Phytochemicals and Micronutrients: A Review of Their Immunomodulatory Properties

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Abstract: **The demand for herbal medicines is growing among individuals due to their favorable benefit-risk ratio, which is often hard to achieve with synthetic and semi-synthetic drugs. It is essential to investigate the effectiveness and health advantages of various herbs. Research indicates that medicinal plants can treat numerous infectious diseases by influencing the components of the immune system. The antiviral properties of these herbs and their ability to enhance the Immunological response against infections & viral loads are noteworthy. Furthermore, effective prevention of infectious diseases can significantly decrease economic burdens and mortality rates in a cost-effective manner. However, one major hurdle to the acceptance of herbal treatments is the lack of rigorous testing and limited patient monitoring. Herbal extracts contain a variety of phytochemicals, including alkaloids, polyphenols, terpenoids, glucosinolates, and glycosides. Herbs can support the immune system in several ways. For instance, some enhance phagocytic activity in macrophages, with plants like Centella asiatica and Murraya koenigii functioning through this method. Others, such as Euphorbia hirta and Moringa oleifera, improve antibody production, linking to both cellular and humoral immunity. Additionally, herbs like Withania somnifera and Nigella sativa can boost cytokine levels and helper T-cell activity. Antioxidant and anti-inflammatory properties of these herbs also contribute to enhanced immune responses. Other contributing mechanisms, though less significant, include the inhibition of nitric oxide production, activation of superoxide dismutase, and free radical scavenging. A well-balanced immune system is crucial for human health; insufficient immune defense can lead to infections and tumors, while an overactive immune response can result in immune mediated diseases. Immunocompetence depends on proper nutrition, dietary adjustments, and adequate consumption of specific vitamins (like vitaminC, D, and folic acid) and minerals (like magnesium, zinc, and selenium). Consequently, deficiencies in these nutrients can weaken immunity. Many natural ingredients have demonstrated powerful immunomodulatory effects. Micronutrients play an important role in enhancing the immune system and may serve as effective agents in creating new immunomodulators, particularly in response to pandemics such as COVID-19.**

Key Words: **Antibodies, Herbal remedies, Immunity, Infections, Macrophages, T-cells.**

I. INTRODUCTION

Every living organism has evolved a defense system known as the immune system, which constantly adapts to combat new infections. The core components of this system are white blood cells, including neutrophils, basophiles, monocytes, and macrophages, which play a crucial role in establishing active and physiological defenses that make up natural immunity[1].

The purpose of this review article is to emphasize the often-overlooked medicinal properties of specific herbs and their function as immunomodulators. The idea of immunization is widely applied in various health issues and crises, with a strong belief among people that "prevention is better than cure." Immunization serves as a crucial initial strategy for any nation facing a pandemic, as seen during the COVID-19 outbreak. Observers noted that the pandemic led to the production of numerous inflammation-promoting factors, such as cytokines, interferon, and interleukins, which signal the immune system's recognition of the COVID-19 virus. This immune response can be strengthened by supplementing with essential amino acids and micronutrients like selenium, zinc, copper, and iron, as well as vitamins A and C. Incorporating foods rich in immunomodulatory properties—such as papaya, grapefruits, pineapple, guava, bananas, melons, oranges, coriander, broccoli, green peppers, garlic, and ginger—into the regular diet, along with millet and brown rice, is recommended. The human body has its own immune system, supported by physiological barriers like the skin, mucous membranes, and body temperature. Various external stimuli, whether physical or chemical, can trigger an exaggerated immune response. This response to external stimuli may occur immediately or be delayed. Antigens, which can take the form of bacteria, viruses, or pollen grains, stimulate the defense sytem. Notably, the defense system retains a

memory of antigen-antibody interaction from the initial exposure, allowing the body to produce antibodies more rapidly upon subsequent encounters. The ability of immune system to differentiate between extraneous substances plays a crucial role in its response to infections or allergens[1,2]. In certain infectious diseases such as influenza, pneumonia, HIV, and tuberculosis, the body becomes vulnerable to additional infections due to a significant reduction in white blood cells (WBC), CD4+, and CD8+ cells. These immune cells, including macrophages, CD4+, and CD8+ cells, are crucial for generating an immune response. When the immune system is compromised, supportive therapy is necessary to bolster the body's defenses alongside the primary treatment. In addition to synthetic immunomodulating agents, many herbs have been known to boost immunity. For centuries, herbs have served as a fundamental source of medicinal treatments. Studies have shown that individuals with a robust immune system are less prone to various infectious diseases, as seen during the COVID-19 pandemic. Extracts from ashwagandha leaves and roots, or its powdered form, have been found to help hypoglycemic condition and hypocholesterolemia, alleviate symptoms of depression, increase strength and muscle mass, and may even be effective in preventing COVID-19 infection[2]. he idea of enhancing the body's immune system is widely recognized and valued by communities and health organizations globally. There is a growing trend towards using various herbs as complementary treatments for a range of health issues. Many herbs commonly found in our daily lives can enhance our immunity, enabling us to combat infections more effectively and swiftly, while also minimizing the risk of complications and disabilities that may arise during treatment. Nutrients such as dietary fiber and amino acids like leucine, glutamine, and methionine are known to promote the growth of immune cells[3]. Numerous secondary metabolites or phytochemicals present in plants can promote human health by preventing and treating various diseases. Both contemporary and historical diseases contribute significantly to global mortality rates. Many individuals who understand how the immune system operates strive to keep it functioning well. While numerous companies produce synthetic drugs aimed at enhancing immune responses, a majority of people prefer to support their immune system through natural means. Furthermore, prolonged use of synthetic medications can result in reduced effectiveness and potential side effects. As a result, utilizing herbal remedies is often seen as a superior alternative to allopathic treatments. This has driven researchers to seek out plant-based substitutes for these synthetic drugs. At this point, plant metabolites take center stage. Many phytochemicals documented in ancient texts have undergone clinical trials to assess their ability to influence immune function. Herbal medicines can naturally bolster the body's immunity without leading to adverse effects[44]. Rasayanas in Ayurveda and Traditional Chinese Medicine boost the body's natural capacity to protect itself from external threats. The human immune system is a sophisticated system made up of a variety of dynamic cellular and molecular elements.Different internal and external factors can create pathophysiological conditions that disrupt the immune "homeostasis." Immunomodulators can help manage these conditions and restore balance. The therapeutic and restorative properties of immunomodulators bolster the immune system's mechanisms of protection.These substances can act as immunostimulants, immunosuppressants, or immunoadjuvants, either boosting or inhibiting the immune response as required.Given the significant toxicity and negative side effects commonly associated with synthetic immunomodulators, there is a growing interest in plant-based alternatives that may offer a safer option. While immunosuppressants can be beneficial in treating various autoimmune and hypersensitivity disorders, immunostimulants are often employed in cancer therapies. Numerous well-known plants are currently being studied for their potential immunomodulatory effects[45].Ginger is rich in bioactive substances such as phytosterols, flavonoids, and saponins, which provide antibacterial, antioxidant, and chemo-protective benefits. The anti-inflammatory phenolic compounds present in ginger inhibit the cyclooxygenase and lipoxygenase pathways. Additionally, ginger extract has proven effective against avian influenza, with gingerol showing significant ability to inhibit viral replication[9].Garlic, an herb known for its strong smell, possesses antibiotic, anti-inflammatory, and antibacterial qualities thanks to its organosulfur and phenolic compounds[10].Amla is packed with compounds that enhance the activity of specific white blood cells, which play a crucial role in combating diseases and triggering an immune response when facing viral threats in the body. Rich in antioxidants, particularly vitamin C, amla aids in detoxifying the entire body, thereby promoting overall health and strengthening immunity. Similarly, garlic contains

sulfur-based bioactive compounds that stimulate the activity of natural killer cells, further supporting the immune system[4].

The use of antibiotics and antiviral medications can certainly enhance the condition of a disease; however, a significant issue with these drugs is the emergence of bacterial resistance, which can lead to a deterioration of the condition and render the medications ineffective. Additionally, unavoidable side effects may result in permanent deformities with prolonged use and escalate hospitalization costs. A study indicates that parents often prefer administering natural herbal remedies to their children due to their perceived safety. Among the most potent antiviral phytochemicals are curcumin and resveratrol. A key reason natural medicines receive approval for treatment is the insufficient evidence from studies and clinical trials[5].

II.THE CONCEPT OF IMMUNITY

The human body is constantly confronted with millions of microorganisms, including bacteria, viruses, and fungi, every second. The body's defense system serves as a complex protection mechanism that safeguards the body against these potentially harmful agents. It accomplishes this vital function through various processes, such as producing B-lymphocytes and antibodies that either target or eliminate infected cells and microbes, triggering inflammatory responses. Among vertebrates, the immune system is particularly intricate and advanced, capable of generating a wide array of cells and molecules to combat various infectious agents and their toxins. Additionally, it retains memories of past infections, allowing it to recognize minor or significant changes within the body's internal environment. This remarkable ability is largely attributed to the similar sequences of amino acids and genes found in each organism[1].During an infection, T and B cells undergo significant metabolic changes, which lead to a greater absorption of nutrients, glucose, and oxidative phosphorylation. This process supplies the necessary nutrients and amino acids that support the immune response of these cells. The effectiveness of this protective response can be further improved by utilizing immunomodulating herbs—substances that can stimulate or boost the immune response[3]. The body responds to an antigen in two primary ways. The first is through a basic defense mechanism that includes physiological barriers. The second response is more intricate and varied, capable of retaining a memory of the immune response. This response can be classified into humoral immunity and cell-mediated immunity. Humoral immunity is associated with B-lymphocytes and antibodies, whereas cell-mediated immunity involves cytotoxic T-cells, macrophages, and natural killer cells. These immune cells are generated in the bone marrow and mature in the thymus gland. Additionally, cytokines and interleukins act as secondary mediators, facilitating communication between specialized cells and the immune system[7]. Herbs like Azadirachta indica and Ocimum sanctum serve as immune boosters by enhancing specific immunity and promoting antibody production, thereby playing a crucial role in immunomodulation[13].

1. Functions of the Immune System

The immune system performs its functions in several ways.

Adaptive immunity identifies antigens or infections within the body, while innate immunity serves as a barrier against foreign invaders. The immune system recognizes antigens to effectively safeguard the individual from illnesses. Active immunity is essential for maintaining the memory of immune responses through the formation of memory B-cells.. Various physiological mechanisms and immune effectors, such as the production of antibodies against antigens and complement factors, contribute to the possible eradication of pathogens. Additionally, the immune response helps to stabilize infections and protects the host from potential harm[7].

Table 1: Organization and components of immune system [5]

Acquired immunity	Innate immunity
1) Cell mediated immunity: a) T lymphocytes b) Cytotoxic killer T-cells c) Helper T-cells d) Suppressor T-cells	1) Present at the birth: a) Complement cascade phagocytes: macrophages natural killer cells, neutrophils, basophils, eosinophils.
2) Humoral immunity: Plasma cells	2) Physical barrier:

Clonal B-cells	Skin,saliva,mucous membrane, acid into the stomach, urine, tear.

2.TYPES OF IMMUNITY

Immunity can be divided into two main types: innate immunity and adaptive (or acquired) immunity. Innate immunity is the type that is inherited from one's parents and is present from birth. Unlike adaptive immunity, innate immunity is not specific to particular antigens; instead, it primarily works to block the entry of pathogens into the body through various physiological barriers. In contrast, adaptive immunity is specialized for targeting specific antigens and typically responds more effectively to pathogens than innate immunity. This form of immunity includes the creation of immune cells, antibody production, activation of CD4+ and CD8+ cells, and the presentation of MHC-I and MHC-II proteins by macrophages and antigen-presenting cells. The initial defense in innate immunity consists of physical, mechanical, and biochemical barriers that help prevent pathogens from entering the body. The second line of defense triggers an inflammatory response, which is part of the acquired immunity. This inflammatory reaction occurs in response to tissue injury or infection and is driven by various cellular and biochemical defense mechanisms, including the movement of cytotoxic and phagocytic cells, as well as the release of interleukins[2,3].White blood cells (WBCs) are crucial for the production of antibodies.Normally, the white blood cell count ranges from 5,000 to 10,000 cells per mm^3 of blood. These cells are produced in the bone marrow and circulate through the blood and lymphatic system. When pathogens break through the body's initial defense, which includes the skin and mucous membranes, they invade and quickly reproduce by exploiting the body's resources. Immune cells, like macrophages and T-killer cells, move to the infection site.Macrophages engage in phagocytosis and present the antigen on their surface with the aid of MHC proteins, which are recognized by T-helper cells. This recognition triggers the production of B-lymphocytes, leading to the generation of antibodies in response to the antigen. The resulting antigen-antibody reaction helps immobilize the pathogen and triggers inflammation, as well as the release of interleukins, cytokines, and prostaglandins. These substances cause blood vessels to expand and increase their permeability, allowing fluid accumulation in the affected area. Neutrophils, the most prevalent type of granulocyte, also participate in the immune response and can eliminate infected cells. Additionally, dendritic cells play a vital role in immunity by retaining memory of the immune response to specific pathogens. Natural killer cells are involved in destroying both pathogens and tumor cells, as well as cells infected by viruses[7,8].

2.1. Innate Immunity

Innate immunity plays a crucial role during the initial phase of an infection by either preventing pathogens from entering the host or triggering the early immune response. This form of immunity involves several physical barriers, including the skin, mucous membranes, stomach acid, tears, and body hair., which work to keep pathogens outside the host's body, ultimately aiming to prevent their entry into the circulatory system. While innate immunity is generally considered non-selective, functioning similarly against all foreign substances, certain barriers, like mucous membranes and skin, may be more sensitive, potentially leading to allergic reactions upon encountering pathogens. These barriers are present from birth and persist throughout life. However, it is inaccurate to claim that innate immunity lacks selectivity, as it can distinguish between foreign invaders and the body's own cells. Research into innate immunity has revealed a specific family of receptors that respond to environmental stimuli, similar to the mechanisms of acquired immunity. These receptors are capable of recognizing pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs). Initially discovered in insects, these receptors share genetic similarities with those in mammalian cells. PAMP recognition receptors are found on both the cell surface and within the nucleus. Their capacity to recognize these patterns is believed to arise from various environmental factors that present sequences of amino acids comparable to those of pathogens. When activated, these receptors prompt an early immune response, resulting in inflammation and the release of cytokines and interleukins. Early pathogen detection by the immune system significantly aids in the survival and complete elimination of the pathogen from the host. Additionally, it provides the acquired immune system with more time to recognize the antigen and confirm its presence through co-stimulation, which subsequently leads to antibody production and phagocytic activity. Innate immunity

also contributes to the activation of natural killer cells and inflammatory responses facilitated by these receptors.Sometimes, the immune system may have difficulty distinguishing between different antigens. The body can mistakenly identify its own proteins as harmful antigens, leading to serious conditions known as autoimmune diseases. In these cases, the immune system treats these self-antigens as foreign invaders and produces antibodies against them, resulting in damage to the body's organs. However, the likelihood of developing autoinflammatory diseases is lower due to a co-stimulation mechanism, where two distinct pathways confirm activation: one through antigen-specific receptors, such as pathogen-associated molecular patterns (PAMPs), and the other through a theoretical co-stimulatory pathway. This dual confirmation triggers the immune response. Additionally, certain molecules act as mediators, such as Toll-like receptor 4 (TLR4), which binds to bacterial or pathogenic cells, prompting the release of inflammatory substances like cytokines and leading to inflammation and sepsis. Herbs contribute significantly to this system by offering nutritional support and essential amino acids necessary for the proliferation of immune cells. They also help maintain physiological barriers over extended periods and regulate immune responses to antigens while acting as anti-inflammatory agents, mitigating the effects of inflammation caused by immune cells to preserve immune system homeostasis[1,2].

2.2.Acquired or Adaptive Immunity

As the term implies, this immune system has an adaptive quality; it is not fully developed at birth but grows and evolves as life progresses. Its development is influenced by various life stages and environmental factors, improving through interactions with new infections. One of its key features is the ability to retain memory of past encounters with specific pathogens, which facilitates quicker elimination and faster antibody production when facing the same pathogen again. This system is more effective than innate immunity due to its specificity and adaptability. While innate immunity can address a broad range of pathogens and treats all antigens similarly, it primarily functions to halt infections early on. Adaptive immunity may not respond to an antigen during the initial encounter, but it provides thorough identification and differentiation of antigens, which helps minimize the risk of auto-inflammation. This immune response can be triggered directly by pathogens or through the innate immune system's actions.Furthermore, adaptive immunity can be categorized into humoral and cell-mediated immunity depending on the types of immune cells that are involved. In humoral immunity, B-lymphocytes generate antibodies that serve two purposes: they attach to antigens on antigen-presenting cells while simultaneously binding to B-lymphocytes that recognize the antigen[1].Conversely, cell-mediated immunity involves T-helper cells, T-killer cells, macrophages, and monocytes, all of which engage in phagocytic activity. This system is activated when an infected cell releases interferon, a glycoprotein that not only protects neighboring uninfected cells but also trigger helper T-cells. These helper T-cells subsequently activate B-lymphocytes and 促 ate the movement of phagocytic cells to the site of infection.. Macrophages carry out phagocytosis and present antigen proteins on their cell surfaces, engaging CD4+ and CD8+ cells that differentiate into memory T-cells, MHC proteins, T-killer cells, and natural killer cells. In turn, B-lymphocytes identify the antigens and produce specific antibodies that protect other organs and facilitate selective elimination of pathogens. Dendritic cells, often referred to as the "brain" of the immune system, maintain a memory of immune responses and serve as a link between innate and acquired immunity. In addition, suppressor T-cells help regulate the immune response and suppress the activity of natural killer cells.[4,5].During an infection, changes occur in T-cell metabolism and differentiation, characterized by an increased absorption of nutrients like glucose and amino acids such as methionine and leucine[4].This demonstrates the immunomodulating properties of herbal medicines that are high in these nutrients, as they can enhance metabolism and cell growth during illness. This increased demand for nutrients and amino acids can be met through the use of herbs as a complementary treatment. Additionally, adaptive immunity can be categorized into active acquired immunity and passive acquired immunity based on how antibodies are produced. In active acquired immunity, the host's immune system generates antibodies in response to an antigen, which could be natural or delivered via a vaccineIn contrast, passive acquired immunity involves receiving antibodies from an external source, such as through plasma therapy[8].

III. INDIAN AYURVEDA

Rasayanas Historical texts such as the Atharva Veda, Charak Samhita, and Sushrut Samhita highlight the use of plants for medicinal purposes. Ayurveda, often referred to as a long-standing Indian herbal medicine system, has been practiced for more than 6,000 years.A variety of plants, known as Rasayanas for their therapeutic qualities, are recognized for boosting both the immune system and mental health[107].In ancient times, doctors created various therapeutic methods aimed at revitalizing the body's functions. This practice is referred to as 'RasayanChikitsa,' which translates to rejuvenation therapy[108].Rasayana therapy enhances and rejuvenates the quality of rasa by enriching it with nutrients that support anti-aging, longevity, better memory, a strong immune system to fight diseases, glowing skin and complexion, and the growth of sensory organs. Prominent Rasayanas mentioned in Ayurveda include Triphala Rasayana, Chawanprash, and Brahma Rasayana[109].Some non-Rasayanic plants have properties that strengthen the immune system, fight pathogens, and offer anti-inflammatory benefits. Rasayanas can be divided into two categories based on their specific needs[106].Kamya Rasayanas: are health-enhancing substances that enhance the body's energy and strengthen the immune system. Examples of Kamya Rasayana include Pranakamya, which promotes vitality; Medhakamya, which boosts mental capacity; and Srikamya, which improves skin complexion[110].Naimittika Rasayana: refers to a category of Rasayanas designed to combat specific illnesses. This category is further divided into two types based on the treatment location: Kuti Praveshika Rasayana (Indoor therapy) and Vatatapika Rasayana (Outdoor therapy). Prior to beginning Rasayana therapy, it is crucial to undergo detoxification, called Samshodhana, through the Panchkarma method. The effectiveness of these Rasayanas on the body is greatly enhanced after detoxification[109].

IV.TRADITIONAL CHINESE MEDICINE

Shares functional similarities with Traditional Indian medicine, or Ayurveda, as both approaches focus on enhancing the immune system to promote overall health rather than solely treating specific illnesses. Ancient philosophies recognize five elements—Wood, Earth, Metal, Fire, and Water—as the foundation of the material world. They perceive this world as an interconnected whole, where movement generates the concept of Yin and Yang, representing opposites. The balance of Yin and Yang is maintained through four essential energies in the body: qi, blood, moisture, and essence, alongside the internal organs. For the body to function optimally, these energies must circulate, be maintained, and generated in harmony. Any imbalance among them can lead to illness. In traditional Chinese medicine, treatments are usually divided into four categories: the principal drug, associate drug, adjuvant drug, and messenger drug, known as emperor, minister, assistant, and envoy in ancient texts. The earliest records of traditional Chinese medicine date back to the Eastern Han dynasty (AD 25-AD 220). In 1977, the "Zhong Yao Da Ci Dian," a comprehensive Chinese medical encyclopedia, was published, containing over 5,000 entries, with more than 4,000 substances derived from plants and the rest from animals, minerals, and other sources. Although Western medicine was later introduced to China by Europeans, many practitioners in China continue to combine traditional Chinese medicine with modern treatment methods and technology[111].Various Chinese herbal plants, especially their secondary metabolites like Radix Glycyrrhizae and Lentinus edodes, affect the immune response through several mechanisms. These include stimulating tumor cell growth, inhibiting viral replication, enhancing antioxidant activity, and raising antibody levels, among other effects[112].

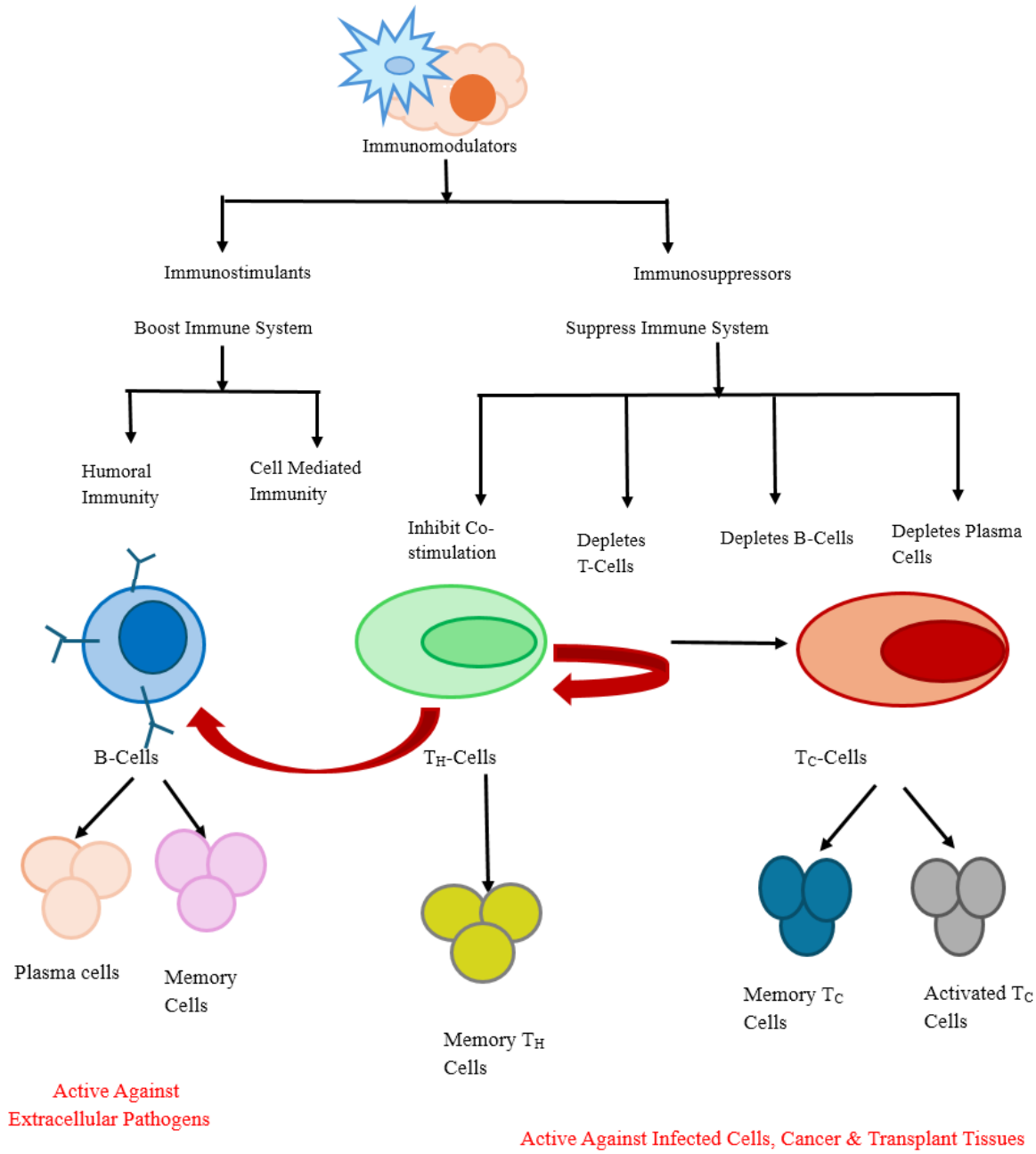

Fig 1.A summary of the actions and functions of immunomodulators.

V. MECHANISMS BY WHICH HERBS MODULATE IMMUNITY

1. Boosting the Immune System

Herbal plants have not been researched to the same extent as other medications in human clinical trials, which limits our understanding of their mechanisms of action. However, scientific literature and observational studies indicate that these herbs play a role in supporting physiological barriers, enhancing digestion, and reducing body heat and inflammation, as seen with Murraya koenigii (L.)[11]. Aloe gel has been shown to be helpful for various skin issues, including rashes, dryness, burns, and wounds[112]. By boosting acquired immunity, herbs offer essential nutritional support during infections, as the metabolism of T-cells shifts and necessitates additional nutrients and amino acids for their growth and development. Furthermore, the use of herbs enhances phagocytic activity and promotes the differentiation of CD4+ cells into T-memory cells[3].

Impact on Cytokine Production: Cytokines are a category of proteins, including interleukins (ILs), interferons, and chemokines, that are crucial for both innate and adaptive immune responses. Certain herbal plants can amplify the activity of these cytokines; however, many other plants utilized for

their anti-inflammatory properties tend to inhibit cytokine production[2,3].Bioactive substances like flavonoids, lignans, terpenoids, polyphenols, sulfides, saponins, and plant sterols can either prevent DNA formation or enhance the function of protective enzymes such as glutathione transferase[2]. During an infection, the metabolism of B-cells and T-cells ramps up, necessitating a greater intake of nutrients for their replication and the development of an immune response. Consequently, these nutrient needs can potentially be met through the use of herbs[3]. The impact of herbs on the innate immune system is advantageous for preventing pathogen entry, which can be facilitated by increasing mucus production, as seen with broccoli. Herbs can also activate the immune system through various mechanisms, including stimulating natural killer cells and promoting the production of antibodies such as IgE and IgM, which enhance the humoral immune response, particularly with astragalus.

2.Suppression of Immune System

certain herbs play a role in reducing B and T-cell activity, as demonstrated with withania somnifera. The COX and LOX pathways, which are involved in inflammation, can be inhibited by herbs like ginger. Additionally, suppressing TNFα can lower immune responses and inflammation, an effect achieved with tanacetum parthenium. Berbamine, an active compound in berberis vulgaris, can inhibit STAT-4 expression and IFN-γ production during inflammation, alleviating symptoms. Stabilizing mast cells can also help reduce inflammation, as their degranulation can lead to inflammatory conditions. Immunosuppressive effects can further result from reducing oxidizing free radicals and the scavenging actions of herbs. Cannabis receptors (CB1 and CB2), predominantly found on immune cells, play a crucial role in immune response suppression and are utilized for their anti-inflammatory effects in inflammatory disorders. Herbs rich in polyphenols exhibit effectiveness in managing inflammation due to their anti-inflammatory properties. Additionally, bioactive compounds in herbs that inhibit calcineurin can limit the proliferation of various immune cells, especially T-cells, as calcineurin is vital for cell growth. Beyond inhibiting cell proliferation, immune suppression can also occur by reducing oxidizing agents like nitric oxide and free radicals through the scavenging effects of herbal constituents and diminishing nitric oxide production. Herbs can also induce anti-inflammatory responses through gene expression and suppress LPS inflammatory signals, as observed with allin, an amino acid derivative found in allium sativum. Certain herbs possess the ability to inhibit the cytotoxic immune response and decrease the expression of CD4+ and CD8+ cells[6].

VI.PHYTOIMMUNOMODULATOR:PLANTS.AND.THEIR.PHYTOCHEMICALS.WITH IMMUNOMODULATORY PROPERTIES

Many researchers continue to focus on the development of synthetic, semi-synthetic, biochemical, and biological compounds aimed at enhancing immunity. However, the challenge remains to identify a single compound or chemical entity that offers high selectivity, potency, and low toxicity while targeting various receptors involved in immunomodulation (Abbott, 2011; Pan et al., 2013). Consequently, considerable efforts have been directed toward discovering promising immunomodulatory compounds derived from plants (Mukherjee et al., 2014; Musaeva et al., 2021). Table 2 outlines several key medicinal plants recognized for their immunomodulatory effects[46].

Table 2: Immunity modulating herbs

Sr no	Common name	Binomial name	Family	Immunomodulatory Phytoconstituents	Impact on immunity	Reference
01	Indian pennywort or gotu kola	Centella asiatica	Apiaceae	Asiaticoside, Asiatic acid, madecassic acid, madecassoside	Enhanced skin mucus lysozyme(SMLA), peroxidase activity(SMPA) and phagocytosis by macrophages	14
02	Drumstick tree, horseradish tree	Moringa oleifera lam.	Moringaceae	Vitamin c, kaempferol,quercetin, Myrecytin	Increase cellular and humoral immunity, anti-oxidant, increase PO and PR activity	15

03	Ashwagandha, Indian winter cherry	Withania somnifera	Solanaceae	Withanine, withanolides	modulate cytokines ,IL-12 by macrophages, stimulate immune response by TLR3 receptors on dendritic cell	16
04	Curry leaves, sweet neem	Murraya koenigii	Rutaceae	Murrayastine, murrayaline,	Act as antioxidant, Rise in phagocytic index	17
06	Mentha , peppermint	Mentha piperita	Lamiaceae	Eriocitrin, narirutin, hesperidin, phosphorus, calcium	Prevent cellular damage, anti-inflammatory, cytotoxic to macrophages	19
07	Astragalus, Milkvetch	Astragalus L.	Fabaceae	Glucoronic acid, Galacturonic acid, Rhamnose, Polysaccharides	Elevate NK cells activity, IgG, IgM level, modulate T-cell function	20
08	Liquorice	Glycyrrhiza glabra	Fabaceae	Glycyrrhizin, 18 beta-glycyrrhetinic acid, Glabrin A,B	Increase in pinocytosis activity	21
09	Black cumin	Nigella sativa	Ranunculaceae	Thymoquinone, Thymol, t-anethole Sequiterpene, Carvacrol	Improve phagocytosis, helper T-cell, Nitric oxide production.	22
10	Purple coneflower	Echinacea purpurea	Asteracaeae	Glycoproteins, Alkamides, Cichoric acid	Activate cellular immunity, T-helper cells.	23
11	Vidarikhand	Pueraria tuberose	Fabaceae	Puerarin, Diadzein, Ganistein, Quercetin, irisolidone, Biochanin A,B	Anti-inflammatory effect by Inhibiting COX,LOX,NF-Kb	24
12	Kutki	Picrorrhiza kurroa	Plantaginaceae	Kutkin	Regulating the cell mediated immunity, increase humoral response	25
13	Jhandu	Tagetes errecta	Asteraceae	Tannins ,terpenoids ,flavonoids	Increase phagocytosis, Radical scavenging, antioxidant	26
14	Haridra , Indian saffron	Curcuma longa	Zingiberaceae	Curcumin,dihydrocurcumin	Increase serum interleukins concentration	27
15	Draksha	Vitis vinifera	Vitaceae	Anthocyanin ,polyphenols ,resveratol	Anti-inflammatory, it prevents mast cell degranulation by reducing the FcεRI-mediated tyrosine phosphorylation of extracellular signal-	28

					regulated kinase and PLCγ1 (17)	
16	Brahmi	Bacopa monnieri	Plantaginaceae	Alkaloid brahmine,bacosides A,B stigmastanol,beta-stiosterol	Inhibits Nitric oxide generation, antioxidant , have free radical scavenging activity.	29
17	Guduchi	Tinospora cordifolia	Menispermaceae	Terpenoids,lignanes,steroids,berberine	Increase bone marrow cellularity, serum immunoglobulin level, cytokines level	30
18	Amla	Emblica officinalis	Phyllanthaceaae	Embalicanin A, B, pedunclagin	Antioxidant activity	31
19	Green tea	Camellia sinensis	Theaceae	Epigallocatechin gallat, theaflavin	Stimulate NK cells by NKG2A receptor, dendrite cells, inhibit neutrophils.	32
20	Broccoli	Brassica oleracea	Brassicaceae	Ascorbic acid, zeaxanthin ,lutein ,beta carrotein	Stimulate innate immunity, antioxidant enzymes in specific immune cells	33
21	Ginger	Zingiberoffi cinale roscoe	Zingiberaceae	Gingerol, zingiberene, bisabolone and farnesene	Increase proliferation of macrophages and phagocytic index.	34
22	Chinese skullcap	Scutellaria biacalensis	Lamiaceae	Baicalein,baicalin, wogonin,wogonoside,oroxylin	inhibit the production of IgE and Th2-mediated cytokines release	35
23	Andrographis	Andrographis paniculata	Acanthaceae	Diterpenoids ,polyphenols ,7-o-methylwogonin ,apigcnin onysilin ,3-4-dicaffeoylquinic acid	Increase lymphocytes,T-cells,CD4+,T-helper cells and cytokinin.	36
24	St. Johns Wort	Hypericum perforatum	Hypericaceae	hypericin and the phloroglucin, derivative hyperforin, flavonoids and phenolic acids.	anti-inflammatory and reduced oxidative and chlorinating activity of human leukocyte MPO, inhibit proliferation of T lymphocytes	37
25	Tulsi	Ocimum sanctum	Lamiaceae	Vicenin, isorientin and ursolic acid , tulsinol	Increase Th1 mediated immune response and INF-γ, NK cell and T-cell count .	38
26	Neem	Azadirachta indica	Meliaceae	Nimbidin,nimbin, nimbolide	Up regulation of type 1 responses and SEB-induced CD4+ T cell activation.	39

27	Black pepper	Piper nigrum	Piperaceae	Piperin, flavonoids	Anti-inflammatory, augmented humoral immune response through the production of antibody (IgM)	40
28	Devil, s plague,Bees Nest plant	Daucus meritimus	Apiaceae	Phenols,carotenoids, polyacetylenes, ascorbic acid	Seed extract shows antiviral activity against HIV type, inhibit viral polymerases	41
29	Papaya	Carica papaya	Caricaceae	Flavonoids	Flavonoids stimulate the activation of TLR-7 and TLR-9, promote the maturation of dendritic cells, and enhance the differentiation of B cells into plasma cells.	42
30	American gensing	Panax gensing	Araliaceae	Ginsenoisides ,triterpene,saponins	Mitogenic activity on lymphocytes	43

VII. NATURAL INGREDIENTS AS IMMUNITY BOOSTER

Herbal remedies, beekeeping products, probiotics and prebiotics, melatonin, and other natural substances with immunomodulatory effects could provide novel therapeutic strategies to enhance immunity against various diseases.[53-56].A variety of vitamins and minerals are crucial for supporting the optimal functioning of the immune system.[54].The expensive nature of synthetic medications, along with their potential toxicity and numerous side effects, is unappealing to patients. On the other hand, herbal remedies as health enhancers have garnered growing interest in both the scientific community and among consumers[57].Certain medicinal plants can display immunomodulatory properties, including the enhancement of phagocytosis and activation of macrophages, regulation of cytokine release, stimulation of immunoglobulin production, and promotion of lymphocyte proliferation[57].There has been a significant rise in interest in "superfoods" like berries, nuts, green tea, seafood, and honey, among others, during the coronavirus pandemic[58]. The COVID-19 pandemic has increased the interest in identifying new and effective natural remedies for immune modulation to help prevent the disease. Plant-based therapies have been regarded as beneficial in boosting the immune system in the context of COVID-19[59].Even with the significant advancements in creating different vaccines for COVID-19, we should not overlook the value of natural substances as agents that boost the immune system[54].Herbal remedies have recently been regarded as the preferred option for boosting immunity in patients both before and after COVID-19[60].Natural ingredients derived from plants enhance health and bolster the body's defenses against infections by strengthening immune responses. Certain phytochemicals enhance the levels of beneficial gut bacteria, which play a vital role in supporting immunity. A recent study by Rondanelli et al. emphasized the crucial role of vitamins C and D, zinc, and Echinacea supplements in self-care practices for preventing or managing common colds[61].Garlic (Allium sativum) contains natural compounds that boost the immune system by enhancing the function of innate immune cells, such as lymphocytes, γδ-T cells, and natural killer (NK) cells, which play a key role in eliminating invading pathogens[62].β-Glucans are naturally occurring compounds found in certain plants, fungi, and bacteria that affect both innate and adaptive immune responses. However, the immune response triggered by β-glucans varies depending on their structural composition[63]. Consuming appropriate amounts of specific polyphenols, vitamins, and minerals can boost immune function and aid in fighting infections like COVID-19[64].Flavonoids offer immune-boosting benefits that help fight cancer, inflammation, and viral infections[65,66].It is essential to understand that a properly functioning immune response also requires the regulation of

excessive and harmful immune reactions. Dendritic cells (DCs) are vital in linking the innate and adaptive immune systems, and their improper activation can lead to chronic inflammation, transplant rejection, and autoimmune diseases. Studies have demonstrated that quercetin, a flavonoid, can act as an immunosuppressant by inhibiting the activation of dendritic cells[67].Recent studies have shown that nanoformulations effectively address the issues of inadequate water solubility and low bioavailability found in certain natural compounds, including curcumin, quercetin, and gingerol[68-70].Nanodelivery systems for medications enable precise targeting of bioactive substances, allowing for a marked decrease in the required dosage. Additionally, micronutrients like vitamin C enhance immune function by boosting chemotaxis and phagocytosis, while also promoting the production of free radicals by immune cells[71].In the same way, vitamin D enhances the Th2 cell response while inhibiting the activation of Th1 cells [72]. In general, a lack of specific vitamins and minerals can weaken the immune system[73].It's important to note that propolis, a well-known product from beekeeping, is commonly utilized for treating upper respiratory tract infections that arise when immunity levels drop[55,74]. Additionally, recent studies have shown that the proper use of the hormone melatonin significantly enhances immune function[75,76].

Micronutrients(Vitamins and Minerals): Many micronutrients are crucial for improving immune function and acting as immune boosters[80].Some dietary micronutrients have been recognized as key components of the well-known Mediterranean diet[81].An effective immune response relies on various essential components, such as zinc, selenium, magnesium, and vitamins, which are crucial and often work together in harmony. It's well established that many vitamins can be sourced from natural foods; for example, numerous fresh fruits and vegetables are rich in vitamin C. However, in today's world, some vitamins are produced synthetically. The daily requirement for micronutrient intake to support optimal functioning may exceed the suggested dietary allowances[82].Recent studies suggest that micronutrients are essential as immunomodulatory agents in managing COVID-19[78].

1.Vitamin C

Vitamin C, or ascorbic acid, is well-known for its anti-inflammatory properties. It can boost the production of cortisol and vasopressors while neutralizing free radicals that affect leukocyte function through the extracellular traps of neutrophils, thus strengthening the body's defense against pathogens like viruses and bacteria. However, there is ongoing debate regarding vitamin C supplementation, as evidenced by several meta-analyses and reviews, largely due to the varying methodologies used in these studies and the assessment of its clinical effectiveness[83].Vitamin C, present in fresh fruits and vegetables, helps reduce oxidative stress in cells, enhances immune function by supporting both innate and adaptive immune responses, and acts as a cofactor in numerous enzymatic processes.. Additionally, higher levels of vitamin C in neutrophils improve their ability to move toward infection sites and enhance their phagocytosis activity, which is crucial for destroying bacterial cells. It also aids in removing dead neutrophils from the site of infection, thereby preventing further tissue damage[77].The protective benefits of vitamin C against the common cold are well-documented. Research shows that taking vitamin C supplements (1–2 g/day) can reduce the severity of cold symptoms in both children and adults. During viral infections, vitamin C levels in the body drop, and a deficiency in vitamin C has been associated with postherpetic neuralgia. In a study of 67 individuals with shingles, intravenous administration of vitamin C (Pascorbin® 7.5 g/50 mL) for two weeks, alongside standard treatment, led to a reduction in pain and other herpes zoster symptoms. This suggests that vitamin C may be helpful during viral infections[84].In a randomized clinical trial with 200 patients, the combination of vitamin C and vitamin E supplements along with a triple antibiotic therapy (lansoprazole, amoxicillin, and clarithromycin) given over a 14-day period led to a higher rate of Helicobacter pylori clearance. This improvement was attributed to enhanced antibiotic efficacy and boosted immune responses[85].

2. Vitamin D

Vitamin D can be synthesized in the skin upon sunlight exposure and is also available through dietary sources. The main natural sources of vitamin D include fish oil, cod liver, egg yolks, butter, and certain fungi[86].Vitamin D is widely recognized for its ability to be synthesized in the skin upon sunlight exposure, and it can also be acquired from dietary sources. Key natural sources of vitamin D include fish oil, cod liver, egg yolks, butter, and certain fungi[87].Increasing evidence indicates that vitamin

D is vital for the body's defense against bacterial and viral infections through innate immune signaling pathways. This involves the production of cytokines, antimicrobial proteins, and pattern recognition receptors. Furthermore, vitamin D supplementation has been found to help combat viral infections, including those caused by SARS-CoV-2. Clinical studies are increasingly confirming the benefits of vitamin D supplementation, particularly for individuals with vitamin D deficiency, which is common in many regions of North America and Europe. This deficiency is especially prevalent in nursing homes, which have been severely affected by the COVID-19 pandemic[88].Recent studies suggest that to improve both innate and adaptive immunity and reduce harmful cardiovascular effects during the COVID-19 pandemic, it is important to prevent vitamin D deficiency in the population. This can be accomplished by taking vitamin D supplements at the dosages recommended by the Endocrine Society, aiming to maintain blood serum levels of 25-hydroxyvitamin D at or above 30 ng/mL. Keeping these levels in check may reduce the risk of SARS-CoV-2 infection and its severe consequences, including death[89]. A study involving 100 participants—50 diagnosed with COVID-19 and 50 healthy individuals—found that those with COVID-19 had significantly lower serum levels of 25-hydroxyvitamin D compared to the healthy group [23.10 ± 10.89 vs. 32.06 ± 17.22, $p = 0.0024$]. Additionally, COVID-19 patients showed a marked decrease in the total counts of lymphocytes, TCD4+, TCD8+, and NK cells ($p < 0.0001$). Levels of IL-12, IFN-γ, and TNF-α were significantly higher in the COVID-19 group compared to the healthy controls, while IFN-α levels were lower in the COVID-19 group. These findings suggest a potential connection between vitamin D levels, immune function, and vulnerability to COVID-19 infection [90].Following the recent COVID-19 pandemic, individuals with deficiencies in vitamin D and selenium faced a higher incidence of acute respiratory tract infections. Vitamin D is essential for boosting the immune system by promoting the production of antimicrobial peptides. It also helps reduce cytokine storms by lowering the release of inflammatory cytokines from immune cells. Likewise, selenium supports the cytotoxic responses of immune cells[80].It's noteworthy that both the innate and adaptive immune systems express vitamin D receptors and associated enzymes, which may account for the immune-modulating effects of vitamin D. Consequently, a deficiency in vitamin D is frequently associated with allergies, infections, and autoimmune diseases[91].

3. Folic Acid

Folic acid, also known as vitamin B9, is found in several natural sources. Major dietary sources of this vitamin include peanuts (246 µg per 100 g), sunflower seeds (238 µg per 100 g), asparagus (149 µg per 100 g), and lettuce (136 µg per 100 g), among others. The National Institutes of Health (USA) recommend a maximum daily intake of 1000 µg of folic acid for adults[92]. A cellular study was conducted to investigate the impact of folic acid on the pro-inflammatory and antiviral molecular pathways in B-lymphocytes infected with a modified live vaccine. The results suggested that folic acid could enhance the B-lymphocyte response, thereby boosting the molecular pathways related to their antiviral and innate immune pro-inflammatory responses[93]. A research study focused on identifying key genes and powerful compounds by analyzing effective substances and drug targets for COVID-19 found that folic acid interacts with the SARS-CoV-2 N protein through molecular docking. It also mitigates the protein's inhibitory effect on the RNA interference pathway, indicating potential therapeutic uses for folic acid supplements [94].Notably, these findings were supported by the more severe progression of COVID-19 and the worse outcomes associated with micronutrient deficiencies, especially low folic acid levels[95].

4. Magnesium

Magnesium is an essential micronutrient required for various physiological functions, and increasing evidence highlights its important role in supporting the immune system's proper functioning. Key natural dietary sources of magnesium include bananas, nuts, black beans, whole grains, flaxseed, leafy green vegetables, and pumpkin seeds[96]Low magnesium levels may play a role in the onset of various chronic inflammatory diseases[79]. Several studies suggest that magnesium may have a protective effect against COVID-19 by reducing lung inflammation[97].The results of this study show that patients with more severe COVID-19 symptoms had lower magnesium levels, with a median of 38.33 mg/L. In contrast, those with mild symptoms had a median magnesium level of 39.46 mg/L, yielding a p-value of 0.002 between the two groups. This suggests that maintaining higher magnesium levels may help protect against severe COVID-19 symptoms[98].

The mechanisms include the calcium channel-blocking effects, which lead to the reduction of interleukin-6, CRP, nuclear factor Kβ, and other potentially harmful factors. Additionally, magnesium deficiency is associated with increased levels of IL-6, a pro-inflammatory cytokine that could be a critical target for COVID-19 treatment [99]. Magnesium helps regulate the immune response by affecting the cells that participate in both the innate and adaptive immune systems.

5. Zinc

Zinc, a crucial trace element, is essential for various physiological functions. It plays a key role in maintaining immune balance by affecting the function of cells in both the innate and adaptive immune systems. Zinc also regulates cytokine and antibody production, as well as the activity of the complement system. A deficiency in zinc can impair immune function, which can have a significant impact on overall health[100].The highest levels of zinc are found in animal-based foods, such as seafood, meats, and dairy products.[101] .Certain cereal-based products and vegetables are also considered good natural sources of zinc. A meta-analysis assessing zinc levels in COVID-19 patients compared to controls, categorized by severity and survival status, used a random effects model from 11 studies. The analysis showed that the overall standardized mean difference (SMD) in zinc levels between COVID-19 patients and controls was −0.83 (−1.19 to 0.46, $p < 0.05$), indicating that COVID-19 patients had significantly lower zinc levels. Additionally, the study examined zinc level differences between severe and non-severe cases, as well as between survivors and non-survivors. It found that patients with severe COVID-19 had notably lower zinc levels than those with non-severe cases (SMD: −0.47, 95% CI: −0.75 to −0.18, $p < 0.05$). However, there was no significant difference in zinc levels between COVID-19 survivors and non-survivors (SMD: −1.46, 95% CI: −3.98 to 1.06, $p < 0.05$)[102].

6. Selenium

Selenium is a trace mineral found in small quantities in the body, but it plays a crucial role in immune function, particularly in defending against viral infections. It participates in the enzymatic activities of glutathione peroxidase, deiodinase, and thioredoxin reductase, functions as an antioxidant, and protects cell membranes and organelles from damage caused by peroxides [103].Selenium may act as a potential preventive measure against viral infections, including the coronavirus, by enhancing the proliferation of natural killer (NK) cells. Moreover, T-lymphocytes exhibit positive effects when combined with vitamins D and E[104]. Since increased oxidative stress and the excessive production of inflammatory cytokines are key factors in coronavirus disease, selenium helps reduce viral infection rates, alleviates oxidative stress and inflammation, strengthens the immune system, and is crucial for critically ill patients. Additionally, selenium deficiency is often associated with higher severity and mortality rates of the disease, providing new insights into how a lack of selenium correlates with the severity of COVID-19[105].

VIII. CONCLUSION

The immune system is an impressive network of specialized organs and cells that helps the body prevent unwanted reactions, and its proper function is vital for maintaining the body's balance. Numerous plants and their components possess immunomodulatory properties, which can be harnessed by incorporating them into your diet as a means to enhance immunity against illnesses. Herbs do not rely on a single mechanism to boost immune responses; instead, they utilize several effective pathways for immunomodulation. This enhancement occurs through increased immune cell proliferation, heightened phagocytic activity of macrophages, and a stronger humoral immune response mediated by IgE and IgM, along with the involvement of antigen-presenting cells like MHC proteins, CD4+, and CD8+ cells. On the other hand, immune suppression can result from anti-inflammatory actions, reduced interleukin production, and the inhibition of pathways like COX and LOX that are associated with inflammation. Given the complexity of the immune system, no single herb can fully enhance immune responses; therefore, further research is necessary to explore combinations of these herbs and their interactions. Certain herbs, such as Withania somnifera and ginseng, are often touted as panaceas for various ailments. Generally, herbs function by reducing oxidative stress, promoting T-helper cell proliferation, and increasing the production of phagocytic cells and cytokines, including interleukins. These plants contain functional ingredients that can protect against multiple threats, enhancing the immune system's strength and effectiveness.They accomplish this by activating and

inhibiting specific immune cells and modulating various signaling pathways, enhancing immune responses and defense mechanisms. Moreover, some of these plants possess free radical scavenging and anti-inflammatory properties, which may aid in preventing cancer development.

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