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Review article

Exploring the therapeutic potential of some medicinal plants in modulating the immune function

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The immune system is essential in protecting the human body against harmful bacteria, viruses, and fungi. Deficiencies in immune defenses can open the door not only to infections but also to the development of tumors. This article provides a concise overview of the key immune-modulating properties of several commonly used herbs and their active ingredients, including purple coneflower (Echinacea), black cumin (Nigella sativa), turmeric (Curcuma longa), ginger (Zingiber officinale), and cinnamon (Cinnamomum zeylanicum). These plants were chosen for their popularity, ease of access as supplements, known immune-boosting effects, and extensive scientific investigations on their active ingredients and extracts. Various natural herbs and spices have demonstrated significant immunomodulatory properties. This immune-enhancing impact is ascribed to the presence of bioactive phytoconstituents in these remedies, including polyphenols, terpenoids, β-glucans, and vitamins. Bioactive compounds found in natural ingredients directly improve the cytotoxic activity of natural killer cells, macrophages, and neutrophils, thereby strengthening the immune response. Additionally, many phytoconstituents possess powerful anti-inflammatory, antimicrobial, and antioxidant properties, protecting cells from damage and promoting overall immune function. In conclusion, this review explores widely recognized herbs with immune-boosting properties. The findings are promising, indicating that these herbs could be beneficial as preventative measures in natural medicine.

Keywords: Black cumin; Cinnamon; Echinacea; Ginger; Immunomodulatory; Turmeric

List of abbreviations
Akt: Protein kinase B; Anti-SRBC: Anti-sheep erythrocytes; DCs: Dendritic cells; E: Echinacea; FoxP3: Forkhead box P3; HSP70: Heat shock protein 70; IFNs: Interferons; IFN-β: interferon-beta; IFN-γ: Interferon-gamma; IL-1: Interleukin-1; JNKs: c-Jun N-terminal kinases; MHCII: Major histocompatibility complex class II; NK: Natural killer; NO: Nitric oxide; NF-κB: Nuclear factor kappa B; p38 MAPK: p38 mitogen-activated protein kinases; PBMC: Peripheral blood mononuclear cells; RORγ: RAR-related orphan receptor gamma; TNF-α: Tumor necrosis factor-alpha; Th1: Type 1 T helper; Th17: T-helper 17; URTIs: Upper respiratory tract infections.

INTRODUCTION

The body is protected from various illnesses and infections caused by bacteria, viruses, and foreign substances and cells by a complex system of organs, tissues and cells called the immune system. Natural killer (NK) cells and phagocytes (monocytes, macrophages, and neutrophils) are the principal effector cells of innate immunity. Both types of cells are tissue-borne and circulate throughout the body, encountering and eliminating microbes that have gotten past the epithelial barriers beside dead or transformed self-cells.[1] The natural immune system works as our body's initial line of defense against harmful substances and viruses. Specialized receptors on cells detect viral components, triggering the motivation of innate immunity. This activation leads to the production of interferons (IFNs) and cytokines, which fight viruses and help eliminate them.[2] The adaptive innate immunity is crucial for fighting viral infections. The most effective players in this fight

are B cells (producers of antibodies), CD8+ T cells, and CD4+ T cells.[3] The body's acquired immune system produces antibodies in response to the innate immune response. These antibodies specifically target the virus's spike protein, effectively "neutralizing" it. Macrophages, specialized immune cells, further assist by destroying many virus cells.[2]

External (exogenous) and internal (endogenous) threats constantly attack the immune system. These threats can cause the immune system to become overactive (immunostimulation) or underactive (immunosuppression).[4-5] Numerous naturally derived compounds influence the roles of antibody production and immune cells, contributing to infection management and immune homeostasis.[6] These compounds have demonstrated the ability to enhance innate immune responses through macrophage activation and lymphocytes, regulate cytokine synthesis, reduce the risk of infection, and trigger programmed cell death.[7]

Concerns about cost, toxicity, and side effects of synthetic drugs are driving interest in herbal remedies for health promotion.[8] Medicinal plants offer natural ways to improve immunity through various mechanisms, including stimulating phagocytic activity, activating macrophages, regulating cytokine release, promoting antibody production, and enhancing lymphocyte proliferation.[9] Functional foods activate NK cells, which are important immune cells. They regulate the specific immune cell activity involved in Th17 and Th2 immune responses. They suppress the inflammatory cytokines production and promote the anti-inflammatory cytokines production. These findings confirm that functional foods can act as immune modulators and boosters, helping to combat inflammation.[10] Nutraceutical interventions hold the potential to fortify the immune system and contribute to improved public health outcomes.[11–14] Plant-based components promote well-being and help fight infections by enhancing the immune response. Recently, herbal medicines have gained favor as go-to solutions for strengthening immunity in patients before and after COVID-19.[15]

Studies of plants from various regions have yielded many herbs with immune-stimulating properties, including them in official medicine. Herbal preparations are valued for their effectiveness and affordability as natural immune modulators.[13,16,17] Recently, the use of herbs has transcended human healthcare, finding its way into the realm of poultry farming[18]. Poultry and fish farmers employed many herbs to enhance immune function and increase weight gain.[19] As plants have been used for centuries for their medicinal properties, and modern research is increasingly validating their effectiveness in managing infections and diseases linked to immune dysfunction. This review aimed to explore the exciting potential of various natural plants (**figure 1)** and their active ingredients in supporting and enhancing our immune system.

1. ECHINACEA

Purple coneflower (Echinacea (E), family *Asteraceae*), a genus of flowering plants native to North America, has been traditionally used for its therapeutic properties. Three species, *E. pallida, E. angustifolia*, and *E. purpurea*, have been employed by Native Americans to treat respiratory infections and inflammatory conditions.[13] Modern medicine has also embraced the therapeutic potential of Echinacea, utilizing phytopreparations derived from its rhizomes and roots. These preparations, considered effective natural immune boosters, are among the most common herbal medicines in Europe and the United States.[20] *E. purpurea* tinctures harbor a lipophilic fraction composed of more than fifteen diverse N-alkylamides. These N-alkylamide exhibit the ability to activate the cannabinoid receptor type 2 and are thought to exert immunomodulatory and anti-inflammatory effects.[21] In addition to phenolic and alkamides constituents, the polysaccharide arabinogalactan extracted from *E. purpurea*, which resembles bacterial lipopolysaccharide, has been recognized as the primary macrophage activator.[22]

While clinical trials on Echinacea preparations have produced inconsistent findings, some evidence suggests that it can effectively reduce the intensity and duration of cold symptoms. This efficacy, however, seems to be dependent on the specific Echinacea preparation, with *E. purpurea* showing the most promising effects.[23–25] *E. purpurea*-based treatments are herbal therapies that alleviate respiratory tract infections and manage various inflammatory conditions. These remedies function as non-specific immune enhancers and modulators of specific cellular immunity. Furthermore, they exhibit antiviral, anti-inflammatory, and antimicrobial properties. One *Echinacea purpurea* containing drop enhanced anti-sheep erythrocytes (anti-SRBC) antibody production and modulated splenocyte proliferation in mice, but not chemokinesis. However, another *Echinacea purpurea* containing drop enhanced splenocyte proliferation but not antibody production.[16] Several investigations have demonstrated the role of alkamides in the *in vivo* and *in vitro*

immunomodulatory effects of Echinacea extracts. Echinacea preparations have anti-inflammatory properties, which are mostly attributed to its polysaccharides. Highly standardized Echinacea root hydroethanolic extracts with a unique phytochemical profile that includes echinacoside (>4%), the high molecular weight polysaccharide IDN 5405 (>5%), and an isobutyl amide fraction (<0.1%) with a significant absence of alkylamides could be utilized as a self-care strategy to boost immunity to vaccination and protect against the common cold.[23,26] The authors suggest taking 2400 mg of Echinacea daily for four months for preventive purposes. During acute cold episodes, a treatment dose of 4000 mg/day is recommended.[23]

Echinacea has demonstrated the ability to regulate both innate and acquired immune responses. Research indicates that Echinacea can enhance immune function in healthy and immunocompromised individuals.[27] Extracts of Echinacea have been shown to improve the ability of macrophages to engulf and destroy foreign particles (phagocytosis) and increase the synthesis of immune-signaling molecules (cytokines), such as interferon-beta (IFN-β), tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1). Moreover, Echinacea has been demonstrated to promote leukocyte movement (leukocyte mobility) and activate NK cells, which play an essential function in defending against viruses and tumor cells. These effects have been detected in both human and animal studies.[22,25,28,29]

Extracts from different parts of the *E. purpurea* plant exhibit contrasting effects on human dendritic cells (DCs), immune cells that perform a critical function in stimulating other immune cells. Root extracts promote DC maturation and function, while stem plus leaf extracts regulate DC migration and immune responses. These findings reveal that the extracts of *E. purpurea* have possible therapeutic applications in immune regulation.[30] *E. purpurea* extracts with high polysaccharide content can enhance the maturation of DC by regulating the c-Jun N-terminal kinases (JNKs), p38 mitogen-activated protein kinases (p38 MAPK), and nuclear factor kappa B (NF-κB) signaling pathways.[31] Additionally, *E. purpurea* extracts can promote the differentiation of macrophages into their M1 subtype, which plays a role in combating infections, by modulating the JNK signaling pathway.[32] Echinacea extract (100 µg /mL) strongly stimulated macrophages generated from mouse bone marrow, increasing the expression of CD86, CD80, and major histocompatibility complex class II (MHCII) molecules. Moreover, it stimulated the release of markers of M1 macrophage activation, such as nitric oxide (NO), TNF-α, IL-12p70, IL-1β, and IL-6.[33]

In alignment with the idea that Echinacea has broad antiviral activity, *in vitro* and clinical studies demonstrated that the ethanolic extract of *E. purpurea* effectively inhibits the highly pathogenic SARS-CoV-2 virus.[34-36] A recent clinical trial examined the effectiveness of an *E. purpurea* preparation made from roots /fresh herbs at daily doses of 2.4-4 g over five months compared to a non-treatment group. The research found a significant decline in the risk of SARS-CoV-2 infections, assessed by RT-PCR-positive samples, symptomatic COVID-19 disease, or seroconversion.[37] Very recently, researchers developed a mixture of *E. purpurea* (L.) Moench and *Humulus lupulus* L. show promise in preventing and treating viral respiratory diseases. The mixture exhibited antioxidant, cytoprotective, and immunomodulatory effects and antiviral activity against the PR8/H1N1 influenza virus. Nrf2 adjustment was proposed as a potential mechanism of action. The mixture combined activities, likely due to the unique phytocomplexes of *E. purpurea* and *Humulus lupulus*, suggest promising therapeutic potential.[38]

A clinical trial investigated the efficiency of two new, high-dose Echinacea formulations (lozenges and spray) compared to two conventional, lower-dose formulations (tablets and drops) in treating upper respiratory tract infections (URTIs) in healthy individuals. The new formulations provided a higher initial dose of Echinacea extract followed by a lower maintenance dose. Participants who received the new preparations had a significantly shorter mean time to remission (complete symptom resolution) than those receiving the conventional preparations. Additionally, viral clearance by day 10 was more frequent among participants receiving the new formulations. Tolerability and safety were good, and adverse event incidents were alike between preparations. Based on these findings, the new, high-dose Echinacea formulations appear to be more effective in treating URTIs than the conventional, lower-dose formulations.[39]

Echinacea purpurea, zinc, selenium, and vitamin C have been shown in a double-blind, randomized, placebo-controlled experiment to potentially reduce exacerbation symptoms in 108 patients with a mean age of 65·8 years (40-81 years) with URTIs and chronic obstructive pulmonary disease (COPD).[40] According to a parallel-group, randomized, double-blinded,

placebo-controlled trial (mean ages of the study sample were 34.8 ± 11.39 years), echinacea also appears to have the same synergistic effect when combined with *Justicia adhatoda* and *Eleutherococcus senticosus*. This combination of extracts significantly reduced the incidence of acute URI.[41]

Among studies that were carried out in children, Ogal et al.[42] findings suggest that Echinacea is a safe and effective way to protect children from RTIs. A study found that a dietary supplement for children from biological echinacea (400 mg freshly harvested *Echinacea purpurea* alcoholic extract) can help prevent URTIs and reduce the need for antibiotics in children aged 4-12 years. Children who took Echinacea had significantly fewer URTIs, shorter overall illness duration, and less antibiotic use compared to those who took vitamin C. Echinacea also effectively prevented influenza and other viral infections. A 2020 study on children with recurrent tonsillitis found that echinacea may boost the effectiveness of antibiotics even in cases where they are necessary. According to the study, echinacea (5 ml oral suspension; 3 times daily for 10 consecutive days every month for 6 consecutive months) and azithromycin together were more efficient than azithromycin alone at lowering the incidence and severity of tonsillitis recurrence.[43]

2. BLACK CUMIN

Black cumin (*Nigella sativa* L.) (*Ranunculaceae* family), a fragrant plant, has been employed as a natural therapy for various illnesses for more than two millennia. The active components of its seeds include the essential oil, comprising carvone, p-cymene, terpene or D-limonene, also known as carvene, and unsaturated ketone. Black cumin seeds have been extensively utilized in folk remedies for numerous benefits, including appetite enhancers, digestive stimulants, and immunity boosters [44], as well as antioxidants and antibacterial agents [45]. The primary active components of essential oils that are pharmacologically active are dithymoquinone, thymoquinone, thymol, and thymohydroquinone[46], while DL-γ-tocopherol, DL-α-tocopherol, all-trans-retinol, and selenium are among the significant antioxidants found in black cumin seeds.[47]

Various cultures have long-standing traditions of using black cumin to strengthen the immune systems.[48] Black cumin oil can remarkably boost T-cell-mediated cellular immunity, while other components have been shown to inhibit B-cell-mediated immunity. The stimulatory effects of black cumin on cellular immunity are influenced by the specific immune response.[49] Laboratory studies examined the effects of soluble black cumin fractions on human peripheral blood mononuclear cells (PBMC) response to numerous mitogens. The results revealed that while these fractions did not significantly stimulate PBMC in response to the T cell mitogen phytohemagglutinin, they did enhance PBMC response to pooled allogeneic cells. Additionally, cumin-fractionated proteins demonstrated stimulatory activity in lymphocyte cultures.[49,50]

Black cumin has been demonstrated to boost T helper cells (T4) activity, NK cells, and suppressor T cells (T8) in healthy individuals.[51] Black cumin oil supplementation significantly benefits most individuals, as evidenced by a rise (55%) in CD4 and CD8 T cell ratios and improved NK cells cell activity.[52] A recent placebo-controlled, randomized, double-blind trial evaluated the impact of black cumin administration (0.5, 1 g, and 2 g capsules) on immune indicators in young healthy subjects (age 18-25 years, n=52). Only the 1 g dose significantly boosted total lymphocyte count, CD3+, and CD4+ counts, implying an optimal dose of 1 g for enhancing helper T cells in this age group.[48] Another recent double-blind, randomized, placebo-controlled study assessed the impact of a black cumin oil thymoquinone-rich extract (200 mg/day for 90 days) on immunity, stress and sleep in 72 healthy subjects with self-reported sleep difficulties. Results indicated that black cumin oil thymoquinone-rich extract modulates the immune system (significant ($p < 0.001$) increases in IgM and IgG).[53]

Incorporating black cumin seed powder into broiler diets enhanced various immune system markers, suggesting beneficial effects on immune function.[54] Feeding broiler chickens increasing amounts of black cumin seed (0, 5, 10, and 20 g/kg diet) induced a linear decline in *Salmonella* spp. ($P = 0.05$) and a quadratic rise in antibody titers against the Newcastle disease virus on day 35 ($P < 0.001$).[55] Similarly, rabbits supplemented with black cumin seed (300 and 600 mg/kg diet) for eight weeks exhibited significantly enhanced IgG and IgM immune responses relative to the control group.[56] Fish (common carp (Cyprinus carpio) fingerling) supplemented with black cumin-enriched diets at 0.25, 0.5, and 1% for sixty days exhibited greater resilience to glyphosate (pesticide) exposure compared to control fish and maintained elevated immune defenses (lysozyme and immunoglobulin).[57]

Administration of a diet supplemented with black seed and its combination action with chloroquine enhanced immune responses in mice

infected with *Plasmodium berghei*, as evidenced by elevated serum immunoglobulin levels, including IgG and IgM.[58] Another study that investigated the efficacy of black seed oil in counteracting the adverse effects of ribavirin on natural immunity in rats has demonstrated the ability of black seed oil to boost natural IgG and IgM levels.[59] Black seed oil holds promise as a natural radioprotective substance to counteract the immunosuppressive effects of whole-body gamma-irradiated rats. Oral ingestion of black seed oil (1 ml/kg b.wt./day) for 5 days/week prior to irradiation significantly stimulated the regeneration of lymphoid follicles in the thymus and spleen.[60]

Besides enhancing immunity, black cumin extract exhibits anti-HIV protease activity.[61] Black cumin's ability to increase CD4+ T cell count makes it a promising therapeutic agent for combating HIV infection.[62] A study examined the efficacy of black cumin oil supplementation in patients infected with hepatitis C virus. The study found that administering 450 mg black cumin oil capsules three times daily for three months led to significant improvements in oxidative stress, viral load, albumin, total protein, platelet, and RBC levels.[63] A woman (27-year-old) with HIV-positive received a honey and black cumin mixture (10 mL) for a year three times/ day as an alternative to antiretroviral therapy. Her HIV serology tests subsequently turned negative, and her viral load became undetectable. She gave birth to three children (2007, 2010, and 2012) who were all breastfed, and none of them contracted HIV. Her CD4 count remained above 750 cells/μL throughout this period.[64]

Besides its antiviral activity, thymoquinone, the principal active ingredient of black cumin, has also demonstrated immunomodulatory properties.[65] Thymoquinone may improve macrophage function during early innate immunity by enhancing phagocytosis and increasing human leukocyte antigen DR isotype expression and interferon-gamma (IFN-γ) secretion, potentially improving macrophage antigen presentation.[66] In animal studies, administration of thymoquinone in the broiler quail's diet with a dose of 200 mg per kg caused elevation in the lymphoid organs (spleen, thymus, and Bursa) relative weights and enhanced antibody titers against *Haemophilus influenzae*, *Avian influenza*, infectious bronchitis virus, and Sheep red blood cell vaccination. Additionally, thymoquinone administration increased mean skin thickness after the dinitrochlorobenzene challenge and decreased wing web swelling response to phytohemagglutinin mitogen injection, indicating improved cell-mediated immunity.[67] Administration of thymoquinone to gamma-irradiated rats mitigated T lymphocyte depletion and programmed cell death by regulating the expression of PD-1, caspase-3, Bcl-2, and Bax, key players in the apoptotic pathway.[68] Hydrothymoquinone and dithymoquinone, two compounds synthesized from thymoquinone through simple chemical processes, hydrothymoquinone demonstrated anti-SARS-CoV-2 activity at non-toxic nanomolar levels *in vitro*. In contrast, dithymoquinone exhibited high cytotoxicity.[69] Molecular docking studies revealed that thymoquinone possesses remarkable antiviral activity against a SARS-CoV-19 strain isolated through its interaction with the viral receptor.[70]

Various clinical studies proved the safety of black cumin in pediatric population.[71] A study showed that black cumin oil influences the balance of Th1/Th2 cytokines and enhances children's asthma control.[72] For eight weeks, 28 children (aged 6-15 year) received 15–30 mg/kg/day of black cumin oil. The improvement in asthma control was evaluated using the results of the asthma control test. Following treatment, there were no appreciable variations in either the Th1/Th2 ratio or the quantity of Th1 and Th2 cells across the groups. In comparison to the placebo group, the youngsters treated with black cumin oil had significantly higher levels of serum IFN-γ and lower levels of IL-4. There was no discernible difference in the asthma control test scores across the groups. Improved lung function resulted from another clinical research conducted in Khartoum on asthmatic children and adults (8 to 40 years old) who were given 2 g of black cumin and 1 teaspoon of honey daily for three months.[72] Black cumin capsules at a dose of 40–80 mg/kg/day were also shown to significantly lower cortisol levels, eosinophil count, and plasma and urine levels of IgE in children and adults (age 6–17 years) with allergic diseases, including atopic eczema, asthma, and allergic rhinitis.[73] Additionally, after receiving 2 g of powdered black cumin seeds daily for three consecutive months, a randomized, placebo-controlled clinical trial involving 25 children (6–18 years) with beta-thalassemia major showed a significant increase in WBC and neutrophil counts in addition to a significant increase in CD4 as well as CD8 counts.[74] However, more research is needed to confirm how safe and effective these herbs are as medicine, especially for children. Herbs are not a substitute for conventional medical treatments, and it's important to follow international guidelines for managing health conditions.

3. GINGER

Ginger (family *Zingiberaceae*), obtained from the dried rhizome of the plant *Zingiber officinale* Roscoe, is a prevalent spice utilized internationally. Its historical usage as a folk medicine span millennia. According to certain regulatory agencies, ginger is categorized as a safe herbal supplement.[75] Ginger boasts a rich chemical profile, with over 200 identified compounds. Its bioactive components include terpenes, anthocyanins, tannins, and phenolic constituents like zingerone, paradols, gingerols, and shogaols.[76–78] Gingerols are the principal compounds responsible for ginger's characteristic pungency.[79] Numerous studies have delved into the pharmacological properties of ginger extracts and their isolated phenolic compounds, particularly 6-gingerol, demonstrating a diverse range of beneficial effects[80]. Gingerols' immunomodulatory properties have gained significant attention due to their capability to modulate the immune system.[81, 82] These compounds have been revealed to suppress NF-κB and protein kinase B (Akt) activation, leading to a reduction in proinflammatory cytokines and an elevation in anti-inflammatory cytokines.[83, 84]

Many scientific investigations have clarified the effects of gingerols immunomodulatory, especially 6-gingerol. A study investigating the anti-allergic effects of ginger and 6-gingerol, its major compound, utilized a primary/cell line culture system and a mouse allergy model. Oral administration of a diet with 2% ginger to mice with allergic rhinitis induced by ovalbumin reduced the severity of nasal rubbing and sneezing. It also suppressed mast cell infiltration in the nasal mucosa and secretion of ovalbumin-specific IgE in serum. 6-gingerol inhibited the expression of both Th1 and Th2 cytokines in ovalbumin-sensitized spleen cells. Consequently, 6-gingerol suppressed the *in vitro* differentiation of both Th2 and Th1 cells from naive T cells. Additionally, 6-gingerol inhibited T cell proliferation induced by both the anti-CD3 and superantigen staphylococcal enterotoxin B. Furthermore, 6-gingerol prevented T cells activated by phorbol 12-myristate acetate plus ionomycin and superantigen staphylococcal enterotoxin B from producing IL-2, indicating that its effects target T cell receptor-mediated signal transduction rather than the antigen-presentation process.[85]

A study examined the impact of bioactive compounds of ginger, gingerol, oleoresin, and shogaol, on human lymphocytes. To evaluate NK cell function, cells were treated with paraquat and incubated with the compounds at 50, 100, and 200 μg/ml concentrations. Gingerol and oleoresin stimulated the proliferation of B and T cells at 50 μg/ml, Shogaol exhibited similar proliferative effects at higher concentrations. Notably, both oleoresin and gingerol significantly increased NK cell lytic activity when paraquat was present.[86] Research has shown that 6-Gingerol effectively suppresses the growth of *Mycobacterium tuberculosis* bacteria in the lungs, spleen, and liver of infected mice. Gingerol treated mice displayed increased expression of pro-inflammatory cytokines and enhanced the responses of Th17 (T-helper 17) and Th1 (type 1 T helper) in their spleens, providing evidence for the gingerol immunomodulatory effects. Gingerol treatment induced an elevation in the number of CD8+ T and CD4+ cells along with CD11c and Cd11b and cells, leading to the phosphorylation of p38 MAPK.[87] Red ginger, enriched with bioactive compounds has emerged as a promising immunomodulator for psoriasis treatment. Research suggests that red ginger influences T lymphocyte activity.[88]

6-Gingerol possesses immunomodulatory properties, exerting a modulatory impact on both cell-mediated immune and humoral responses in rats. The following results provide compelling evidence for the ability of 6-gingerol to stimulate lymphocyte proliferation. Oral ingestion of 6-gingerol (800 mg/kg body weight) of over a seven-day period induced a statistically significant rise in circulating antibody titer (88.2) and delayed-type hypersensitivity (3.5) relative to the control group (8.9 and 0.2, respectively). Furthermore, 6-gingerol augmented cellular immunity and improved the humoral antibody response, as evidenced by an accelerated footpad thickness in rats immunized with sheep red blood cells.[89] Treg cells and Th17cells play antagonistic roles in regulating inflammation and immunity. Th17 cells contribute to inflammation by secreting pro-inflammatory cytokines and attracting neutrophils, whereas Treg cells counteract inflammation by releasing anti-inflammatory cytokines and inhibiting immune cell function.[90] 6-gingerol effectively counteracted the dextran sulfate sodium-induced increase in Th17 cells and decrease in Treg cells in a mouse model of colitis.[91]

A study by Deng et al. demonstrated that both ginger and its major component, 6-gingerol, exhibited tumor-suppressive properties Ginger demonstrated superior anti-tumor efficacy compared to 6-gingerol, with a 56% inhibition rate compared to 33% and 37%, respectively. Ginger's anti-tumor activity is mediated by its ability to promote function in CD8+ T cells and

mitochondrial biogenesis.[92] Animal studies showed that supplementation with ginger and propolis extracts in drinking water (1 mL/L) boosted both humoral and cellular immunity in chickens. It elevated antibody production, cytokine production (INF, IL10, and IL2), and Toll-Like Receptor 3 gene expression in relevant immune organs. Additionally, it raised the expression of CD8, CD4, and CD3 markers, indicating enhanced cellular immunity. Importantly, the supplementation maintained the normal histology of lymphocytes in these organs.[93] Garlic and ginger extracts exhibited immunomodulatory effects in chicks after 21 days of administration, as evidenced by enhanced innate immune response and improved resistance to *E. coli* O78 challenge.[94]

The findings of Aryaeian et al. suggest that ginger may have therapeutic potential for rheumatoid arthritis by modulating Treg and Th cell responses. Ginger powder consumption for 12 weeks significantly raised the expression of FoxP3 (forkhead box P3), a marker of Tregs. It decreased the expression of RAR-related orphan receptor gamma (RORγ) and T-box expressed in T cells (T-bet), markers of pro-inflammatory Th1 and Th17 cells, in rheumatoid arthritis patients. Ginger intake also significantly reduced disease activity score.[95]

4. TURMERIC

Curcuma longa, commonly known as turmeric, is a spice plant originating from the *Zingiberaceae* family and is valued for its numerous therapeutic properties. Turmeric's composition extends beyond proteins, lipids, minerals, and carbohydrates; it is enriched with curcuminoids, a group of molecules that includes bis desmethoxy curcumin, monodesmethoxy curcumin, and curcumin (diferuloylmethane).[96,97] Curcuminoids have demonstrated numerous positive effects in humans and animals. Their antibacterial properties can help fight infections, while their growth-promoting effects support healthy development, especially in young animals. Curcuminoids also boost the immune system, reduce inflammation, and protect cells from oxidative damage, potentially lowering the risk of chronic diseases.[98] Turmeric and its components (especially curcumin) may improve immune function, offering potential benefits for various immune disorders. This has been shown in lab and real-world studies involving animals and humans.[99]

Figure 1. Examples of some immunomodulator herbs

Table 1. Summary of immunomodulator herbs; their active constituents, molecular effect, immunomodulatory roles, and proposed uses.

Herbs	Active constituents	Molecular effects	Immunomodulatory roles	Uses
Echinacea	- N-alkylamides[21] - Polysaccharide arabinogalactan[22]	- Activates the cannabinoid receptor type 2[21] - Nrf2 adjustment[38] -Regulates JNKs, p38 MAPK, and NF-κB signaling pathways[31]	-Immune stimulant[22,25,28,29] 1-Improves phagocytosis 2-Increases the synthesis IFN-β, TNF-α, IL-1 3-Promotes leukocyte mobility 4-Activates NK cells -Promotes the differentiation of macrophages into their M1 subtype (phagocytosis) [32] - Promotes DC maturation, function, migration and immune responses[30]	Prevention and treatment of: -Common cold -Flu -Upper respiratory tract infections -Lower urinary tract infections - PR8/H1N1 influenza virus[38] - COPD[40]
Black cumin	-Dithymoquinone -thymoquinone -thymol -thymohydroquinone [46]	- Regulates the expression of PD-1, caspase-3, Bcl-2, and Bax, key players in the apoptotic pathway[68]	- boosts T-cell-mediated cellular immunity[49, 51, 52] 1-CD4 helper T cells 2-suppressor T cells (CD8) 3-NK cells - Increases in IgM and IgG[53, 56, 58,59] - Improves macrophage function (phagocytosis) and increases IFN-γ[66]	-Immune enhancer[48] -Black cumin seed powder is incorporated into broiler, rabbit, and fish diets to prevent virus infections[54, 55, 56, 57] -A promising therapeutic agent for combating HIV infection[62,64], hepatitis C virus[63] -Asthma control[75, 76, 77]
Ginger	-6-gingerol[76–78] -Oleoresin[86] -Shogaol[76–78, 86]	-Suppresses NF-κB -Activates Akt[83,84] - Phosphorylates p38 MAPK[87] - Raises FoxP3 expression[95] -Decreases RORγ expression[95]	-Reduces proinflammatory cytokines -Elevates anti-inflammatory cytokines[83,84] -Inhibits both Th1 and Th2 cytokines (IL-2)[85] -Suppressed the differentiation of both Th2 and Th1 cells from naive T cells[85] -Inhibited T cell proliferation[85] - Increased NK cell lytic activity[86] -Enhances Th17 and Th1 - Increased CD8+ T and CD4+ T[87] -Decreases Treg cells[91]	-Therapeutic potential for rheumatoid arthritis[95]
Turmeric	Curcuminoids: [96,97] -Bisdesmethoxy curcumin -Monodesmethoxy curcumin -Curcumin	-Raises the expression of IFN-γ -Inhibits FoxP3 expression	-Improves serum IgE[102] -Increased CD4, CD8, CD69 and NK cells[103, 104] -Converts Tregs to Th1 -Modulates IgG, IgA, and IgM -Regulates anti-inflammatory and pro-inflammatory cytokines[106] -Increases IL-1β, complement component C3, HSP70 and 90[108] -Decreases CD14+, TLR2-expressing cells, IL-10[114]	potentially lowering the risk of chronic diseases[91] -Boost the immune system -Reduce inflammation -Reduce oxidative damage -Antibacterial help fight infections -Growth-promoting in young animals
Cinnamon	-Cinnamaldehyde[106] -Eugenol[106] -Carvacrol[108]	-Inhibits FoxP3 expression[115] -Activates T-bet[115] -Induces TLR4 via the TRIF/MyD88 axis[117] -Modulates sphingosine-1-phosphate receptor 2 pathway and the regulation of specific genes (lncRNA H19 and MIAT)[118]	-Strengthens the immune system[118] -Anti-inflammatory properties[118] -Increases lysozyme[119, 121] -Raises phagocytic activity[119, 121] -Increases IgA and IgM[119, 120] -Increases CD3+CD8+ and CD3+CD4+[123, 125] -Suppresses Th17 and Tregs[124, 127] -Boosts IFNβ and IFNα[126]	-Treats influenza and other related illnesses[114] -Growth-promoting in young animals[119]

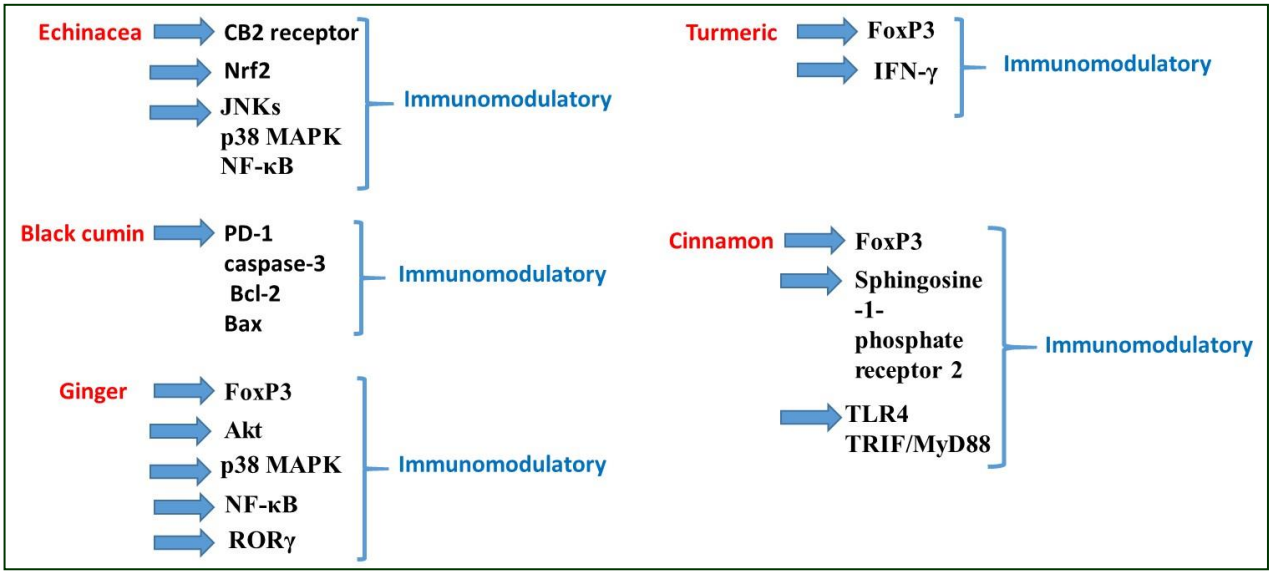

Figure 2: Summary of the molecular mechanisms of the immunomodulatory action of some common herbs.

Clinical trials conducted between 2008 and 2020 have demonstrated that curcumin-containing complexes can normalize overall antioxidant status and restore the quantity, quality, and functional-metabolic state of immune cells. Additionally, data from epidemiological prospective studies indicate that turmeric extract exhibits partial immunotropic, anti-inflammatory, and antioxidant activity in both *in vivo* and *in vitro* settings.[100] A combination of pomegranate, turmeric, and ginger exhibits significant promise as an adjuvant remedy for moderate to mild COVID-19 cases.[101] Taking a daily capsule containing 500 mg of curcumin and piperine for three consecutive menstrual cycles, starting 7 days before and ending 3 days after each period, may improve serum IgE levels in healthy young women with premenstrual syndrome and primary dysmenorrhea. However, no significant changes were observed in serum levels of IL-10 and IL-12.[102] Taking oral curcumin daily (2 g/day) for two months lowered overall lymphocyte count but boosted specific immune cell types (CD4, CD8, and NK cells) in patients with high lymphocyte levels.[103]

Curcumin phytosome modestly boosts immune response in endometrial cancer patients. Patients with endometrial cancer received oral curcumin phytosome for 2 weeks. Curcumin phytosome altered the activity of specific immune cells, with some being suppressed and others being boosted. Notably, curcumin phytosome increased CD69 levels in CD16-NK cells, potentially enhancing their immune response. Patients also reported improved quality of life after curcumin phytosome treatment.[104] Curcumin may boost anti-tumor immunity by converting Tregs to Th1 cells. Curcumin treatment in patients with lung cancer diminished the number of Treg cells in their peripheral blood. Curcumin converted isolated Tregs into Th1 cells in laboratory experiments. This conversion was achieved by strengthening the expression of interferon-γ and suppressing the gene transcription of forehead protein-3.[9]

Emerging research suggests that bisdemethoxycurcumin, a derivative of the natural compound curcumin, holds promise as a novel treatment for Alzheimer's disease. This potential therapeutic effect stems from its ability to boost immune function in specific cells of Alzheimer's disease patients, thereby facilitating the efficient removal of amyloid beta from the brain.[105] Fermented turmeric-camel milk may be a profitable and beneficial supplement for enhancing immunity and preventing oxidative stress. In an immunosuppression rat model caused by cyclophosphamide, administering fermented turmeric-camel milk improved weight gain, enhanced antioxidant status, modulated immunoglobulin levels (IgG, IgA, and IgM), and regulated anti-inflammatory and pro-inflammatory cytokines.[106]

Adding curcumin to the diet of finfish has been demonstrated to promote their growth, strengthen their immune system, elevate their antioxidant

capacity, and boost their ability to withstand diseases in aquaculture settings.[88,107] Supplementing *Clarias batrachus* catfish with 0.9 grams of turmeric per kilogram of feed enhances their immune system's ability to combat *Aeromonas hydrophila* infections.[9] The study by Kumar et al. suggests that turmeric oil enhances stress resilience, antioxidant defenses, and immune responses in *Pangasianodon hypophthalmus* fingerlings, thereby improving their survival against co-infection. Turmeric oil supplementation at an optimal level of 10 ppm significantly elevated survival rates and induced anti-stress and antioxidant responses, as evidenced by reduced cortisol levels and elevated superoxide dismutase and catalase activity. Additionally, turmeric oil supplementation enhanced both specific and non-specific immune responses, as indicated by significantly higher concentrations of immune genes (IL-1β, transferrin, and the (complement component, C3), the heat shock protein 70 (HSP70) and 90, and IgM in the treated groups.[108]

Crude turmeric extract significantly outperformed purified curcumin in bolstering the immune system of rats exposed to carbon tetrachloride. This was observed through its ability to revitalize key immune cells, namely immature thymocytes and CD4+ T lymphocytes.[109] The administration of dried turmeric rhizome powder can mitigate some of the heat stress-induced adverse effects in broilers. Turmeric supplementation enhances immune function and stress tolerance in broilers heat stressed. The heterophil/lymphocyte ratio and total IgG antibody titers against sheep red blood cells for secondary responses in the turmeric group were comparable to those of the broilers in the control group and significantly ameliorated ($P < 0.05$) than those in the heat stress group.[110] Dietary supplementation with 15 g/kg curcumin significantly enhanced growth performance, serum antioxidant parameters, skin mucosal immunity (lysozyme, protein level, alkaline phosphatase, protease activity, and total immunoglobulin), and disease resistance in common carp.[111]

Immune modulation results from lactoferrin and curcumin (LC) supplementation, which may have therapeutic benefits. Children in good health who had recurrent respiratory tract infections were studied to see how LC supplementation affected their clinical and immunologic responses. Children getting LC had fewer infections. Immunologic investigations revealed a considerable skewing of CD8+T cells with LC. Furthermore, it was found that: 1) children receiving LC had lower levels of CD14+, TLR2-expressing cells, whereas CD14+/TLR4+ cells produced less IL10.[112] According to a recent preliminary investigation, children with acute lymphoblastic leukemia (ALL) who received 500 mg of curcumin twice a day for a month as a nutritional supplement exhibited encouraging results (the majority of patients were under 10 years old). [113]

5. CINNAMON

Cinnamon (*Cinnamomum zeylanicum*) is a traditional treasure for fighting the flu and more. Cinnamon is a valuable tree from the *Lauraceae* family. Evidence suggests cinnamon's effectiveness in treating influenza and other related illnesses.[114] A study of the chemical makeup of cinnamon identified its two major components. These components are cinnamaldehyde (87.013%) and eugenol (9.317%).[115] Cinnamon bark essential oil extracted is rich in cinnamaldehyde, a potent bioactive compound.[116] While cinnamon oil and extracts are known for containing cinnamaldehyde, they also boast a variety of other beneficial phenolic and polyphenolic compounds, including carvacrol.[117]

Extracted from the leaves or bark of the cinnamon tree, cinnamon oil offers a range of health benefits. It aids digestion and strengthens the immune system. Additionally, it possesses detoxifying, blood sugar-regulating, and anti-inflammatory properties.[118] Adding a phytobiotic containing citric acid and cinnamon oil to chicken drinking water improved their growth performance and overall health. The most effective dosage was 0.25 mL/L of water administered for 42 days. This dosage improved the gut microbiome and immunity (increasing lysozyme, phagocytic activity, and IgA levels).[119] Adding dried cinnamon to the diet of laying Japanese quail can strengthen their immune system. This was demonstrated by increased levels of IgM in quail fed a diet containing 800mg of dried cinnamon/ kg of food compared to those fed a regular diet without any cinnamon.[120] Dietary supplementation with 15g of cinnamon per kg of food significantly increased the immune activity of European sea bass. This effect was observed in lysozyme and phagocytic activity, indicating a broader immune system boost.[121] Dietary supplementation with 300mg/kg of cinnamon essential oil significantly improved the immunity of ISA brown laying hens during their production phase (28-76 weeks old). This improvement was observed in parameters related to resistance against

Newcastle disease, Avian influenza H5, and Avian influenza H9.[122]

Cinnamon essential oil exhibits promising anti-tumor and immune-stimulating effects against Ehrlich ascites carcinoma in female mice. This effect appears to be mediated by significantly increasing the percentage of cytotoxic T cells (CD3+CD8+) and T helper (CD3+CD4+) cells in the spleen, indicating an enhanced immune response against the tumor.[123] Cinnamon promotes the growth of Th1 cells, a type of immune cell important for fighting tumors in mice with single low-dose total body irradiation. It also suppresses the expansion of Th17 and Tregs by activating T-bet and limiting transcriptions of Foxp3. By balancing these T-cell subsets, cinnamon helps restore a healthy immune system and improve its ability to fight tumors.[124]

Treatment with kaempferol (25 mg/kg) prevented the decline in the number of two important immune cell types (CD4+ and CD8+ T cells) in mice exposed to cold stress.[125] A combination of five herbal extracts—pumpkin seeds, purple turmeric, pearl barley, corn pistil, and cinnamon—that are popularly used in Japan and other countries for their potential to boost immunity and improve general health were examined in terms of their ability to induce type I IFNs in murine bone marrow-derived macrophages. Within two hours, the combination was shown to potently generate IFNβ and IFNα. TLR4 acted as a mediator for this induction by transducing signals via the TRIF/MyD88 axis.[126] Cinnamaldehyde offers a potential treatment for ulcerative colitis, a chronic inflammatory bowel disease. It achieves this by suppressing Th17 cells, a type of immune cell involved in inflammatory processes. This suppression is mediated through the sphingosine-1-phosphate receptor 2 pathway and the regulation of specific genes (lncRNA H19 and MIAT).[127]

CONCLUSION

Medicinal plants and pharmaceuticals play a significant role in both modern and traditional medicine. Their lack of harmful side effects and widespread acceptance as a daily culinary spice make them particularly valuable in medicine and wellness. Fortifying the body's natural defenses is vital for optimal health. In this review, the analysis of several well-known and highly promoted herbs with immune-modulating properties clearly indicates their impressive potential as preventative measures within a general naturopathic approach, with additional therapeutic possibilities remaining highly probable (Table 1 and Figure 2).

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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