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THE ROLE OF HERBAL MEDICINE IN IMMUNE SYSTEM ENHANCEMENT: A TRADITIONAL AND MODERN PERSPECTIVE

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ABSTRACT: Herbal medicine has been an integral component of traditional healing systems worldwide, particularly in enhancing immune function. This review explores the historical significance of herbal remedies in immune modulation across various traditional medical systems, including Ayurveda, Traditional Chinese Medicine (TCM), and indigenous healing practices. It further examines the scientific advancements that validate the immunomodulatory effects of these herbal formulations. The mechanisms of action of key herbal immunomodulators, along with their clinical efficacy, are discussed in detail. Additionally, the review highlights recent innovations in immune enhancement, including messenger RNA (mRNA)-based vaccines, immunomodulatory therapies, and the role of the gut microbiome in regulating immune responses. The potential of bioengineered immune cells and the integration of artificial intelligence (AI) and big data in immunity research are also explored, offering novel strategies for immunoregulation and the treatment of immune-related disorders. Finally, the paper addresses the challenges associated with standardizing herbal formulations and examines emerging trends and future directions in their development. By bridging traditional knowledge with modern scientific advancements, this review provides valuable insights into innovative approaches for immune system modulation and disease management.

INTRODUCTION:

Immune System in Health & Disease Prevention: The immune system is essential for defending the body against illnesses and infections. Resistance to illness, particularly infectious disease, is the definition of immunity. The immune response is the result of the immune system's coordinated response to pathogenic bacteria. The immune system is made up of cells, tissues, and chemicals that mediate resistance to infections. Our immune system's main roles are as follows: Basic immunology: immune system functions and diseases [1].

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Protection against Pathogens: The immune system fights illnesses brought on by bacteria, viruses, fungi, and parasites in addition to identifying foreign invaders (antigens) and mounting a suitable defense to eradicate them.

Distinguishing Self from Non-Self: The immune system identifies and combats foreign molecules to stop autoimmune reactions while also recognizing and tolerating the body's own cells.

Removal of Damaged or Dead Cells: The immune system eliminates aging, damaged, or dead cells to preserve tissue integrity and homeostasis.

Tumour Surveillance: Immune cells stop the growth of tumors by identifying and eliminating aberrant or malignant cells.

Wound Healing and Repair: By triggering inflammatory responses and attracting cells for

repair, the immune system plays a critical role in tissue repair and healing.

Regulation of Immune Responses: The immune system makes certain that immune reactions are properly controlled, avoiding either an overreaction (as in allergies) or an under reaction (as in immunodeficiencies). Innate immunity and adaptive immunity are the two main parts of our immune system, which are thought to cooperate to protect the body against infection [2].

Innate Immune System: The body's earliest defence against invaders is the innate immune system. It is frequently referred to as the "non-specific" immune system because it reacts to all pathogens and foreign chemicals in the same way.

The skin and mucous membranes offer protection, as do immune system cells and proteins, which are provided by the innate immune system.

The Skin and Mucous Membranes Protection: The innate immune system includes every surface of the human body, both internal and external. A physical barrier that prevents germs from entering is already formed by the skin and mucous membranes closed surface. Furthermore, materials like mucus, enzymes, and acid stop bacteria and viruses from proliferating. Additionally, some bodily movements prevent germs from settling, such as the intestinal muscles or the lungs cilia, which resemble hairs. Some bodily fluids, such as perspiration, tear fluid, and urine (which cleanses the urinary system's organs), have comparable effects.

Protection Offered by Immune System Cells and Proteins: The body's innate immune system uses specific immune system cells and proteins to combat bacteria that manage to get past the skin or mucous membranes.

Known as scavenger cells, phagocytes are able to immediately halt bacteria or viruses from entering the body. These unique white blood cells, known as leukocytes, encapsulate and "digest" pathogens, rendering them innocuous. The phagocytes' surface is where the germ remnants travel, where the adaptive immune system can identify them. Other immune system cell types also release chemicals that kill bacteria and other pathogens.

However, tissue cells and immune system cells also perish and decompose in addition to the pathogens. Their residues combine to make pus, a yellowish fluid.

The innate immune system's cells benefit from a number of proteins, or enzymes. In a sort of chain reaction, nine distinct enzymes work together to activate one another: First-stage enzymes alert multiple second-stage enzymes, which in turn activate multiple third-stage enzymes, and so on. This makes it possible for the immune response to rapidly strengthen.

The third main component of the innate immune system is the natural killer cells. Their primary responsibility is to detect virus-infected cells and aberrant cells that have the potential to develop into tumor cells or have already done so. They accomplish this by looking for cells with an aberrant surface and then employing chemicals known as cytotoxins to destroy the cell surface. Herbal medicine has been used for millennia to maintain health, prevent disease, and increase immunity. Interest in using herbs as immunomodulators has increased recently due to the trend toward natural and alternative medicines. This essay seeks to demonstrate the value of herbal therapy in boosting the immune system from both conventional and contemporary scientific viewpoints [3-4].

Adaptive Immune System: The adaptive (specialist) immune system steps in if the innate (generic) immune system is unable to eliminate the pathogens. The type of germ causing the infection is the specific target of the adaptive immune system. However, it must first identify the germ as such before it can accomplish that. This indicates that while it reacts more slowly than the innate immune system, its responses are more precise. The ability to "remember" pathogens is another benefit. Thus, the adaptive immune system can begin combating the germ more quickly the next time it encounters one it has already encountered.

This memory also explains why some illnesses are only able to affect you once in your lifetime because your body becomes "immune" to them after a while. When the body first encounters the germ, it might take a few days for the adaptive

immune system to react, but the next time, it can do so right away. Usually, the second infection is either undetectable or at least less severe.

The adaptive immune system is made up of:

- T cells in the tissue between the body's cells.
- B cells (also in the tissue between the body's cells).
- Antibodies in the blood and other bodily fluids.

Herbal medications have a major impact on T cells, B cells, and antibodies, among other important elements of the adaptive immune system. These organic substances improve the body's defense systems, boost immunological responses, aid in immune regulation, and promote general health. For millennia, herbal therapy has played a significant role in regulating the immune system. Many herbs have long been used to increase immunity in traditional medical systems like Ayurveda, Traditional Chinese Medicine (TCM), and Unani. In recent years, modern scientific research has confirmed the effectiveness of these herbs, leading to their incorporation into modern medicine. The body uses the immune system as a defense against infections and illnesses, and enhancing immune function is essential for general health and wellbeing [5].

Historical Background of Herbal Medicine in Immune Support: The World Health Organization (WHO) estimates that over 75% of people worldwide receive their medical care from traditional methods, mostly herbal ones. The earliest human companions were plants and herbs, which provided not only food and shelter but also remedies for a range of illnesses. Various cultures and civilizations, such as Ayurveda (India), Egyptian, Western, Chinese, Kampo (Japan), and Greco-Arab or Unani-Tibb (South Asia), have relied heavily on herbal medicine, also known as traditional or natural medicine. Nowadays, traditional medicine is becoming more popular all over the world, and a lot of study is being done on the many plant species and their therapeutic qualities [6].

Traditional Use of Herbal Immuno Boosters: Ayurveda promotes the use of treatments and medications derived from plants. Significant pharmacological qualities are present in many of the plants identified in this traditional Indian system. Ayurveda, one of the oldest medical systems, uses several different ethnopharmacological techniques.

A large section of the Ayurvedic Materia Medica is devoted to "Rasayana" treatments, which are thought to increase the body's resistance. The Sanskrit terms "rasa" and "ayana," which signify "nutrition" and "transportation," are the origin of the word "rasayana." It is thought to enrich bodily fluids, or rasa, with nutrients, improving their quality. Rasayana contains a variety of plants that are believed to enhance longevity, fortify the body's defenses, and improve mental and physical health. These traits are similar to the contemporary idea of adaptogens, which support the body's ability to adjust to different stimuli and preserve equilibrium.

Numerous therapeutic herbs that fall within the Rasayana category are thought to have immunomodulatory properties. Haritaki, amla, shilajit, ashwaganda, holy basil, guduchi, shatavari, and so on are a few examples. In general, or in reaction to particular foreign substances, these plants may either strengthen or weaken the body's defenses against infections and cancers [7].

The ancient Indian medical system known as Ayurveda places a strong emphasis on using Rasayana (rejuvenating) herbs to boost immunity. Important herbs in Ayurveda include:

Withania somnifera, or ashwagandha, has adaptogenic qualities that strengthen the immune system and fight stress.

Tulsi (*Ocimum sanctum*): Promotes immunological and respiratory health with its antibacterial and anti-inflammatory qualities.

Guduchi (*Tinospora cordifolia*): Renowned for its detoxifying and immunomodulatory properties.

Amla (*Emblica officinalis*): Increases immunity and is high in vitamin C and antioxidants [8].

Traditional Chinese Medicine (TCM): Herbal medicine, nutritional therapy, acupuncture, and manipulative treatment are the four main practice

areas that make up TCM. It is thought that the use of Chinese herbs dates back to the Xia period, more than 4,000 years ago. This discipline is credited to Shen Nung, who is frequently called the Father of Chinese medicine. The Classic of Shen Nung's Materia Medica, his book, is regarded as the first to list the characteristics and uses of over 300 herbs. Chinese medicine gradually grew to rely heavily on fundamental ideas like Qi, Yin and Yang, and the Five Elements. These ideas link bodily imbalances to emotions (Joy, Anger, Grief, Anxiety, Melancholy, Terror, and Fright) and climatic elements (Wind, Cold, Summer Heat, Dampness, Dryness, and Fire).

Below are key TCM practices and remedies for immunomodulation:

Herbal Medicine: Numerous TCM medicines are utilized for their regulatory and immune-boosting qualities.

Astragalus (Huang Qi): Boosts endurance, fortifies the immune system, and guards against infections.

Ganoderma Lucidum (Ling Zhi): Also referred to as reishi mushroom, this plant possesses anti-inflammatory, antiviral, and adaptogenic qualities.

Shisandra (Wu Wei Zi): Prevents stress and boosts the immune system.

Licorice Root (Gan Cao): Has anti-inflammatory and immune-modulating properties.

Ginseng (Ren Shen): Boosts vitality, boosts immunity, and controls stress reactions.

Dietary Therapy: TCM emphasizes food as medicine to support immunity:

- Warming foods that boost immunity include ginger, garlic, and cinnamon.
- Tonifying Soups: herbal and chicken soups including goji berries and astragalus.
- Medicinal drinks: Red date and ginseng drinks to boost immunity.

Acupuncture: Acupuncture restores balance and enhances Qi flow, which helps control the immune system. It can treat autoimmune diseases, lessen inflammation, and strengthen the body's defenses.

Qi Gong and Tai Chi: By harmonizing Qi, these mind-body exercises boost immune system function, lower stress, and increase physical strength.

Cupping and Moxibustion: Cupping therapy helps the body cleanse and increases circulation.

Moxibustion: It is thought that burning mugwort close to acupuncture sites increases bodily warmth and immunity.

Balance of Emotions: The immune system has a direct impact on emotional well-being, according to TCM. In order to preserve emotional equilibrium and advance general health, techniques like mindfulness and meditation are advised [9].

Several Herbal Compositions are used in Unani Medicine to Increase Immunity, such as: Ginger, or *Zingiber officinale*, has antiviral and anti-inflammatory qualities.

Black seed, or *Nigella sativa*, is well-known for its antibacterial and immunomodulatory properties.

Garlic, or *Allium sativum*, boosts immunity and guards against infections.

A Contemporary Scientific Viewpoint: Scientific studies have demonstrated that a variety of herbal remedies have immunomodulatory effects, thanks to developments in phytochemistry and pharmacology. Among the mechanisms are:

Antioxidant Activity: By neutralizing free radicals, herbs like amla and turmeric (*Curcuma longa*) lessen oxidative stress on immune cells.

Improvement of Innate and Adaptive Immunity: By promoting the activity of macrophages and lymphocytes, herbs like astragalus and echinacea help to fortify both innate and adaptive immunity.

Effects on Inflammation: Compounds in herbs like Ginger and Reishi mushroom help regulate cytokine production, preventing excessive inflammation.

Gut Microbiota Modulation: Probiotic-rich herbs such as Garlic and Fenugreek (*Trigonella foenum-graecum*) improve gut health, indirectly improving immunity. Herbal medications are commonly employed in immune-enhancing formulations, dietary supplements, and functional foods. However, variables like dosage, bioavailability, and personal medical circumstances affect how effective they are. Even though they are usually safe, some plants can trigger allergic responses or interfere with prescription drugs. Consequently, for their safe usage, appropriate standardization and clinical validation are essential [10].

Indigenous and Folk Medicine Practices For: Many societies around the world have relied heavily on immune support. These customs frequently rely on the application of age-old rituals, natural cures, and lifestyle choices. Here are a few instances of these practices [11]:

Herbal Remedies

Echinacea (North America): Native tribes use this herb to boost the immune system and combat infections.

Ashwagandha (India): A staple in Ayurvedic therapy, it helps strengthen the body's defenses and relieve stress.

Moringa (Africa and Asia): Known for its great nutritional and antioxidant characteristics. Asian ginger and turmeric are widely utilized for their immune-stimulating and anti-inflammatory qualities.

Traditional Teas and Decoctions:

- Globally, honey and lemon tea is used to boost immunity and ease sore throats.
- Siberian chaga mushroom tea: renowned for its strong immune-boosting qualities.
- Latin American herbal infusions: Yerba mate and chamomile are frequently ingested for their medicinal properties.

Fermented Foods:

- Europe and Korea produce kimchi and sauerkraut, which are high in probiotics that boost immunity and digestive health.
- Middle Eastern kefir: An immune-boosting fermented dairy product.

Lifestyle Practices:

Native American Sweat Lodges: used to boost the immune system and aid in detoxification.

Breath Control and Meditation (India): Techniques like pranayama assist control stress and enhance general well-being.

Forest Bathing (Japan): Research has demonstrated that spending time in nature boosts immunity.

Animal Products:

- European and Asian bee propolis: Used for its immune-boosting and antimicrobial qualities.
- Globally, bone broth is consumed for its high nutritional value, which promotes general health.

Spiritual and Ritual Practices: Many Indigenous cultures believe that prayer and blessing rituals promote emotional equilibrium, which tangentially boosts immunological function.

Modern Perspectives on Herbal Immuno-modulators: Herbs that boost immune system function are generally classified as either immunostimulants, adaptogens, or both. Adaptogens, like ginseng, are thought to improve the body's capacity to handle stress, including that caused by infectious agents; since prolonged stress can impair immune function, these herbs may help lower the risk of infections. Actoprotectors are a subgroup of adaptogens that benefit people in physically demanding or high-stress occupations without producing withdrawal symptoms, in contrast to stimulants like caffeine. Echinacea and other immunostimulants, on the other hand, boost the body's innate immunological responses, which aid in the removal of infections and even the fight against cancer cells. Finally, by increasing a deficient immune response or reducing an excessive one, immunomodulators aid in balancing immune system activity. Some study indicates that they may increase the production of cytokines, which are essential for white blood cell communication and aid in regulating

immunological activity, including the prevention of tumor development, even if their precise mechanisms are not entirely understood. It's interesting to note that plants might create these substances in reaction to physiological stress, just like some microbes do when they make antibiotics. These plant chemicals' efficacy may be impacted by environmental factors like climate and cultivation circumstances [12].

Phytochemicals and Their Role in Immune Enhancement: Several bioactive substances, including flavonoids, alkaloids, polysaccharides, and terpenoids, have been identified by modern research as being present in herbs and contributing to their immune-modulating qualities **Fig. 1**. It is well known that these substances increase the activity of immune cells such as natural killer cells, T-cells, B-cells, and macrophages [13].

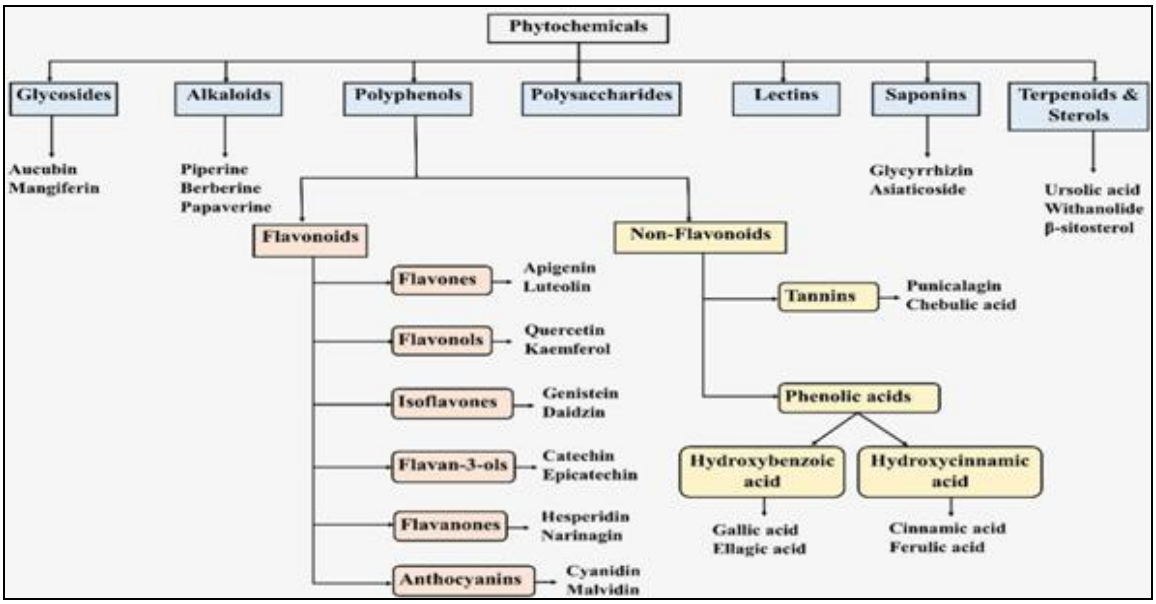

FIG. 1: POTENTIAL IMMUNOMODULATORS PHYTOCHEMICALS (BEHL. T *ET AL*. JAN 2021)

Classification of Immunomodulators with Herbs: Agents known as immunomodulators can either enhance or decrease the immune response. Depending on their source and mode of action, they are divided into various groups. Because of their capacity to control immunological activities, herbal immunomodulators are frequently employed in traditional medicine.

Classification Based on Function:

Immunostimulants (Enhancing Immune Response): These herbs stimulate both innate and adaptive immunity, which strengthens the immune system.

Certain Immunostimulants: Increase the T, B, and antibody components of adaptive immunity.

- T-cell proliferation is stimulated by *Withania somnifera*, also known as ashwagandha.
- *Tinospora cordifolia*, often known as Guduchi, stimulates the generation of antibodies and activates macrophages [14].
- *Emblica officinalis* (Amla), according to Syed Nasir Abbas Bukhari, is high in vitamin C and strengthens the immune system.

Immunostimulants without Specificity: Boost the production of cytokines, NK cells, and macrophages as part of innate immunity.

- Tulsi (*Ocimum sanctum*) increases the synthesis of cytokines.
- *Echinacea purpurea*: Promotes NK cell activation and phagocytosis.
- Ginger, or *Zingiber officinale*, has immunostimulant and anti-inflammatory qualities [15].

Immunosuppressants (Suppressing Overactive Immune Response): These herbs reduce an overactive immune response, which helps with disorders like allergies, autoimmune diseases, and organ transplants.

- Curcumin, which is found in turmeric (*Curcuma longa*), controls cytokines and lowers inflammation.
- *Glycyrrhiza glabra*, or licorice, inhibits cytokines that promote inflammation.
- *Boswellia serrata*, often known as Salai Guggul, inhibits leukotrienes and TNF-α.

Immunoadjuvants (Enhancing Vaccine and Drug Effectiveness): These plants improve the body's reaction to medications or vaccinations, acting as adjuvants.

- By boosting the immune system, Panax ginseng (ginseng) improves the effectiveness of vaccines.
- *Allium sativum* (garlic): Promotes the formation of antibodies and the release of cytokines.
- *Aloe vera*: Increases dendritic and macrophage activity.

Classification Based on Source: Herbal immunomodulators made from therapeutic plants.

- Ashwagandha, or *Withania somnifera*, is an adaptogen and immune-stimulating herb.
- Tinospora cordifolia, also known as Guduchi, is an immunostimulant and anti-inflammatory.
- Turmeric, or Curcuma longa, has immunomodulatory and anti-inflammatory properties [16–17].

Microbial immunomodulators made from microorganisms (probiotics, bacterial cell wall extracts, etc.).

- Lactobacillus species (probiotics): Control intestinal defenses.
- Mycobacterium w. (MW vaccine): Used to treat tuberculosis.

Immunomodulators that come from Animals:

- Shilajit, or mineral pitch, strengthens the immune system.
- Lactoferrin and immunoglobulins are abundant in bovine colostrum.

Classification Based on Traditional Medicine Systems: Immunomodulators Based on Ayurveda (Rasayanas):

- Chyawanprash is a polyherbal immunity compound based on amla.
- The herb ashwagandha is a rejuvenating one.
- Brahmi (Bacopa monnieri): Adaptogen and cognitive enhancer.

Immunomodulators in Traditional Chinese Medicine (TCM):

- Ginseng is a herb that improves Qi.
- White blood cells and cytokines are stimulated by *Astragalus membranaceus*.

Immunomodulators of Unani and Siddha:

- Kushta Marjan: Applied to strengthen the immune system.
- Habbe Kabid Naushadri: Boosts Immune Function [18]

Flavonoids-Antioxidants and Adjuvants: Plants contain at least 4,000 different kinds of flavonoids, which are significant components that have been found to modulate the immune system and give leaves and flowers their color. Because they are free radical scavengers and have antioxidant action, they may be useful in anti-aging and anti-cancer treatments [19].

Terpenoids & Saponins-Importance in Cancer and the Chronic Inflammatory Environment: Numerous triterpenoids have been found to either induce apoptosis through a variety of mechanisms (increased P53 gene expression, apoptotic protein levels) or inhibit the proliferation of tumor cells *in-vitro* (induction of growth phase arrest). The terpenoids' third mode of action may be that they inhibit HMG-CoA reductase, which limits the body's ability to produce cholesterol. Since proliferative tumor cells require cholesterol, this effectively "starves" them of nutrients. Lastly, by activating the protective phase II enzyme glutathione transferase, terpenes can also prevent the growth of tumors.

Saponins offer an alternative method of treating tumors because, in contrast to their triterpenoid relatives, they work as adjuvants substances that increase immune reactivity without actually taking part in the reaction. Modified forms of triterpenoids, saponins have been demonstrated to trigger potent T cytotoxic cell responses against mucosal antigens as well as the induction of pro-inflammatory cytokines, particularly IL-2. Herbal Phytochemicals as Immunomodulators Diana R. Cundell.

Plant Cell Wall Polysaccharides-Hemicelluloses, Pectins and Arabinogalactans: Many polysaccharides are found in plants, most of which combine to form intricate cell wall components. Cellulose, hemicelluloses, and pectin are the three main groups of cell wall components that have been found.

Polysaccharide's involvement in innate immunity modulation, particularly macrophage function, is the mechanism underlying its immunomodulatory effect. These substances can stimulate cytokines like IL-2, IL-4, and IL-10 and reduce the levels of cytokines like TNF-α and IL-6.

Alkaloids: Alkaloids are a broad class of strong secondary metabolites that have a significant physiological impact on both innate and adaptive immunity, controlling the immune systems of both humans and animals.

Alkaloids derived from plants have been used as powerful medicines and have been shown to enhance immunological function, suggesting that they may have immunomodulatory effects.

Tannins: Water-soluble complex phenolic compounds known as tannins are found in vascular plants and angiosperms in large quantities. They have a variety of anti-infective properties and cause notable physiological activities such host-mediated tumor activity, phagocytic cell stimulation, and more [20].

Popular Herbs Used For Immune Enhancement:

Ashwagandha (*Withania somnifera*):

- It is used as tea, powder, or capsules and has withanolides as one of its active components.
- Increases phagocytosis and macrophage activity, which strengthens the innate immune response.
- Boosts nitric oxide levels, which aid immune cells in their fight against infections.
- By regulating cortisol levels, it mitigates the immune suppression brought on by stress.

Turmeric (*Curcuma longa*):

- It has curcumin, a phytoconstituent, and can be used as a supplement, in drinks, or as a spice.
- By blocking NF-κB signaling, curcumin lowers the synthesis of pro-inflammatory cytokines (TNF-α, IL-6).
- By scavenging free radicals, it functions as an antioxidant and boosts adaptive immunity by increasing T-cell proliferation and B cell counts [21-22].

Tulsi (*Ocimum sanctum*):

- Eugenol and urosolic acid are its active ingredients, and it is ingested as tea, fresh leaves, or extracts.
- Controls the release of cytokines, including TNF-α and IL-1β.
- Boosts T-helper (Th) and natural killer (NK) cell activity.
- Lowers cortisol levels, which lessens immunological suppression brought on by stress [23].

Guduchi (*Tinospora cordifolia*):

- Its active ingredients are tinosporide and tinoporine, and it can be taken as an extract, powder, or capsule.
- Encourages antigen presentation and activates macrophages.
- Promotes both innate and adaptive immunity by increasing the synthesis of IL-1β and IL-6.
- By raising glutathione levels, oxidative stress is decreased [24].

Aloe Vera (*Aloe barbadensis*):

- It is used as a brewed tea or supplement and includes polysachharides.
- Aloe vera's polysaccharides promote the generation of cytokines and macrophage activity. The release of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) has been demonstrated to be enhanced by aloe vera polysaccharides, suggesting that macrophage activity and cytokine production are stimulated.
- Inhibits the action of the COX-2 enzyme, which lowers inflammation. Aloe vera has shown anti-inflammatory qualities, possibly by modifying inflammatory pathways and suppressing the generation of inflammatory cytokines [25-26].

Green Tea (*Camellia sinensis*):

- Catechin is its primary phytoconstituent.
- By modulating cytokine release, catechins (EGCG) lower pro-inflammatory cytokines (TNF-α and IL-6).
- Boosts T-cell and natural killer (NK) cell activity.
- Reactive oxygen species (ROS) are scavenged, making it a powerful antioxidant [27].

Ginseng (*Panax ginseng*):

- Its primary ingredients are ginsenosides, which are utilized in extracts, teas, and capsule form.
- Ginsenosides increase T-cell and NK cell activity by inducing the synthesis of cytokines (IL-2, IFN-γ).
- Enhances antigen presentation by encouraging dendritic cell development and lowering inflammation and oxidative stress [28-29].

Echinacea (*Echinacea purpurea*):

- It is used as teas, tinctures, or capsules and contains alkamides and polysaccharides.
- Activates macrophages and boosts TNF-α, IL-1, and IL-6 production.
- NK cell activity is raised and T-cell proliferation is improved.
- By inhibiting viral receptors, it prevents viruses from entering and replicating [30].

Neem (*Azadirachta indica*):

- Its phytoconstituents include azadirachtin and nimbin.
- Promotes cellular immunity by increasing the production of T-helper (Th1) cytokines.
- Inhibits NF-κB signaling, which lowers the generation of pro-inflammatory cytokines.
- Promotes neutrophil and macrophage activity [31].

Garlic (*Allium sativum*):

- Allicin is its primary active element, and its raw clove is utilized as a food ingredient or in capsule form.
- T-lymphocyte and NK cell production is stimulated by allicin.
- Promotes the release of cytokines (IL-2, IL-10) and increases macrophage activity.
- By preventing the formation of prostaglandins, it lowers inflammatory reactions [32].

Recent Advancements in Enhancing Body's Immunity: The understanding of human immunology has advanced significantly in recent years, and new discoveries are eagerly awaited.

Despite the immune system's extreme complexity, our understanding of it has improved significantly thanks to the creation of new instruments and research techniques.

The creation of a large variety of monoclonal antibodies, which make it easier to identify various cell subpopulations and allow for the functional examination of immune cells, is one of the major factors that has contributed to these developments. Furthermore, our understanding of immune system functions has been further enhanced by the incorporation of cutting-edge technologies including imaging techniques, single-cell analysis, and omics platforms like high-throughput DNA-RNA sequencing, proteomics, and metabolomics.

Immunological research has also benefited greatly from the use of artificial intelligence, machine learning, and mathematical modelling in the processing of massive information. Furthermore, experimental immunology has been transformed by the use of genetically modified animal models, such as transgenic, knockout, and knock-in mice, as well as contemporary genome-editing technologies like CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats–CRISPR-associated protein 9), which offer a deeper understanding of immune responses and mechanisms [33].

M-RNA and Next-Generation Vaccines:

Messenger RNA (mRNA)-Based Cancer Vaccines: Messenger RNA (mRNA) is essential for telling cells to make particular proteins that trigger an immunological reaction. By giving cells genetic instructions, mRNA can be utilized in vaccines to make innocuous viral proteins that elicit protection without exposing the body to live viruses.

Immunological System Activation: mRNA vaccines trigger an immunological response by introducing genetic material that codes for a viral antigen, such as the spike protein of SARS-CoV-2.

Memory Cell Formation: After the immune system identifies the antigen, memory T and B cells are created, allowing for a prompt reaction when the virus is encountered again.

Quick and Targeted Reaction: mRNA vaccines, in contrast to conventional vaccinations, do not call for the use of inactivated or weakened pathogens, which lowers the risk of infection while maintaining robust immunity. Following its success with COVID-19 vaccinations, mRNA vaccine technology is currently being used to treat cancer. In preclinical models, lipid nanoparticles containing mRNA expressing cytokines such as IL-12 have demonstrated encouraging outcomes, effectively suppressing tumor development with negligible damage. This method not only enables accurate regulation of cytokine expression but also gets beyond some of the pharmacokinetic issues that arise with conventional cytokine treatments [34].

Personalized Cancer Vaccines: Scientists have created vaccines that are specific to the mutations in each tumor. Such vaccines could produce strong immune responses, potentially avoiding cancer recurrence, according to a study involving melanoma patients. In order to achieve their immunotherapeutic goals, tumor vaccines are made to improve antigen presentation, trigger memory T cell-mediated death, and activate antigen-specific effector function. Due of their poor tumor specificity, traditional cancer vaccines that target tumor-associated antigens (TAAs) have had limited success. Neoantigens, or tumor-specific antigens (TSAs), are self-antigens generated by tumor cells as a result of genetic alterations. They are caused by non-synonymous mutations and other genetic alterations in cancer cells, including open reading frames (ORFs) generated by viral coding, dysregulated RNA splicing, genomic alterations, and disordered post-translational modifications.

Neoantigen vaccines offer a number of benefits over conventional vaccinations: (1) They are highly feasible, generally safe, and easier to manufacture; 2) Their strong affinity for major histocompatibility complex (MHC) molecules can prevent immune cells from attacking patients' normal cells and ensure the safety of treatment; and 3) They can effectively stimulate, enhance, and diversify anti-tumor T cell responses, maximizing therapeutic specificity and overcoming immune tolerance. Personalized tumor neoantigen vaccines are currently showing encouraging outcomes in treating a variety of cancers and have advanced significantly in clinical trials. According to research, after two years, more than 60% of melanoma patients who received customized tumor neoantigen vaccinations either did not advance or were recurrence-free. Personalized neoantigen vaccines have advanced further in recent years when used in conjunction with other immunotherapies [35].

Immunomodulatory Therapies:

Monoclonal Antibodies (mAbs): In order to improve immune responses against conditions like cancer and autoimmune illnesses, monoclonal antibodies are designed to target particular antigens.

Checkpoint Inhibitors: These mAbs strengthen the body's defenses against cancer by blocking proteins like PD-1/PD-L1 that suppress immune

responses. According to studies, people with melanoma may have better results when checkpoint inhibitors and customized vaccinations are used together.

Cytokine Therapies: Signaling proteins called cytokines control immunological responses. Cytokine-based therapies are designed to strengthen the body's defenses.

Therapy using Interleukin-2 (IL-2): By promoting T cell proliferation, IL-2 has been utilized to treat melanoma and metastatic renal cell carcinoma. Research on altering IL-2 to lessen adverse effects and increase effectiveness is still ongoing [36-37].

Artificial Intelligence (AI) and Big Data in Immunity Research: Immunology is undergoing a revolution because to AI and big data analytics, which make it possible to analyze intricate information in order to forecast immune responses and create efficient treatment plans.

Personalized vaccines can be developed more easily thanks to AI algorithms that can identify which tumor neoantigens are most likely to elicit a robust immune response.

Immune Profile: Big data techniques enable thorough immune system profile of each individual, which helps with immunotherapy tailoring [38-39].

Immunity and Gut Microbiota: Immune function is significantly regulated by the gut microbiota. Immunity can be improved by altering gut flora through a variety of strategies.

Prebiotics and Probiotics: Probiotics are live beneficial bacteria that can alter immune responses and enhance gut health when consumed. According to studies, probiotics can lower the risk of respiratory infections and increase the synthesis of antibodies.

Mechanism of Immunity Enhancement by Probiotics:

Regulation of Gut Microbiota: Probiotics help maintain microbial diversity, preventing the overgrowth of harmful bacteria.

Strengthening the Gut Barrier: They enhance the intestinal lining, preventing pathogen entry and infections.

Modulation of Immune Cells: Probiotics influence T-cells, B-cells, and macrophages, promoting an adaptive immune response.

Anti-Inflammatory Effects: Some probiotic strains (e.g., Lactobacillus and Bifidobacterium) reduce inflammation by regulating cytokine production.

Probiotic Strains with Immune Benefits

- Lactobacillus rhamnosus GG – Enhances gut immunity and reduces respiratory infections.
- Bifidobacterium bifidum – Strengthens mucosal immunity and fights infections.
- Saccharomyces boulardii – Prevents antibiotic-associated diarrhea and improves gut immunity.
- Lactobacillus casei – Boosts natural killer (NK) cell activity, improving antiviral defense.

Prebiotics: fibers that are indigestible but promote the growth of good microorganisms. Prebiotics have been shown to alter immune responses and enhance the function of the intestinal barrier.

Mechanism of Immunity Enhancement by Prebiotics:

Support Beneficial Bacteria: Prebiotics increase the population of probiotics in the gut.

Stimulate Short-Chain Fatty Acids (SCFAs): SCFAs like butyrate and acetate reduce inflammation and enhance gut immunity.

Improve Gut Barrier Function: Prebiotics help maintain intestinal integrity, preventing infections.

Enhance Antibody Production: They promote the secretion of IgA, an antibody that strengthens mucosal immunity.

Common Prebiotics and Their Sources

- Fructooligosaccharides (FOS) – Found in bananas, onions, and garlic.

- Galactooligosaccharides (GOS) – Present in legumes and dairy products.
- Inulin – Found in chicory root, asparagus, and whole grains.
- Resistant Starch – Found in cooked and cooled rice, potatoes, and green bananas.

Transplanting Faecal Microbiota (FMT): To restore the equilibrium of the gut microbiota, FMT entails moving stool from a healthy donor to a recipient. It is being investigated for other ailments, such as autoimmune illnesses, and has demonstrated effectiveness in treating recurrent Clostridium difficile infections [40–41].

Improvements in Nutrition and Lifestyle:

Nutraceuticals: Nutraceuticals, or bioactive substances obtained from food, have been researched for their potential to strengthen the immune system. Turmeric contains curcumin, which has antioxidant and anti-inflammatory properties that may improve immunological function.

Resveratrol: A substance found in berries and grapes, resveratrol has been researched for its anti-aging qualities and may alter immunological responses.

Periodic Fasting: Periodic fasting, which involves abstaining from food and caloric intake for specific periods, has gained attention not only for its metabolic benefits but also for its role in enhancing the immune system. Different forms include intermittent fasting (such as 16:8 or 5:2), alternate-day fasting, and prolonged fasting. According to research, IF can strengthen resilience to metabolic stress, lower inflammation, and promote immune cell activity.

Mechanisms of Immune Enhancement through Fasting:

Autophagy Activation: Fasting promotes autophagy a cellular "clean-up" process where damaged cells and proteins are broken down and recycled. This helps eliminate pathogens and old immune cells, paving the way for regeneration.

Reduced Inflammation: Fasting lowers levels of pro-inflammatory cytokines (e.g., IL-6, TNF-alpha), helping to modulate chronic inflammation and promote a more balanced immune response.

Stem Cell Regeneration: Extended fasting has been shown to trigger stem cell-based regeneration of new white blood cells, especially during prolonged fasts (over 48–72 hours), improving immune resilience.

Improved Gut Health: Fasting may enhance gut microbiota diversity and integrity, contributing to stronger gut-associated lymphoid tissue (GALT), a major component of the immune system.

Reduction of Oxidative Stress: By lowering insulin levels and improving mitochondrial function, fasting reduces oxidative stress, which plays a role in immune aging and chronic disease.

Supplementing with Vitamin D: Immune system function is significantly impacted by vitamin D. Increased vulnerability to infections has been associated with deficiencies. Supplementation can improve monocytes' and macrophages' ability to combat pathogens [42-43].

Immune Cells that are Bioengineered: Modified immune cell therapies have been developed as a result of advances in genetic engineering.

CAR-T Cell Treatment: Through the use of chimeric antigen receptor (CAR) T-cell therapy, a patient's T cells are altered to express receptors unique to cancer cells. This method is being investigated for solid tumors and has demonstrated efficacy in treating specific hematologic malignancies.

Natural Killer (NK) Cells that have been Engineered: The innate immune system includes NK cells. Research is ongoing to engineer NK cells to better target cancer cells, which could have benefits in a number of malignancies [44-45].

Longevity and Anti-Aging Strategies: Immunosenescence is the word for the deterioration in immunological function that comes with aging. Methods to thwart this mechanism are being researched.

Senolytics: Senolytics are a class of therapeutic agents that selectively induce death of senescent cells cells that have stopped dividing but resist

apoptosis and contribute to aging and chronic inflammation. By targeting these cells, senolytics are being explored for their potential to rejuvenate the immune system and improve overall health.

Mechanisms of Immune Enhancement by Senolytics:

Reduction of Inflammaging: By clearing senescent cells, senolytics reduce systemic inflammation, allowing the immune system to function more efficiently.

Improved T cell Function: Senolytics may help restore T cell proliferation and function, especially in the elderly, leading to better adaptive immunity.

Enhanced Vaccine Response: Lower inflammation and better immune cell performance may improve vaccine responses, which often decline with age.

Boosted Tissue Regeneration: Removal of senescent cells supports the regeneration of immune-related tissues like the thymus, contributing to increased production of naïve immune cells.

Cancer Surveillance: Senescent cells can promote tumorigenesis. Their clearance helps the immune system recognize and eliminate potential cancer cells more effectively.

Common Senolytic Agents:

Dasatinib + Quercetin (D+Q): Shown to reduce senescent cell burden in human trials.

Fisetin: A natural flavonoid with senolytic activity, improves immune function in aged mice.

Navitoclax (ABT-263): A BCL-2 inhibitor that targets apoptosis-resistant senescent cells.

FOXO4-DRI: A peptide that disrupts survival of senescent cells by targeting FOXO4-p53 interaction.

NAD+ Boosters [46-47]: Nicotinamide adenine dinucleotide (NAD^+) is a crucial coenzyme involved in cellular energy metabolism, DNA repair, and immune regulation. With age, NAD^+ levels naturally decline, contributing to weakened immunity, metabolic dysfunction, and increased disease susceptibility. NAD^+ boosters are compounds that raise intracellular NAD^+ levels and are being explored for their immune-enhancing properties.

Common NAD^+ Boosters:

Nicotinamide Riboside (NR): A precursor to NAD^+, shown to enhance mitochondrial function and reduce inflammation.

Nicotinamide Mononucleotide (NMN): A direct NAD^+ precursor with strong evidence for improving energy metabolism and immune response.

Nicotinamide (NAM): A form of vitamin B3, more abundant but may inhibit sirtuins at high doses.

Tryptophan & Niacin (Vitamin B3): Dietary sources that support NAD^+ synthesis via the de novo pathway.

CD38 Inhibitors: CD38 is an enzyme that degrades NAD^+; inhibiting it can help preserve NAD^+ levels.

Challenges in the Standardization of Herbal Formulations:

Complex Chemical Composition: Alkaloids, flavonoids, terpenoids, and phenolic compounds are among the many bioactive substances found in herbal preparations.

It can be challenging to pinpoint the precise elements that contribute to the therapeutic effect because these substances frequently function in concert. Herbal medicines necessitate the identification and measurement of several components, in contrast to synthetic treatments that have a single, standardized active ingredient.

Variability in Plant Sources: The following factors affect the chemical makeup of medicinal plants:

Geographical Location: Plants cultivated in various locations may have varied chemical profiles.

Climate: Weather patterns and seasonal variations have an impact on plant growth and phytochemical composition.

Soil Conditions: The kind of soil and the availability of nutrients might affect the amount of active chemicals present.

Harvesting and Collection Procedures: The potency of herbal materials is influenced by the stage of plant growth at harvest.

Problems with Quality Control: Changes in post-harvest handling, drying, grinding, and storage methods make it difficult to guarantee constant quality in herbal formulations. These elements may cause modifications to the final product's potency and chemical makeup.

Absence of Marker Chemicals: The inclusion of particular marker chemicals that indicate the formulation's therapeutic action is frequently necessary for standardization. However, the lack of clearly defined indicators in many herbal products makes it challenging to establish quality standards and guarantee reproducibility.

Stability and Shelf Life: Exposure to environmental elements like these might cause herbal formulations to deteriorate over time.

Light: Able to degrade delicate substances.

Temperature: Chemical deterioration is accelerated by high temperatures.

Moisture: Encourages chemical instability and microbiological development. As a result, it is challenging to determine precise shelf-life estimates and guarantee product effectiveness over time.

Adulteration and Contamination: Intentional or inadvertent adulteration of herbal items might involve:

Synthetic Compounds: To improve therapeutic results, use steroids or medications.

Heavy Metals: Pollution from manufacturing equipment or soil that contains lead, mercury, and arsenic.

Pesticides: Chemical residues from farming operations.

Microbiological Pathogens: bacteria, fungi, and poisons from incorrect storage. Advanced analytical methods are needed to identify and stop such contamination and adulteration.

Lack of Regulatory Frameworks: Different nations have rather different laws governing herbal remedies. There is less regulatory control of herbal formulations in some areas since they are regarded as dietary supplements rather than medications. Standardization attempts are made more difficult by the absence of unified international guidelines.

Analytical Challenges: Advanced analytical techniques are necessary for quality control due to the intricacy of herbal compositions. These approaches include:

- HPLC, or high-performance liquid chromatography, is a technique used for quantifying and separating compounds.
- GC-MS (Gas Chromatography-Mass Spectrometry): Determines volatile substances.
- The structural details of active substances are provided via nuclear magnetic resonance, or NMR. Due to their high cost, time commitment, and need for trained workers, these methods are not available in many areas.

Batch-to-Batch Consistency: Producing batches with a consistent chemical composition is challenging due to the inherent heterogeneity in plant materials.

Even when plants come from the same area, their chemical profiles might be affected by minor variations in development conditions [48].

Current Trends and Future Directions:

Integration of Traditional Knowledge with Modern Science: The centuries-old knowledge that traditional healers hold regarding holistic health practices, natural cures, and healing methods has been handed down through the years. This wealth of information can be polished, scientifically validated, and incorporated into contemporary medical systems by collaborating with researchers. This kind of cooperation can result in the development of novel medications, better therapeutic approaches, and a more profound comprehension of health and well-being. Fosters respect for cultural heritage and provides a forum for them to share their knowledge. To guarantee

that traditional knowledge holders are acknowledged and adequately compensated, however, ethical factors like intellectual property rights and equitable benefit-sharing must be given top priority. A complementary healthcare system that benefits communities and world health can be established by traditional healers and researchers working together with mutual respect [49].

Herbal Combinations and Synergistic Effects: Herbal combos are expertly prepared mixtures of several plant-based components that complement one another to improve medicinal effects. When these herbs work together to produce a more powerful or effective outcome than the sum of their individual effects, this is known as the synergistic effect. This phenomenon can lessen possible negative effects while increasing the active chemicals stability, effectiveness, and bioavailability [50-51].

Emerging Technologies: Research and development in herbal medicine is being revolutionized by nanotechnology and metabolomics, which improve our knowledge of and ability to use plant-based remedies. The administration of herbal compounds at the nanoscale is made possible by nanotechnology, which enhances their solubility, stability, bioavailability, and targeted transport to particular cells or tissues. This method overcomes drawbacks like uneven potency and poor absorption that are frequently connected to conventional herbal preparations.

However, scientists are able to identify and quantify the bioactive compounds that result in therapeutic advantages thanks to metabolomics, the comprehensive analysis of plant metabolites. Researchers can improve dosage, identify new phytochemicals with possible health advantages, and develop more accurate and standardized herbal formulations by combining metabolomics with nanotechnology. This collaboration closes the gap between conventional medical procedures and contemporary scientific advancements while also improving the effectiveness and safety of natural remedies [52-53].

Global Market and Consumer Trends: The growing demand from consumers for natural and plant-based health treatments is propelling the global market for herbal formulations. Interest in herbal supplements and treatments has increased as a result of growing knowledge of the negative effects of synthetic medications and a move toward preventive healthcare. The use of cutting-edge technologies like nanotechnology for improved delivery, more research and development for standardized formulations, and the growing appeal of herbal products in cosmetics, wellness, and functional foods are some of the major developments. The changing market landscape is further shaped by regulatory developments and an emphasis on sustainability [54].

Personalized Herbal Therapies: Customized herbal formulations based on genomics have the potential to transform personalized healthcare by adjusting therapies based on a person's genetic composition. Through the examination of an individual's genetic profile, scientists can spot differences that impact the body's metabolism and reaction to herbal substances. With this method, specific herbal treatments that are more effective and have fewer adverse effects can be developed.

People who are genetically prone to inflammation, for example, can benefit from specially formulated products that include particular anti-inflammatory phytochemicals. This individualized strategy combines contemporary genetics with ancient herbal medicine, providing a viable avenue for more accurate, efficient, and patient-centered healthcare solutions [55-56].

CONCLUSION: From a traditional and contemporary standpoint, herbal treatment has significantly improved the immune system through a variety of processes. Standardized formulations that can provide natural support for immunological health have been developed as a result of advances in scientific study that have improved our understanding of the immunomodulatory potential of herbs. The future of herbal immuno boosters is bright as they continue to be included into contemporary medical procedures, despite ongoing difficulties with standardization and quality control.

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