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REVIEW ARTICLE

Traditional knowledge and potential of Medicinal plants

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ABSTRACT
As the importance of immune system regulation and its potential benefits in disease prevention have come to light, researchers have taken a keen interest in studying plants for their immunomodulatory characteristics. For a long time, traditional medicine has been using medicinal plants for the proper functioning of the immune system. Plants contain many natural bioactive compounds that stimulate or inhibit different cells and organs of the immune system. Some plant-derived extracts make immune cells more active against certain microorganisms. In contrast to other plant-derived extracts that calm down the overactive cells of the immune system. Researchers attribute the diverse immunomodulatory properties of plant extracts and their influence on the human immune system to a variety of therapeutic effects. These effects can lead to enhanced resistance against infections and a reduction in inflammation-related diseases. As studies continue to explore the intricate relationships between plant compounds and immune responses, there is potential for developing new treatments that harness these natural benefits. In addition, numerous elements of plants and their phytoconstituents involved in immunomodulation have been examined. There is also a brief description of the use and efficacy of pharmacologic immunomodulators. This study also focuses on several medicinal plants found in India that help to boost and suppress a compromised immune system.
Keywords: Immune System, Bioactive compounds, Medicinal plants

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INTRODUCTION

The body's defense system is somewhat challenging; therefore, whatever is governing how well it operates could impact other systems in the human body, including the neurological system, hormonal system, metabolic processes, and so on. This has led to a wide range of studies in this area, with the goal of immune system regulation being both disease prevention and the discovery of new targets that could be the foundation for more successful and innovative treatments. Every traditional medical system uses a healthy, balanced diet that includes a variety of plant-based foods to provide one of its main approaches to safeguarding wellness and good health while also preventing disease (**1**). Research has increasingly shown that incorporating diverse plant-based foods can enhance immune function and promote overall health. As scientists delve deeper into the specific compounds found in these foods, they are uncovering the potential for developing targeted therapies that harness the power of nutrition in disease management. In the literature, numerous components found in such plants, comprising flavonoids, polysaccharides, lactones, alkaloids, diterpenoids, and glycosides, among others, have been implicated in their immunomodulatory qualities (**2**).

Immunomodulation (Fig.1) is generally defined as an alteration in the immune system of the body in response to some foreign entity or pathogen. These pathogens can either stimulate or repress the immune system (3, 4). The constituents that result in the activation or suppression of the immune system are termed immunomodulators (Figs. 2 and 3). Interestingly, several of these substances, like capsaicin, gingerol, and curcumin, seem to block one or more of the processes that connect pro-inflammatory stimuli to the production of cyclooxygenase (COX). Moreover, a number of inflammatory diseases, such as cancer, atherosclerosis, myocardial infarction, diabetes, allergies, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, and septic shock (5, 6), can be attributed to the activation of NF-κB, an essential regulator of the synthesis of COX-2. Accordingly, inhibiting COX should

stop the alternative NF-κB pathway from being activated, potentially reducing inflammation and its associated symptoms.

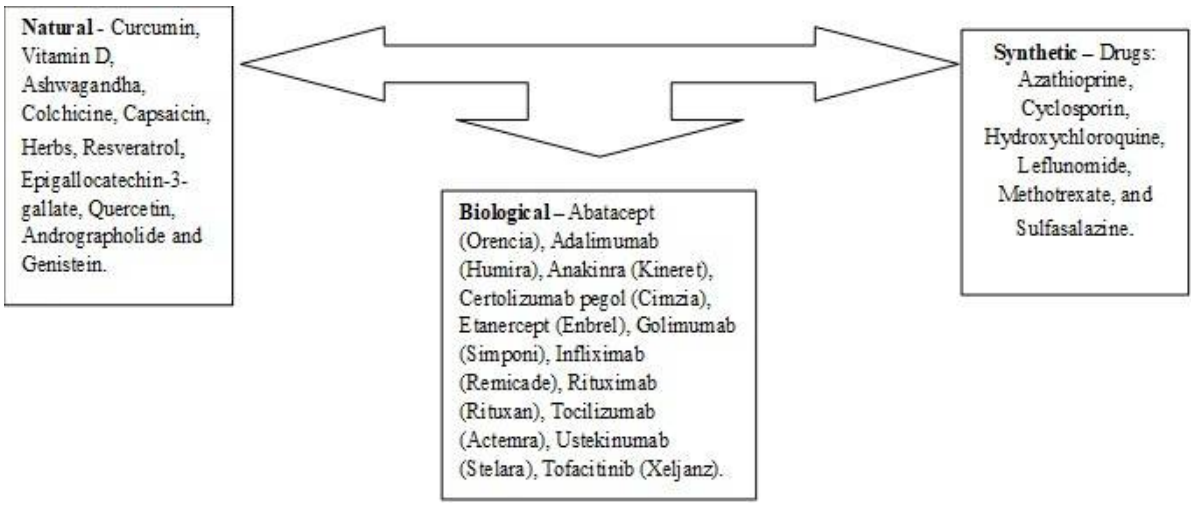

Fig.1. Immunomodulation (Natural, Synthetic and Biological agents)

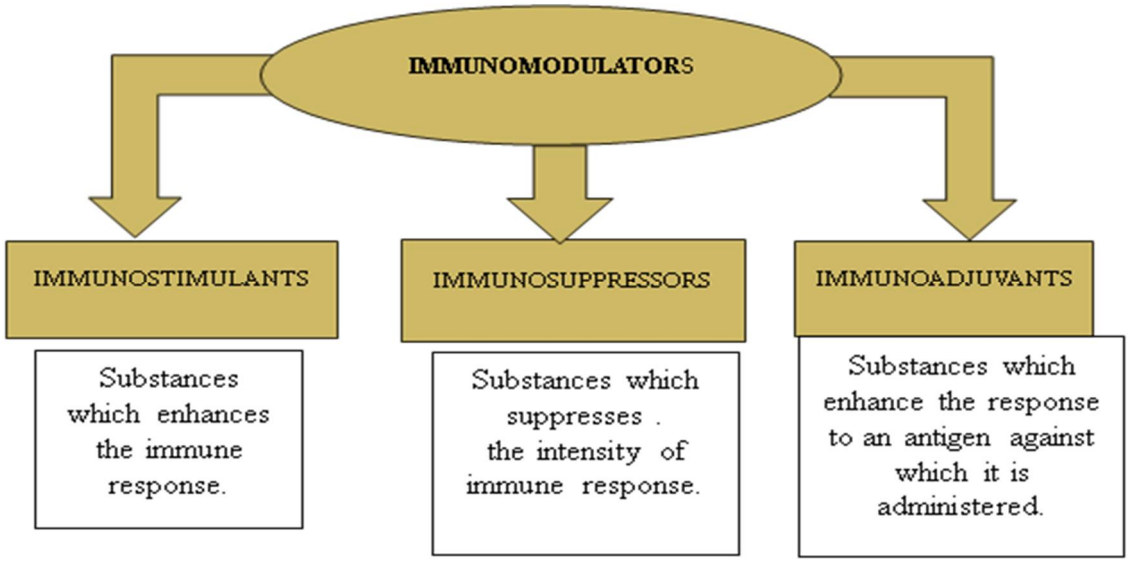

Fig.2. Classification of Immunomodulators on the basis of their Working

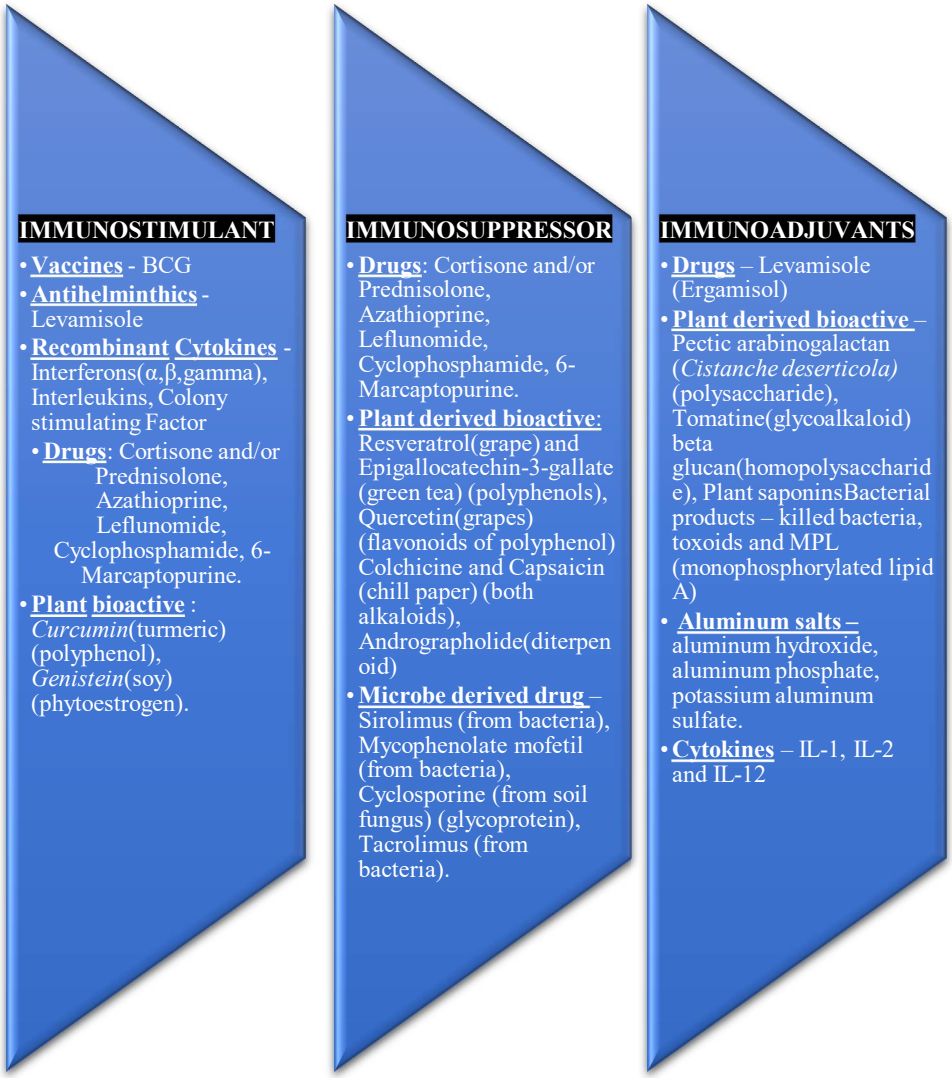

Fig.3. Types of Immunomodulators and its examples

EXAMPLES OF MEDICINAL PLANTS SHOWING IMMUNOMODULATORY PROPERTIES (Table 1)

In the literature, usage of traditional plants and pharmacological properties of medicinal plants used in Ayurveda as medicine, which are effective against inflammatory-related diseases, infections, wounds, or diverse gastrointestinal ailments (**Table 1**).

Table 1. List of medicinal plants and their parent compound along with medicinal properties

S. No.	Plant Name	Parent Compound	Medicinal Properties
1	*Mangifera indica*	Mangiferin	Anti-oxidant, anti-diabetic, antiviral, anti-helmintic and anti-allergenic, antiparasitic, antibone resorption, anti-tumor-anti-HIV, antispasmodic and antipyretic, immunomodulatory, anti-diarrhoeal, anti-inflammatory, antibacterial and antifungal, antimicrobial, hepatoprotective, gastroprotective.
2	*Centella asiatica*	Centelloids	Anti-oxidant, anti-bacterial, anti-fungal, antiprotozoa, anti-filarial, anti-ulcer, anti-diabetic, anti-inflammatory, cytotoxic and antitumor activity, neuroprotective activity, cardioprotective, skin protective, radioprotective activity, immunomodulatory effect, memory enhancing activity, wound healing effect.
3	*Azadirachta indicia*	Azadirachitin	Anti-microbial, anti-inflammatory, antiviral, antibacterial, antiulcer, antidiabetic, antifungal, antimalarial, skin care, dental care, insect repellant, immunosuppressant.
4	*Datura stramonium*	Hycoscyamine and scopolamine	Anti- asthmatic, anticholinergic, antimicrobial, anticancer, anti-inflammatory, larvicidal and mosquito repellant activities, antifungal, vibriocidal activity.
5	*Callistemon viminalis*	1,8-cineole and α-pinene	Anti-inflammatory, antimicrobial, antioxidant, anti-cancer, help with bronchodialation, analgesia and apoptosis, spasmolysis and various respiratory disorders Neuroprotective, anticoagulant, anti-leishmania and antimalarial.
6	*Bougainvillea spectabilis*	Methyl salicylate, Terpinolene and α-E-ionone	Anti-inflammatory, antidiabetic, anticancer, antihepatotoxic, anti-microbial, antioxidant, antiulcer, antifertility and various respiratory conditions.
7	*Justicia adhatoda*	Vasicine	Treat cough and asthma, skin diseases, malaria, hemorrhaging, tuberculosis, anti-inflammatory, antimicrobial, antioxidant, antitumor, antiaging, antimutation, sedative activity.
8	*Yucca gloriosa*	Yuccalides A-C (Roots) Sesquiterpene glycosides and triterpene glycosides (flowers) 5β-spirostanol glycosides and 5β-furostanol glycosides (underground parts)	Blood purifier, anti-inflammatory, various skin conditions, hair growth, arthritis
9	*Cycas revoluta*	Cycasin (carcinogenic and neurotoxic glucoside)	Wound treatment, respiratory issues, menstrual flow, rheumatism, gastrointestinal issues, fever reduction, cancer treatment
10	*Diospyros montana*	Diospyrin	Anti-inflammatory, anti-cancer, anti-microbial, antiviral, antitumor, antimalarial, anthelmintic, hypolipidemic, antileukemic, febrifuge, abortifacient.
11	*Ipomoea purpurea*	Lysergic acid amide	Used to treat infections, pain, mental disorders, diuretic, purgative, anthelmintic, and laxative, anticancer.
12	*Salvia officinalis*	Camphor, 1,8-cineole, thujone	Pain relief, antimicrobial, control blood sugar, anticancer, antidementia, anti-inflammation, antimutagenesis, antioxidant.
13	*Durantaerecta*	Durantosides	Anti-malarial, antiparasitic, antibacterial, antifungal, anti-inflammatory, antioxidant, antiviral, antitumor, diuretic, insect repellant, hepatoprotective, antihistaminic.
14	*Withania somnifera*	Withanolides, alkaloids and steroidal lactones	Antitumor, antistress, antioxidant, immunomodulatory properties, hemopoietic effect, anti-diabetic, antimicrobial, neuroprotective, anti-inflammatory, cardioprotective, sedative, adaptogenic.

***Acacia catechu* –** It is commonly known as wild heartwood or the Khair tree, and in Ayurveda it is also known as Khadira, which belongs to the Fabaceae family. A. catechu occurs naturally in mixed deciduous forests and savannas of lower mountains and hills. The phytochemicals found in this plant are flavonoids, phenolic acids, and catechins. In conventional practice of medicine, the heartwood and bark of this tree are

used to cure sore throats and diarrhea. The majority of people consume boiled water of *Acacia catechu* (**7, 8**).

Katha, the organic product obtained from the heartwood of the khair tree, is therapeutically effective for a variety of conditions such as mouth ulcers, gingivitis, sore throat, diarrhea, and skin conditions like ulcers, boils, eczema, etc. The vital components obtained from his plant, such as catechin or epicatechin, carry out important roles as antioxidants and in anti-inflammatory conditions. Similarly, tannins are ascertained to be accountable for styptic actions in the human body and also play a major role in curing wounds in the human body. Catechin is ample in this plant and acts as an antimicrobial and antioxidant agent. The extract of A. catechu shows various pharmaceutical functions, including immunomodulators, antihyperglycemic, antinociceptive, antihyperlipidemic, and anti-ulcer. Flavonoids, which are present in the heartwood of this plant, show various antibacterial, anti-cancer, anti-viral, anti-inflammatory, and cardiovascular properties.

***Curcuma longa* –**Curcumin is a yellow polyphenolic pigment found in the rhizome of the flowering plant *Curcuma longa* L., also known as turmeric, which belongs to the *Zingeberaceae* family. Historically, it has been implemented in both cooking and medicine, particularly in traditional Chinese and Ayurvedic medicine. In addition to being used as a culinary condiment, turmeric has been utilized historically as an antibacterial, insect repellent, and natural colouring agent for about 5000 years. Turmeric contains bioactive polyphenolics called curcumin, demethoxycurcumin, and bisdemethoxycurcumin; these compounds are collectively known as curcuminoids (CCMs). There are approximately 70% carbohydrates, 6% proteins, 6% essential oils (phellandrene, sabinene, cineol, borneol, zingiberene, and sesquiterpenes), 5% fats, 3% minerals (potassium, calcium, phosphorous, iron, and sodium), 35% curcuminoids, and trace numbers of vitamins B1, B2, C, and niacin in turmeric's chemical composition (9, 10).

The suppression of TNFα-induced activation and nuclear translocation of NF-κB is one of curcumin's well-studied effects on inflammation. Additionally, a number of inflammatory cytokines, including IL-1β, IL-2, IL-5, IL-6, IL-8, IL-12, and IL-18, seem to be inhibited by it. Other actions included the recruitment of macrophages through macrophage inflammatory protein-1α and the downregulation of monocytes through MCP1. Furthermore, curcumin has the ability to inhibit the protein kinases such as phosphorylases, protein kinase A, mTOR, and MAPKs, which are crucial for a number of cellular responses such as controlling cell growth, proliferation, division, survival, and death. Curcumin reduces inflammation, which is an important therapeutic effect even if it lacks analgesic and antipyretic qualities. Although curcumin has many positive benefits and is generally well tolerated, its poor bioavailability is a major barrier to its use as a medicinal drug. However, the curcumin compound's bioavailability appears to be increased by 2000% when piperine, an alkaloid found in black pepper (*Piper nigrum),* is added. This results in a significantly better therapeutic effect (11, 12).

***Zingiber officinale* –** is a member of *Zingeberaceae* family of plants and some studies have proven that ginger is the most used herbal drug in many countries. Scientific evidences support the beneficial properties of ginger, including antioxidant and anti-inflammatory capacities; in contrast, a more specific and less studied bioactivity is the possible neuroprotective effect of ginger. One of the medicinal herbs that have been used extensively in food and medicine is *Zingiber officinale*, which has beneficial impact on health. The pharmacological properties of its crude extract are well established. Formerly employed in conventional medicine, the ginger rhizome is frequently added to meals as a spice or consumed as nutritional supplement. Urinary tract inflammation is one of the main disorders that ginger is used to treat. Furthermore, its anti-inflammatory properties, due to immune response modulation during the cellular phase have been described. Another highlighted ability of this herbal extract is its antinociceptive effects induced by acetic acid. Its bioactive compounds have an analgesic and anti-inflammatory effect by inhibiting COX2 and Lox pathways, therefore preventing arachidonic acid metabolism (13, 14).

Nigella sativa - A popular therapeutic plant in the Ranunculaceae family is black cumin, or Nigella sativa. Nearly all traditional medical systems, including Western herbal medicine, Islamic Tibb-e-Nabawi, Indian and Ayurvedic medicine, and others, are influenced by its popularity. "The herb that cures everything but death" is how it is known in Bulgarian folklore. Analgesic, digestive, anti-diarrheal, appetite-stimulating, antibacterial, anti-hypertensive, diuretic, and (skin) tonic are just a few of the many uses for black cumin. The majority of its medicinal actions are attributed to thymoquinone (TQ), an important bioactive ingredient in black cumin essential oil.*In vitro* studies have demonstrated that black cumin aqueous extract has anti-inflammatory and immunomodulatory properties because it drastically enhances splenocyte proliferation in BLAB/c mice and C57/BL6 primary cells in a concentration-dependent manner(15, 16).

In particular, the aqueous extract seems to promote the release of Th2 cytokines by splenocytes rather than Th1 cytokines; it also significantly reduces the release of important pro-inflammatory mediators like IL-6, TNF-α, and NO by macrophages and increases the cytotoxic activity of natural killer (NK) cells against YAC-1 tumor cells. This implies that the bioactive chemicals found in black cumin might be employed as

therapeutic agents to control multiple immune responses in a range of illnesses and ailments, including cancer. Furthermore, black cumin seeds immunomodulatory properties can also be employed as an adjuvant therapy for some cancer patients and as a preventative measure against opportunistic infections. According to other data, *Nigella sativa* seeds could be a possible cytotoxic agent that suppresses the immune system. The loss of hemolysin antibody titers associated with the administered whole-body gamma irradiation has been demonstrated to be greatly reversed by the daily preventative consumption of N. sativa oil by rats. This implies that the oil might be a potential radioprotective agent against ionizing radiations, especially for defense against the latter's oxidative and immunosuppressive effects. The anti-inflammatory and analgesic effects of black cumin's alcoholic and aqueous extracts are thought to be attributed to high thymoquinone concentration. The latter is twelve times more abundant in the leaf callus than in seed extract, but its quantity varies substantially across the plant. Significantly less NO is produced by inflamed rat mix glial cells, indicating that thymoquinone has anti-inflammatory properties. Also, thymoquinone appears to have a positive impact on osteoporosis-related oxidative stress and inflammation by inhibiting the production of inflammatory cytokines, including IL-1 and IL-6, as well as the NF-κB consensus site element. Likewise, in a concentration- and time-dependent way, it seems to decrease the production of monocyte chemoattractant protein (MCP)-1, TNF-α, IL-1β, and COX-2 by pancreatic ductal adenocarcinoma cells (17, 18). These findings imply that thymoquinone could be a potential substance that combines a proapoptotic mechanism of action with the suppression of proinflammatory pathways. Through the suppression of prostaglandin D2 production and Th2-driven immune responses, other researchers have also shown that thymoquinone has anti-inflammatory effects in the lungs during an allergic reaction. Finally, a prospective, double-blind, descriptive analytic clinical trial was carried out to examine the anti-inflammatory properties of *Nigella sativa* in individuals suffering from allergic rhinitis. According to the findings, *Nigella sativa* decreased nasal mucosal congestion, itching, mucosal pallor, runny nose, and sneezing. This suggests that *Nigella sativa* might be a useful treatment choice when other antiallergic medications must be avoided for several reasons.

***Allium sativum* –**Allium plants are well known for producing organosulfur compounds, which have intriguing pharmacological and biological characteristics. One of the most commonly utilized among them is garlic (*Allium sativum*). Since ancient times, garlic (*Allium sativum*) has been used extensively for both medicinal and culinary purposes. It is still used as a means of treatment in conventional medical practice, which cures diseases by using plants with medicinal properties. More than 200 chemical compounds with a variety of uses have been found in garlic. It contains 2.3% organosulfur compounds, 65% water, 28% carbohydrates, 2% proteins, 1.2% free amino acids, and 1.5% fiber. In addition, it includes minerals (calcium, iron, magnesium, phosphorus, potassium, sodium, and zinc) and water-soluble vitamins (A, K, and E). Garlic's distinct flavor, odor, and medicinal characteristics are all attributed to organosulfur compounds. Also, organosulfur compounds found in garlic are both volatile and non-volatile. Garlic contains sulfur precursors that are non-volatile, such as γ-glutamyl-S-allyl-L-cysteine and its sulfoxide, or alliin (19, 20).

Only whole garlic contains alliin, which is changed into other substances when the bulb of garlic is crushed or mashed. On the other hand, volatile organosulfur compounds, which are separated into three subgroups based on their chemical composition, are produced during the manufacturing process of garlic products. When raw garlic is treated, sulfoxides undergo an enzyme reaction that produces thiosulfinates. When the garlic bulb is crushed, pulverized, or otherwise damaged, alliin reacts with the enzyme alliinase to form volatile organosulfur compounds like allicin (diallyl thiosulfinate), one of the most physiologically active substances. Due to its extreme instability, allicin breaks down quickly into a variety of chemicals, including sulfur dioxide (SO2), diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS). Methyl allyl disulfide and methyl allyl trisulfide are also members of this class. Water-soluble organosulfur compounds, which are produced when garlic is extracted aqueously or alcoholically by breaking down γ-glutamyl-S-allyl-L-cysteine into S-allyl-L-cysteine (SAC). Its most significant biological and pharmacological characteristics are attributed to its organosulfur compounds, which are extracted and isolated for therapeutic uses. Garlic-derived compounds have been linked to anti-inflammatory, antioxidant, and anti-microbial properties that have positive effects against immune system disorders, cancers, and cardiovascular diseases. Garlic activates a range of immune responder cells, including dendritic cells, lymphocytes, macrophages, and natural killer cells, according to numerous laboratories and research studies on animals. Recent research indicates that other important components of raw garlic, such as water-soluble fructans and lectins or agglutinins, also contribute to its immunomodulatory qualities. In a few humans as well as animal research studies, garlic has also demonstrated potential as an anti-cancer agent against a variety of tumors. Over the past three decades, a great deal of research has been done on

aged garlic extract (AGE), an odorless preparation of garlic that exhibits efficacy comparable to raw garlic (21, 22).

Chemical characteristics with respect to polysaccharide and phenolic contents were matched against assays measuring immune modulatory activities in order to assess whether our approach successfully could select plants for further in-depth pharmacological studies.

Water extraction of medicinal plants yields crude extracts with a great diversity of natural products, including, among others, carbohydrates and phenolics. Flavonoids and other polyphenols are known to contribute to anti-inflammatory properties, while polysaccharides may contribute to immune activation. When such crude extracts are screened in in vitro systems, these classes of compounds may mask or counterbalance each other's activities. Therefore, the water extract was fractionated into a polysaccharide-enriched fraction and a fraction enriched in phenolics. The historical sources generally gave no detailed information about how the decoctions or infusions were prepared. The plants were therefore extracted with boiling water using the same conditions for all plants, and a modern pressurized liquid extraction instrument was chosen as it ensured the same conditions for all samples.

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