced to return to the unfinished solution of the problem, whose initial conditions will be amended with new criteria. This SARS-CoV-2 virus has affected many people, not only in China but spreading to almost all countries and territories in a short time.<sup>2</sup>

Complementary and alternative medicine offers a wide variety of herbal plants, which may serve as a key to unlock the many mysteries behind human pathologies. According to a WHO report, 80 % of the population in developing countries depends on traditional plants for health requirements.<sup>3</sup> Several medicinal plants have been explored and found potential against lethal viral infections. Ethnomedicinal literature documents several such herbal plants claiming broad-spectrum antiviral activity. In the light of the advancing technological tools at disposal, exploration of potential antiviral activity of numerous medicinal plants has acquired a phenomenal pace with the emergence and re-emergence of highly infectious viruses. Thus, the present

review aims to document common and easily accessible functional food plants that can modulate the immune system and are biologically active against several medical problems arising from respiratory tract infections. Furthermore, this review will serve as a guideline to the general public to include important medicinal food plants in their daily diet for strengthening and improving their immune system and overall health.

### Herbs with Immunomodulatory Properties

The human immune response is the body's most important defence mechanism against disease and the survival of humans is greatly dependent on this system of fighting against foreign pathogenic microorganisms, including viruses. The possible immunomodulatory function of plants is a recent concept in the field of phytomedicines. Immunomodulators not only enhance humoral and cell-mediated immunity but also activate non-specific immune responses such as activation of the natural killer (NK) cells, macrophages, granulocytes and complement systems, which enhance resistance to infections non-specifically.

Table 1 enlisted twenty functional food plants with immunomodulatory and antiviral properties that have been reported to induce the immune system in several ways. These mainly include liquorice (*Glycyrrhiza glabra* L.), garlic (*Allium sativum* L.), tea (*Camellia sinensis* [L.] Kuntze), ginger (*Zingiber officinale* Roscoe), turmeric (*Curcuma longa* L.), pomegranate (*Punica granatum* L.), black pepper (*Piper nigrum* L.) and several others.<sup>4</sup>

For example, liquorice has been used as a medicinal and flavouring herb since ancient times. Traditionally, the dried roots are first crushed and then boiled to prepare an extract. The extract can be dried to a dark paste or powder and taken orally to treat different types of chronic infections.<sup>5</sup> The root contains a saponin named

glycyrrhizin, which is responsible for immunomodulation, antiviral and other biological activities.<sup>6</sup> Innate immunity and adaptive immunity both greatly depend on the activity and function of the white blood cell (WBC) count and it is also evident that most of the immune cells are produced from haematopoietic stem cells of bone marrow. Raphael and Kuttan reported that mice treated with glycyrrhizic acid showed an increase in WBCs, bone marrow cellularity and  $\alpha$ -esterase positive cells. In addition, they analysed the humoral immune response by measuring the production of antibodies and the number of antibody-producing cells in the spleen, which were found to have increased in the treated mice.<sup>7</sup> Moreover, the *in-vitro* results showed that glycyrrhizin promotes the growth response of splenic T-lymphocytes to anti-CD3 monoclonal antibodies or concanavalin A (Con A) through the improvement of interleukin-2 (IL-2) and IL-2 receptor (IL-2R) expression.<sup>8</sup>

Garlic has been one of the most popular herbal remedies since ancient times. It is believed that freshly crushed garlic mixed with honey or without can strengthen the immune system, as well as having antiviral and other biological properties, which might be due to the presence of several bioactive sulphur-containing compounds including sulphoxide, proteins and polyphenols.<sup>9</sup> Several studies have suggested interesting beneficial effects of garlic on the immune cells and immunity in general. For example, Kuttan reported the immunostimulatory effects of sulphur compounds (diallyl sulphide, diallyl disulphide and allyl methyl sulphide) in mice. Amongst the compounds studied, mice treated with diallyl disulphide showed higher numbers of WBCs (17,900 cells/mm<sup>3</sup>) and antibody titers than mice treated with other compounds. These compounds also significantly improved the bone marrow cellularity, the number of  $\alpha$ -esterase positive cells and the number of plaque-forming cells in the spleen.<sup>10</sup> Other studies have reported that garlic protein fraction 4 (F4) improved the cytotoxicity of human peripheral blood lymphocytes (PBL) against NK sensitive (K562) and NK-resistant (M14) cell lines. F4 further improved IL-2-induced and Con A-induced proliferation and their

receptor expressions of PBL.<sup>11</sup> Moreover, liquid garlic extract and protein fraction showed modulatory effects on macrophages and T-lymphocyte functions. These findings were further supported by the identification of three protein components of ~13 kD (QR-1, QR-2 and QR-3) from garlic extract exhibiting mitogenic activity on certain immune cells that include, lymphocytes, mast cells and basophils.<sup>12</sup>

Similarly, other documented plants also possess immunostimulatory properties, such as curcumin derived from *C. longa*, which can interact with several types of immune cells, including dendritic cells, B- and T-lymphocytes, macrophages and cytokines<sup>13</sup> and enhance the defence mechanism of the host. A black tea (*C. Sinensis*) decoction in cultured human peripheral mononuclear cells showed increased lymphoproliferative action at 72 h.<sup>14</sup>

In human mononuclear cell cultures, green tea (also from *C. Sinensis*) extract showed increased production of neopterin (a potential marker for activation of cell-mediated immunity) in unstimulated peripheral mononuclear cells. Whereas a reduction in neopterin was observed in cells stimulated with Con A, phytohemagglutinin and gamma interferon, confirming the immunomodulatory properties of green tea.<sup>15</sup> These immunostimulatory properties of black tea and green tea are due to the presence of (-)-epigallocatechin gallate, quercetin and gallic acid in the leaves.<sup>16</sup>

Furthermore, Patil *et al* found that oral administration of ethanolic leaves extracts of the common fig (*Ficus carica* L.) ameliorated humoral and cell-mediated immune responses.<sup>17</sup> Traditionally, this plant has also been used against several respiratory, gastrointestinal, inflammatory and cardiovascular.<sup>18</sup> Moreover, methanolic extracts of mango (*Mangifera indica* L.) bark (rich in mangiferin) enhanced delayed-type hypersensitivity and humoral antibody titers, confirming its possible immunomodulatory properties.<sup>19</sup> *In-vivo* oral administration of hexane leaves extract of mango increased the WBC count and the size of the thymus and spleen, indicating immunomodulation in WBCs and bone marrow hematopoietic cells.<sup>20</sup>

**Table 1:** List of plants with immunomodulatory and anti-viral properties

Plant	Family	English Name	Part Used	Formulation	Compounds	References
<i>Allium cepa</i> L.	Amaryllidaceae	Onion	Bulb	Crushed & mixed with honey	Quercetin, thiosulfinates, and anthocyanins	Gansukh <i>et al.</i> , 2017 <sup>21</sup>
<i>Allium sativum</i> L.	Amaryllidaceae	Garlic	Bulb	Crushed & mixed with honey	Diallyl disulphide, alliin, polyphenols, proteins (QR-1, QR- 2, and QR-3)	Anywar <i>et al.</i> , 2019 <sup>9</sup>
<i>Berberis vulgaris</i> L.	Berberidaceae	Barberry	Fruit, stem and root	Boiled extract and poultice	Berbamine, berberine	Kalmarzi <i>et al.</i> , 2019 <sup>22</sup>
<i>Camellia sinensis</i> (L.) Kuntze	Theaceae	Tea Plant	Leaf	Boiled and drunk	Catechins, quercetin, gallic acid, theaflavin-3,3' -digalate	Karimi <i>et al.</i> , 2016 <sup>23</sup>
<i>Carica papaya</i> L.	Caricaceae	Papaya	Fruit and leaves	Leaves are ground to prepare juice; fruit can be directly eaten	Caricaxanthin, violaxanthin, dehydrocarpine I and II and cardenolide	Radhakrishnan <i>et al.</i> , 2017 <sup>24</sup>
<i>Citrus aurantium</i> L.	Rutaceae	Bitter orange	Fruit and Peel	Dried peel or fruit juice	Polysaccharides, polyphenolic compounds	Mannucci <i>et al.</i> , 2018 <sup>25</sup>
<i>Curcuma longa</i> L.	Zingiberaceae	Turmeric	Rhizome	Pounded, tincture, powder	Curcumin	Catanzaro <i>et al.</i> , 2018 <sup>26</sup>
<i>Ficus carica</i> L.	Moraceae	Fig	Fruit, leaves	Decoction with honey	Terpenoids, anthocyanins, steroids	Patil <i>et al.</i> , 2010 <sup>17</sup>
<i>Glycine max</i> (L) Merr.	Fabaceae	Soybean	Seeds	Cooked or roasted	Isoflavones, flavonoids, phytosterols, organic acid and saponins	Anitha <i>et al.</i> , 2015 <sup>27</sup>
<i>Glycyrrhiza glabra</i> L.	Fabaceae	Liquorice	Root	Dried roots extracted.	Glycyrrhizin	Smirnov <i>et al.</i> , 2019 <sup>28</sup>
<i>Lycium barbarum</i> L.	Solanaceae	Wolfberry	Fruit	Fresh fruit directly eaten	Polysaccharide-protein complexes, phenolic compounds	By-ambasuren <i>et al.</i> , 2019 <sup>29</sup>
<i>Mangifera indica</i> L.	Anacardiaceae	Mango	Bark, leaves, roots, fruits, and flowers	Boiling or powdering of bark, leaves, root and flowers, while fruit can be directly eaten	Flavonoids, xanthenes (Mangiferin), phenolic acids, triterpenes	Amin <i>et al.</i> , 2019 <sup>30</sup>
<i>Morus alba</i> L.	Moraceae	Mulberry	Fruit leaf, root	Fruit juice, leaves and root bark decoction or tea	Carotene, vitamin B1, folic acid, folic acid, vitamin D, polyhydroxylated alkaloids, glycoprotein, Anthocyanins, benzofurans, stilbene	Kim and Chung, 2018 <sup>31</sup>
<i>Nigella sativa</i> L.	Ranunculaceae	Black Cumin	Seeds	Roast and eat	Quinones, alkaloids, saponins	Koshak <i>et al.</i> , 2018 <sup>32</sup>
<i>Piper longum</i> L.	Piperaceae	Long pepper	Fruit and root	Decoction	Piperine	Kumar <i>et al.</i> , 2011 <sup>33</sup>

<i>Piper nigrum</i> L.	Piperaceae	Black pepper	fruit	Dried and used as a spice	Piperine	Chaudry and Tariq, 2006 <sup>34</sup>
<i>Prunus domestica</i> L.	Piperaceae	Black pepper	Fruit	Eaten fresh	Anthocyanins, protocatechuic acid	Rasne et al., 2018 <sup>35</sup>
<i>Psidium guajava</i> L.	Myrtaceae	Guava	Fruit, shoots, leaves	Fruit can be directly eaten. Decoction and poultice of leaves and shoots	Phenolic, flavonoid, carotenoid, terpenoid and triterpenes	Sriwilai-jaroen et al., 2012 <sup>36</sup>
<i>Punica granatum</i> L.	Lythraceae	Pomegranate	Fruit, Seeds, Bark	Fruit juice, a decoction of seeds, dried bark	Anthocyanins, fatty acids, alkaloids, vitamins	Moradi et al., 2017 <sup>37</sup>
<i>Zingiber officinale</i> Roscoe	Zingiberaceae	Ginger	Root	Dried or roasted and eaten with honey	Essential oil, fibre, proteins, fatty oils, carbohydrates	Mahboubi, 2019 <sup>38</sup>

**Note:** I. Immunomodulatory properties of these plants are for overall body immune system, not for any disease, infection or organ; II. While antiviral properties are mostly against respiratory tract infectious viruses.

### Herbs with Antiviral Properties

According to WHO, respiratory tract infections are the leading cause of mortality amongst all infectious diseases. Viral diseases are life-threatening due to their rapid outbreak in developing as well as developed countries, whereas treating them is a huge challenge due to, easy adaptation, resistant viral pathogens and the emergence of new viral strains and the ineffectiveness of antibiotics.<sup>39</sup> Bearing this in mind, several common and easily accessible functional food plants have been documented in this review that possesses immunomodulatory, antiviral (especially for respiratory tract infections) and other biological activities. For example, glycyrrhizin isolated from *G. glabra* was tested on SARS-CoV-infected patients admitted to the Clinical Centre of Frankfurt University, Germany.<sup>40</sup> The results of this study showed that glycyrrhizin was the most effective inhibitor of SARS-CoV replication, with a selectivity index of 67 in Vero cells, compared with other tested compounds. Furthermore, this compound inhibited not only replication but also the adsorption and penetration of the virus. Although the exact mechanism by which glycyrrhizin inhibits SARSCoV adsorption, penetration and replication is unclear, a literature review revealed that it affects cellular signalling pathways, including protein kinase C, transcription factors and casein kinase II. Also, glycyrrhizin

enhances the production and expression of nitrous oxide (NO) in macrophages, which remarkably inhibits virus replication.<sup>41</sup>

In addition, glycyrrhizin possesses potent activity against the influenza A virus (H5N1), which is also an emerging virus and, like SARS-CoV, targeting the lungs. These viruses also have certain pathological similarities and differences. Previous studies have reported that a 100 µg/ml concentration of glycyrrhizin reduced the capacity of H5N1 to affect chemokine and interleukin (IL-6) production, as well as H5N1-induced apoptosis.<sup>42</sup> H5N1 replication was found to be enhanced at the high-mobility-group box1 (HMGB1) DNA binding site, but glycyrrhizin inhibited the polymerase activity of H5N1 by affecting HMGB1 binding to DNA.<sup>28</sup> Therefore, this compound could be considered a potent antiviral agent and should be given serious attention. Moreover, the 3C-like protease of SARS-CoV is an important target for drug discovery and development because it is involved in proteolytic procession during the maturation of the virus.

Chen et al tested different compounds derived from *C. Sinensis*, including tannic acid, 3-isothaflavin-3-gallate (TF2B) and several catechins, on 3CL protease activity. It has been suggested that catechins do not show inhibitory potential; however, both tannic acid (IC<sub>50</sub> = 7 µM) and TF2B (IC<sub>50</sub> = 3 µM) were found to be potent inhibitors. These results suggest the potent role of the

tea plant against SARS-CoV infection, but further investigation of its possible inhibitory action on the replication of CoV in cell culture might strengthen its claim to antiviral activity.<sup>43</sup> Furthermore, curcumin derived from *C. longa* decreased the yield of influenza virus by more than 90% in cell culture at 30  $\mu$ M concentration, which might have been because it affected the synthesis of viral proteins such as haemagglutinin, neuraminidase and matrix protein.<sup>44</sup> Curcumin was also found to be effective against RSV, by inhibiting its replication and budding in the nasal epithelial cells of humans, and it also improved epithelial barrier activity.<sup>45</sup> Similarly, other reported immunomodulatory functional food plants in this review also exhibit elevated antiviral activity, particularly against viruses causing respiratory tract problems, and so should be considered as potential antiviral agents.

## CONCLUSIONS

Based on the knowledge of this review of literature study, we hypothesize that plants may help individuals to overcome the infection by (i) modulating the body's immune system, (ii) generating antiviral activity against the infection, and (iii) reducing other respiratory problems. A substantial number of plant extracts and phytochemicals have been explored for their antiviral property. Herbal preparations owing to their holistic approach strengthen the body's immune system, which in turn may help the body fight against invading infectious viruses. Herbal antiviral compounds, which are accessible and do not require laborious pharmaceutical synthesis are emerging as interesting alternatives in today's world of growing resistance to antiviral drug therapy.

**Future Perspectives.** Many promising herbal treatments exist for viral diseases with proof of their efficacy and safety in advanced clinical trials. However, a lot of work remains to be done to determine optimal treatments, doses and formulae for those herbal preparations. Although herbal plant preparations are widely used in several parts of the world, individually or in combination, data about the interactions of these medicinal plants in a living system is non-existent. Therefore, the traditional medicine practise should be

clubbed with scientific research facilitating modern drug discovery from phytochemicals. Scientific data about detailed pharmacokinetic and pharmacodynamics of medicinal plants and their preparations should be made available to researchers and policymakers so that larger randomized multicenter clinical trials may be designed and conducted. By adopting such approaches, the idea of incorporating and implementing a particular herbal formulation in routine therapy may be transformed into reality.

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