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Review Article

Supplements' impact on immunity and COVID-19

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ABSTRACT

The footprint of ancient civilization shows that they were well-informed about the benefits and use of traditional food and medicine system not only used for treatment but also act as immunity booster. In modern medicine we observed that micro-nutrient plays important role in enhancing immunity, which was observed during pandemic of COVID represented a source of global health treatment of SARS-COV 2 infection to mitigate symptom progression in human as many supplements have been given in the treatment earlier for the treatment of COVID-19 many symptomatic medicines were given to the patient according to their clinical condition during the world health crisis. A number of research have been carried out to find out the treatment of the disease and to enhance the immune response of the body. Amongst which the role of various supplements has been a very important factors as immune enhancer which can be used as an early treatment and also has positive response in many bodies function. This study highlights the better understanding and the role of micro-nutrient and herbal medicine in blocking and entry of immunogens by stabilizing or protecting the cell membrane by enhancing the immune response of the body. Which suggest that that treatment along with more than one supplement are more effective and significantly decreases the duration.

Keywords: COVID-19, Immunity, Zinc, Selenium, Gilloy and Bhuvi amla

INTRODUCTION

The health care sector was totally shattered in the COVID-19 in the year 2019-2020, throughout the world. Many developed and developing countries were struggling to fight with the virus because of lack of health care infrastructure. Many alternative therapies were also used to treat the patients of COVID-19 among which Ayurveda was also a boom for mankind which is a traditional and reliable method of treatment.[1]

The year 2019 and 2020 has been remembered for the attack of SARS-CoV-19 on mankind and made us realize the importance of health. Wuhan epidemic was most dangerous, causing various health issues with symptoms like exhaustion, muscle ache, headache, loss of taste or smell, sore throat, congestion, nausea, vomiting, diarrhea as well as death in severe cases. In order to eradicate viral infections, an immune response led by interferons (IFN) and cytotoxic T cells is always necessary.[2] The Ayurveda and micronutrients provide a new spectrum of treatment by acting as immunomodulators which play a vital role to counter the life-threatening conditions arising as repercussions of COVID-19. The herbs like *Andrographolide paniculata* (greenchiretta/kalmegh), *Tinospora cordifolia* (Moonseed/goliy) and *Phyllanthus niruri* (bhumi Amala) were traditional medicines used with a respiratory systematic approach and seemed to improve the immune system by activation or enhancement of various immune cells and pathways; whereas the flavonoids present in these herbs act as bioactive compounds which result in immunomodulatory, antioxidant, anti-inflammatory, and antiviral activities.

The micronutrients like zinc and selenium are important for essential body functions and play an important role in

metabolism as well as immunity. Zinc has the ability to increase the polymorphonuclear cell ability to fight against infection, reduce duration of common cold symptoms, and decrease the severity of symptoms. The components like zinc are closely required for the normal development, differentiation, and function of immune cells and are thus required for both innate and acquired antiviral response.[3] Zinc has anti-inflammatory properties, and selenium enhances the role of T-lymphocytes (T-cells) and natural killer cells (NK cells) and also has immunity boosting properties.

Selenium is one of the most essential trace elements in animals and humans. It can boost the immune function of the body by enhancing the role of T-lymphocytes and NK cells. Selenium is bound with a protein known as selenoprotein which is about 10% and involved in the synthesis of glutathione peroxidase which increases the antioxidant capacity of the body.

ROLE OF ZINC

Patients who suffer from viral diseases frequently use over-the-counter vitamins like zinc gluconate and ascorbic acid. Ascorbic acid is an antioxidant that may contribute to immune response, while zinc has reportedly been shown to improve polymorphonuclear cells' capacity to fight infection.[4,5] High doses of ascorbic acid and zinc gluconate may shorten the duration of common cold symptoms and lessen their intensity, according to scant data.[6-9] The zinc plays a vital role in enhancing the ability of the immune system. The boost of the immune system by the production of INF-Alfa and IFN-gamma reduces mononuclear cells; not only these but it also reduces IFN-Alfa and interleukin 1B.[3] The ionic form of zinc provides immunity to cells by stabilizing the cell membrane and its constituents.[10] Antiviral role: Compared to the control group receiving antiretroviral medication alone, patients' CD4+ T cell counts significantly increased after starting antiretroviral therapy.[9]

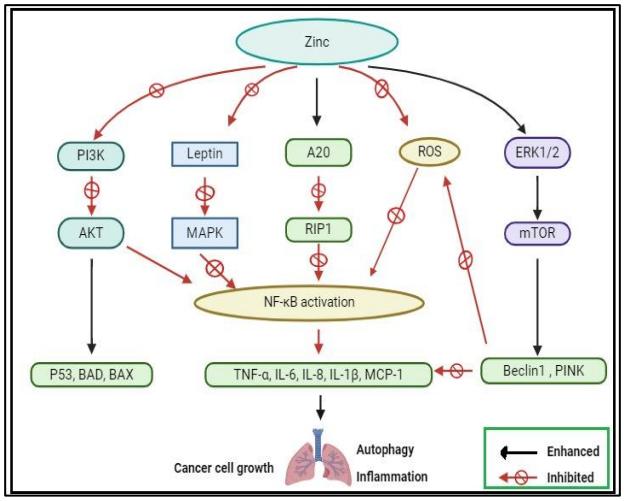

Figure 1: Role of zinc in immune response and its antiviral mechanisms.

Role in novel corona virus

Viruses' viral protease and polymerase enzymatic process inhibition, adhesion, infection, and uncoating, as well as other mechanisms. Studies in cell culture have shown that high zinc ion of pyrithione for stimulation of the cellular import of zinc results in inhibition of the replication of various RNA viruses. Zinc is thought to be essential for the folding and activity of various cellular enzymes and transcription factors as well as many cofactors for numerous viral proteins.[11,12] Viral RNA-dependent RNA polymerase are suitable targets for novel antiviral drugs; their activity is strictly virus-specific and may be blocked without severely affecting cellular function. The inhibitory effect of zinc on the function of viral RdRp was demonstrated in case of rhinovirus and influenza.[13]

SELENIUM

The trace amount of selenium is essential for mammalian redox biology in the form of selenocystine as a catalase in many selenoproteins. The amino acid serine is used for the synthesis of selenocystine, which is incorporated into selenoproteins.[14] The deficiencies of selenium may impact not only the immune response but also the pathogenicity of viruses.[15] Selenium status was found to be significantly higher in those surviving compared to those who did not survive in the context of novel coronavirus.[16-18] The essential selenoenzyme glutathione peroxidase-2, responsible for viral replication, is strongly dependent on adequate selenium supply. Selenium deficiency could play a sub-essential role in the genesis of SARS-CoV-2, as part of a group of enzymes that work together with vitamin C to reduce the formation of reactive oxygen species, which trigger oxidative changes both in microbes and in the cells of the host.[19] One of the main plasma circulatory antioxidants, selenoprotein P (SELENOP), aids in the delivery of selenium to tissues and was proposed to improve redox regulation and immune responses in SARS-CoV-2-infected individuals by minimizing selenium and SELENOP deficits through supplementation.[20] It is estimated that 500 million to 1 billion individuals worldwide suffer from selenium insufficiency, primarily due to insufficient dietary selenium intake. The intake of selenium impacts the immune system's fundamental defenses, and low selenium levels make individuals more vulnerable to viral infections by lowering immunity and accelerating spread.[21]

Majeed et al serum selenium levels were discovered to be a risk factor for COVID-19 infection in a community in Iran after analysis of the selenium status in COVID-19 patients and healthy South Indian persons. Therefore, the possibility that selenium status is one of the risk factors for SARS-CoV-2 infection raises the necessity for adjuvant selenium treatment in patients who are seriously ill and selenium deficient. Because of its antioxidant, anti-inflammatory, and antiviral qualities, selenium

supplementation may help critically sick patients live longer and spend less time in the hospital.[20]

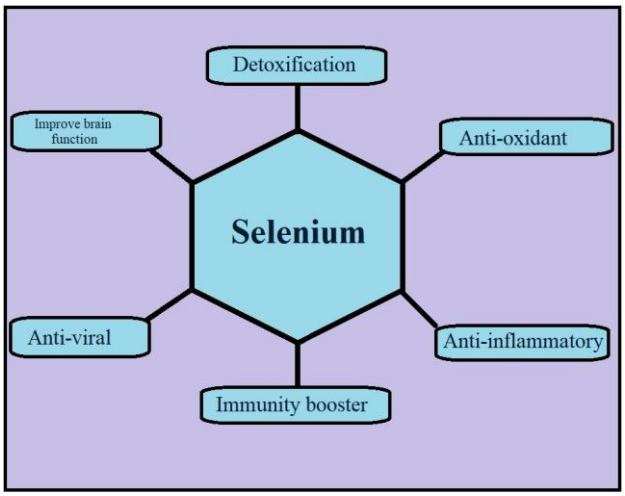

Figure 2: The selenium's biological functions.

SELENIUM ANTIVIRAL ROLES

Organic selenium species has been shown to inhibit COVID-19 virion membrane formation and function. The most effective concentration reported is around 10 µL in certain contexts, with observed antiviral effects in COVID-19 infection models. It is also noted to have hepatoprotective or liver-protective effects in COVID-19-related liver damage by supporting immune mechanisms.[16] Selenium can be used to combat various viruses and is discussed as a potential therapeutic in several disorders, including cancer; while high dosages may be hazardous, low levels may provide antiviral activity.[17-20] Selenium has been described to boost immune responses by influencing cytokine persistence and activity, with interactions noted between selenium status and immune cell populations such as NK cells and T cells.[6,11,26] Selenocysteine and selenoproteins are implicated in supporting immune function and may be considered in the context of NK cell-mediated immunotherapy and broader antiviral strategies.[26]

Table 1: Selenium and it's co factor.

Selenium	Glutathione
Se	Q10
Se	Co Q10

The glutathione is important for adequate intake of proteins containing sulfur groups like cysteine and methionine. In people of the age group 60-79, significantly low erythrocyte GSH was observed compared to younger individuals.[27]

Q10 AND COQ10

Selenium supplementation combined with co-enzyme Q10 supplementation was observed to lessen the non-specific inflammatory response as evaluated by plasma CRP and other indicators of inflammation as well as CVS mortality in healthy elderly patients lacking in selenium.[28] Seen that CoQ10 supplement, even when given alone, can exert an anti-inflammatory effect; it was found in the analysis that there was a reduction in infection in non-specific patients.[29,30]

ANDROGRAPHIS PANICULATA

Burm. f. *A. paniculata* Nees, a traditional medicinal plant, possesses antiviral, anti-inflammatory, and immunomodulatory actions and is frequently used as an alternative therapy for respiratory diseases and influenza. It's worthy to note that previous studies have conducted the pharmacological and phytochemical studies of *A. paniculata*.[37-39] The common English name of *A. paniculata* is king of bitter (or green Chiretta). Other names for it include: Hempedubumi in Malaysian, "fah tha lai" in Thai, "Kalmegh" in Hindi, "Chanxinlian" in Chinese. For thousands of years, the aerial part of *A. paniculata* has been used as a medicinal herb in many traditional regimens for the treatment of skin diseases, respiratory disorders, diabetes, fever related to colds and the common cold.[40] WHO list: In a WHO publication on medicinal plants used in various parts of the world, where plants are listed by species and country, *A. paniculata* is included in the aim of monitoring and the use of herbal medicines.[41] *A. paniculata*, a common medical herb in Asia and Europe, is called kalmegh in India and chuanxinlian in China. The roots and aerial parts of this herb in India are widely used in the preparation of more than 26 ayurvedic medicines, mainly against recurrent fevers and other fevers. *A. paniculata* is considered extremely cooling; hence, in TCM, it is used to clear heat and moisture. It is also common in Southeast Asia, for example, in Thailand and Malaysia, for treating hypertension and diabetes. Such uses are an indication of its past and present utilization in medicine.[40,42-44]

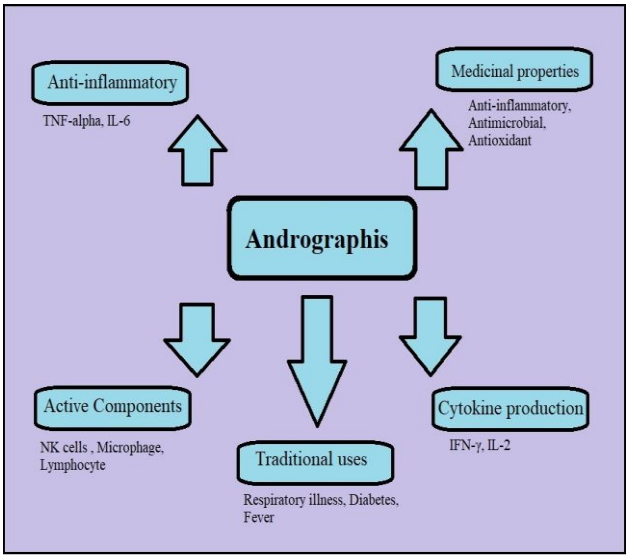

Figure 3: Properties and bioactivity of *Andrographis*.

Extensively studied for its immunomodulatory activities, *A. paniculata* is also known as kalmegh. The active compound, andrographolide, plays a crucial role in the enhancement of the immune system. For example, it has been shown to stimulate the functions of the immune cells, NK cells, macrophages, and lymphocytes, which essentially protect against infections.[45,46] Andrographolide could specifically promote the secretion of various cytokines, including interleukin-2 (IL-2) and interferon-gamma (IFN-γ), which are crucial for protecting against invading microorganisms.[47] Besides its immunostimulatory effects, *A. paniculata* also showed anti-inflammatory activities.[48,49] It has been found that it modulates inflammation and tissue repair during infection by inhibiting inflammatory cytokines such as TNF-α and IL-6. The plant therefore exhibits therapeutic potential when *A. paniculata* balances immunostimulation and anti-inflammation to conditions where there is abnormality of the immune response. There is clinical evidence on the use of *A. paniculata*, particularly in relation to infections of the respiratory tract. Cohort studies, randomized controlled trials, and case reports suggest that *A. paniculata* may reduce the incidence of acute upper respiratory tract infections and adverse effects, supporting its use as an adjuvant therapy.[50] According to traditional belief, the plant has been proved to be safe for use for centuries and more contemporary evidence is adding to the premise that it remains safe during extended times of use.[51] All in all, *A. paniculata* has very promising anti-inflammatory and immunomodulatory activity, supporting its use in aiding respiratory infections and general immune health.[45,50,51]

TINOSPORA CORDIFOLIA (MOONSEED/GOLIY)

T. cordifolia, or popularly known as Giloy, is an immuno-modulator and an inherently therapeutic entity according to many traditional medicinal systems, mainly Ayurveda. It comprises many secondary metabolites such as alkaloids, glycosides, and flavonoids that contribute to their therapeutic activity.[52,53] Studies suggest the enhancement of the immune system via stimulation of immune cells by *T. cordifolia* comprising macrophages and lymphocytes. This stimulation leads to enhanced phagocytosis and cytokine production, which are crucial to fighting infections in the body.[54] The herb also possesses antioxidant potential, which diminishes oxidative stress and inflammation, and thus promotes the immune system.[56]

It is noteworthy that an administration of the plant had been correlated with protecting the immune system and in some cases antiviral effects against different viral pathogens. This includes antiviral activity against some respiratory viruses.[55] It has several active compounds, including andrographolide, which is known to inhibit the entering and replication of viruses, thereby reducing the intensity and duration of viral diseases.[56,57] As the pharmacy develops, historical medicines are still taken for purposes of eliminating diabetes and respiratory infections because of immune-modulation which might be the first in line in curing diseases.[55] Then, it becomes all the more important in view of hepatoprotective properties through which it inhibits liver damage in the presence of agents induced to disrupt the immune system.[56] The nuclear factor Kappa-light-chain-enhancer of activated B cells (NF-κB) complex is thought to bring about inflammation and support immune system function. Extracts of *T. cordifolia* help to control inflammatory diseases and uplift the immune response by blocking the action of NF-κB; thus, they hinder the secretion of inflammatory cytokines such as TNF-α and IL-6.[57] Additionally, by modulating the phosphorylation of several proteins, it also regulates MAPK signalling pathways, thereby stimulating immune cells and curbing inflammation.[58] Moreover, JAK-STAT pathways have an important role in contributing to the transduction of signals of cytokines and growth factors and administration has been shown to enhance expression and activity of JAK-STAT systems, thereby proliferating and potentiating T lymphocytes and NK cells.[59-61] *T. cordifolia* has also been found to activate phosphoinositide 3-kinase (PI3K)-Akt signalling pathways, which are important for cell survival and metabolism, as they promote survival and functioning of immune cells, i.e., B and T cells, during immune responses.[62,63] So, along with the medicinal benefits, there are antiviral and immune-stimulating factors in *T. cordifolia* that serve in its favor. This is exactly why *T. cordifolia* has been a household name across countries. She gives natural solutions for several ailments that are concerned with enhancing immune strength.

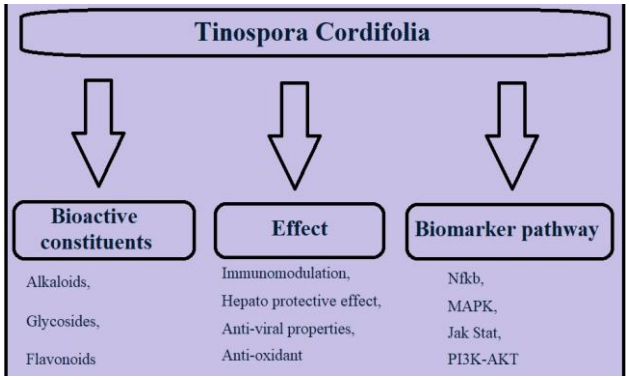

Figure 4: Properties and mechanisms of action of *T. cordifolia*.

CONCLUSION

Nutrition is key to health. These micronutrients are not only necessary for our health day-to-day activity but also provide us immunity to fight against pathogens. The evidence that the micronutrients zinc and selenium might be involved in the course and outcome of COVID-19 disease is observational and weak based on experience from treatment of scars and other viral infections. We understand from observations that nutritive supplements administered at an early stage of the infection are

important for enhancing host resistance against RNA viral infections including severe COVID-19. We hypothesize that in particular, increased resistance towards escalation of COVID-19 into the life-threatening cytokine release syndrome might be obtained. The effectiveness of nutrient supplementation when administered at the stage of advanced illness has been disappointing. The system before escalation of the disease has immune enhancing anti-inflammatory effects. However, the nutritional status of the host has not yet been considered a crucial factor in severe viral infections. Based on the literature currently available, it is reasonable to assume that the pre-infection status of zinc and selenium is particularly important for the resistance against the progressive course of COVID-19. Additional research and clinical trials are therefore requested on both the therapeutic and preventive role of nutritional supplements. Zinc generating both innate and acquired humoral immune responses, maintaining the integrity of the cell membrane, preventing virus entrance, and preventing viral replication by interfering with the viral genome. It suggests that zinc supplementation may be helpful for COVID-19 prevention and therapy. Given the disease's present lack of effective treatments, its high probability, sometimes life-threatening course, and its enormously detrimental effects on the affected person and healthcare system worldwide. Whereas selenium Shows antiviral effect against COVID-19, has confirmed using low-toxicity antioxidants and immunity-boosting capability with other merits which help in improvement of patient health in COVID-19. With people having both the lowest and highest selenium status, China is one of the most selenium-deficient nations. The CFRs steadily climbed from 1.17% in non-selenium-deficient (selenium sufficient) areas to 1.28% in moderate-selenium-deficient areas, and severe selenium-deficient areas were significantly impacted with a CFR of 3.16%. Similarly, dependent on topsoil selenium levels, the CFRs steadily climbed from 0.76% in places with no selenium deficiency to 1.70% in areas with moderate selenium deficiency, and then to 1.85% in areas with severe selenium deficiency. The findings thus imply that regional selenium deficit may be associated with a rise in COVID-19 CFR. Whereas the herbs like *T. cordifolia* and *A. Paniculata* these herbs act as immunomodulators which enhance the body's resistance ability by activating immune cells such as NK cells, macrophages, and lymphocytes. They also act as antioxidants and show antiviral effects by regulating biomarkers like NF-kB, JAK-STAT, and TNF-alpha, along with cytokines like IL-6. These herbs not only reduce the effects of viruses but also help the body recover in the post-illness phase through their active bio-ingredients such as alkaloids and flavonoids, which play a major role in conditions of secondary metabolic disorders.

Recommendations

The various study shows that people with week immune system have to face the devastating effects of COVID -19 virus and these traditions herbs and miro-nutrients can help to boost immunity and also enhances the recovery rate in patients having mild to moderate condition.

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