

A Review on Spices used in Indian Food with Immune Modulation Property for Healthy Living

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ABSTRACT

Advances in the field of immunology explains the cells and cell functioning in individuals' Recent infections like COVID-19 that threaten human community in spite of technological and medical advancements helps us in conceptual understanding of immune cell functioning which is not the same in all individuals. The understanding of the neuro-endocrine-immune axis, or the impact of exercise, circadian rhythms, seasonal variations, and various psychological states on the immune system, has only recently come to light. These and other issues are bringing the modern concept closer to the Ayurvedic principles of Vyadhi-ksamatva, Ojas, and Bala. Immune modulation- The process involves both upregulation and down regulation of immune cells as required for the invading antigen. Indian traditional foods and culinary spices contain a plethora of active principal components, such as polysaccharides, terpenoids, alkaloids, flavonoids, glycosides, and essential oils, which are powerful immune modulators and have the ability to maintain or stimulate the immune system through nonspecific immune reactions. This paper reviews on common spices used in Indian foods on regular basis that improves one's immune system.

Keywords: Immune modulation, Immune stimulants, Ayurvedic medicines, Spices, Quercetin

INTRODUCTION

The functional immune system of every individual is different although the structural components of immune system are similar for all the Individuals. The functional differences are known to be consequence of hereditary and Non-Hereditary influences. But most of these variations are influenced by non-hereditary influences. This concept of individual immunity enabled mankind to establish an immune modulation hypothesis. Understanding the factors involved in immune defense of an individual is the key component to treat many of the infections and diseases. The immune system has evolved to protect the host from a wide range of dangerous pathogens that are also constantly changing. In the instance of COVID-19, areas with mucosal lining and numerous portals of entry are where the immune system assists the host in removing harmful or allergenic substances.

The field of immunology is well advanced and it could explain about the cells, other components involved and immune reactions against any new infections which are different in different individuals and is a subject of discussion. The recent COVID-19 Infection would be an ideal example for this conceptual understanding.

The understanding of the neuro-endocrine-immune axis, or the impact of exercise, circadian rhythms, seasonal variations has just recently come to light, as have the effects of different psychological states on the immune system. The Ayurvedic principles of Vyadhi-ksamatva, Ojas, and Bala are being more closely embraced by the modern notion as a result of these and other factors.

Ayurveda not only included the fundamental idea of immunomodulation; Ayurvedists have been using it in their daily practices for ages. Ayurvedic treatment plans and medications actually work to increase the body's general natural resilience to the disease-causing factor rather than actually neutralizing it.

Evolving new pathogens challenges immune system and

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scientists for better understanding of the infection and elimination of the pathogen to protect the host. Basically, innate immune response- the first line of defense acts rapidly on the invading pathogen and also alerts the second line of adaptive immune response to completely eliminate the causative agent.

CONCEPT OF IMMUNE MODULATION

Modern immunology clearly explains the concept of enhancing the immune responsiveness of an organism against an invading antigen by non-specifically activating the immune system. This property is termed as immune modulation [1,2]. The process involves both upregulation and down regulation of immune cells as required for the invading antigen. Immune modulators are considered now as one of the most effective instruments used by modern medicine to manage health and disease. In fact, the role of immune modulators in modern medicine is yet to be fully deciphered or perceived as our understanding of immune system is changing constantly. Depending on the requirements of the immune response, immune modulation can either take the form of immunological stimulation or immune suppression.

Immune modulation

Optimizing the immune response is known as immunomodulation. It involves both in terms of immunosuppression in autoimmune disorders and immune stimulation in vaccination or cancer immunotherapy. A wide variety of nanomaterials have been studied for these reasons to affect the immune system either directly through their composition or indirectly as intact carriers of the active.

The immune system protects the body from any foreign substances so called antigens by recognizing and removing such particles with various immunological reactions. The main line of defense against most invading pathogens is provided by cells with phagocytic capabilities, such as motile polymorph nuclear neutrophils, dendritic cells and macrophages. Homeostasis of myeloid lineage release many mediators that can be extracted and used in experimental immunocompromised animals to induce appreciable immune response in them. Such immune mediators' therapeutic potential relies on immunopotential, immunosuppression, or the generation of immunological tolerance. One of these mediators, lactoferrin, regulates target cell reactions, particularly those involved in oxidative stress and systemic inflammatory responses, to naturally link innate and adaptive immune activities. It is also known to be a key player in the control of antigen presentation and the development of efficient T helper cell responses.

Immune stimulation

Immuno stimulators are chemicals that boost immune system function by causing the immune system's components to become more active. Immunostimulants can

be obtained from both natural and synthetic sources. Some examples of immunostimulants are beta-glucans, chitin, lactoferrin, levamisole, vitamins B and C, growth hormone, and prolactin. Immune-stimulants are used as helper substances (adjuvants) in vaccines to activate antigen presenting cells (e.g. macrophages) and to stimulate the immune cells to produce more of the signal molecules (cytokines) which activate the group of lymphocytes (B-cells in warm-blooded animals) which produce specific antibodies.

Immunosuppressants

Immune modulators that reduce immune system activity are known as immune suppressants. These immune modulators are used in conditions where the immune system is active, such as autoimmune diseases. Two signals are produced when the immune system identifies cancer cells: The first is identification; immune cells grab onto tumor cells using specific receptors or "sensing molecules" on their surface. The immune cell's reaction to identifying the tumor cell is determined by dozens of biochemical pathways, which constitute the second signal. It may react by increasing the immune system's reaction or by suppressing it, which would weaken the body's capacity to fight cancer (**Figure 1**).

Immune modulating ingredients in Indian foods

Traditional Indian fare and culinary spices are packed with numerous active principal ingredients like polysaccharides, terpenoids, alkaloids, flavonoids, glycosides and essential oils that are active immune modulators and have extraordinary ability to support or activate the immune system through non-specific immunological responses. The functional molecules included in Indian cuisine are crucial for maintaining a healthy body weight healthy blood sugar level and a robust immune system. The usefulness of a handful of these often-used spices with anti-inflammatory, antiviral, and immunomodulatory characteristics is reviewed below:

The top essential spices added in Indian food and its immune induction properties would be discussed below. Cumin, Coriander, Garlic, Ginger, Cloves, Cardamom, Red chili powder, Mustard seed, Fenugreek, Turmeric and Saffron are few added in food commonly

Cumin

Cumin (*Cuminum cyminum L*) [3]. is a leafy plant that grows low to the ground in China, India, the Middle East, and the Mediterranean region? Cumin seed, the plant's fruit, is well-known as a spice throughout the entire world. Cumin seeds are oblong and yellow-grey. Since the beginning of time, cumin seeds, both whole and ground, have been widely employed in a variety of cuisines from numerous food cultures. Cumin seeds have tremendous medical benefit in the Indian Ayurvedic system of medicine, especially for digestive issues. Medical research has turned its attention to

cumin since a variety of health benefits have been ascribed to it in anecdotal reports. The majority of cumin's alleged health advantages relate to your immune system, circulatory

system, and digestion. Some benefits of cumin can be demonstrated with clinical studies, while some remain hard to prove.

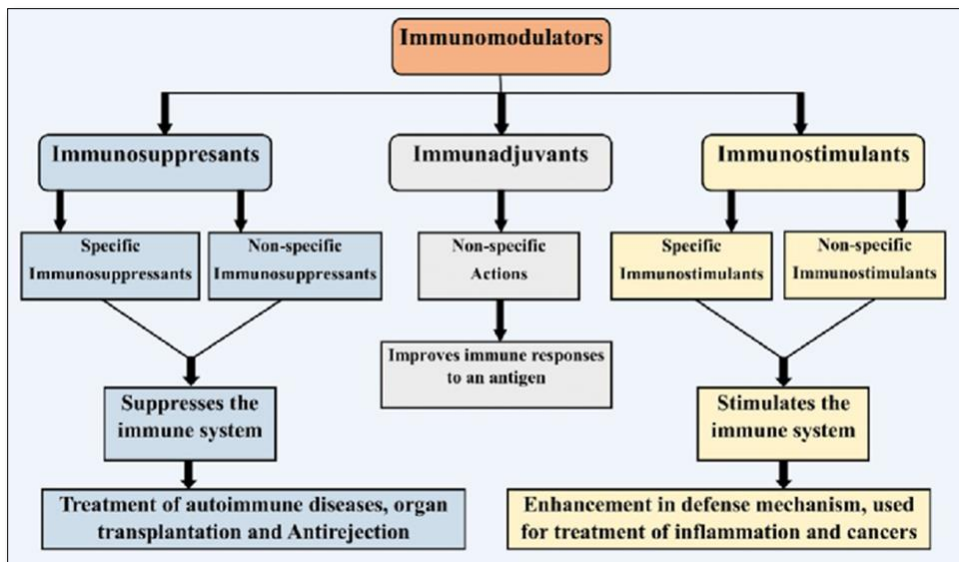


Figure 1. Classification of immunomodulators.

The aqueous extract of cumin seeds enhanced gastric mucin protection and regeneration of gastric mucosa in a research. The main ingredients in cumin oil are cumin, -pinene, -myrcene, -cymene, -terpinene, and -mentha-1,4-dien-7-ol. Cumin has numerous biological activities and a variety of nutritional benefits. Cumin [3,6] seeds have a great deal of medicinal benefit in the Indian Ayurvedic system of medicine, especially for digestive issues. They are used for

dyspepsia and persistent diarrhea. Cumin seeds are highly nutrient-dense; they offer significant amounts of fat (particularly monounsaturated fat), protein, and dietary fiber. Cumin seeds also contain significant amounts of iron, a number of nutritional elements, including vitamins B and E. Cumin's main volatile ingredients include terpenoids, cymene and cumin aldehyde (Figure 2).

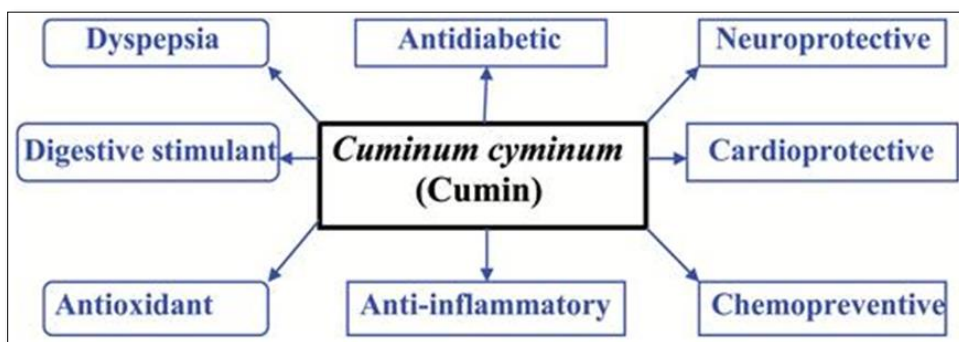


Figure 2. Cumin uses.

According to research reports cumin consumption significantly increase biliary flow rate. Cumin oil inhibit NF-B and mitogen-activated protein kinases, which lead to anti-inflammatory effects in LPS-stimulated RAW cells, showing that cumin oil has anti-inflammatory potential.

Ginger (fresh & dried)

Ginger, a member of the Zingiberaceae family, is an essential spice in Indian cuisine that not only enhances the

flavor of dishes but also has a number of health benefits. Ginger has been used for medical purposes against various ailments for more than 2500 years. Gingerols and shogaols are the primary phytochemical components of fresh and dried ginger, and they are responsible for a wide range of biological activities like anticancer, antibacterial, anti-inflammatory, anti-oxidant, and anti-allergic effects. Additionally, ginger has various active phyto-ingredients

that help with circulation and assimilation throughout the body, including gingerol, shogaol, paradol, and zerumbone.

Coriander (leaves & seeds)

Every Indian home has coriander, which is a common herb. The entire coriander plant can be eaten. Coriander's aromatic leaves and fruit (seed) are both often used ingredients in a variety of Indian recipes. The flavor of many meals can be improved by adding coriander seeds as a culinary spice. Coriander leaves are available in a variety of dishes, including chutney, soups, salads, and as a garnish. Without the use of coriander leaves, many Indian households feel that their dishes are incomplete. Let's talk about some fascinating information regarding this common herb. Because of its anti-inflammatory and antioxidant properties, coriander also helps to reduce brain inflammation. Additionally, it aids in reducing anxiety-related symptoms. Linalool and geranyl acetate, which have antioxidant, anti-inflammatory, and antibacterial properties, are abundant in the essential oil of coriander (*Coriandrum sativum* L.) [4]. According to a study, feeding Nile tilapia supplements of coriander seed powder and extract for 45 days improved their innate immune response and lessened the immunosuppressive effects of lead. The second most farmed fish in the world, tilapia has a 7% yearly growth rate. Due to motile aeromonas septicemia (MAS), which is brought on by *Aeromonas hydrophila*, tilapia farming suffers significant financial losses on a global scale.

Garlic

Garlic (*Allium sativum*) is a bulbous spice in the Amaryllidaceae family with a strong and spicy flavor. Since the sixth century BC, garlic has been regarded as a significant medicinal herb. Allicin (allyl 2-propenethio sulfinate or diallyl thiosulfinate), a naturally occurring sulfur-containing molecule, is the main bioactive component of fresh or crushed garlic.

Along with allicin, the phytochemicals ajoene, diallyl polysulfides, vinylidithiins, and S-allylcysteine also contain sulphur. Other sulfur-free compounds in garlic include saponins, flavonoids, lectins, polysaccharides (fructan), various enzymes, vitamin A, B, and C, minerals, and amino acids.

Garlic has an immunomodulatory impact on pre-eclamptic explants by increasing the synthesis of IL-10 in the healthy placenta and reducing the production of inflammatory cytokines like IL-6 and TNF-. At higher doses, overall effect is one of cytokine synthesis inhibition. Pathogens are directly affected by allicin, and its sulfur-containing constituents have antiviral effects that protect against viral respiratory infections.

In the majority of studies with garlic, the proposed mechanism of antiviral action of aqueous garlic extract was found to involve: direct inhibition of viral infection by

blocking entry of virus particles through disintegration of viral envelope and cell membrane, enhancing host immune response, and inhibiting viral replication by blocking the activity of polymerase enzyme. Additionally, frequent ingestion of raw or crushed garlic has demonstrated a significant influence on enhancing immune levels. Clinical studies also showed that supplementing with garlic extract reduced the severity of cold and flu-affected patients by modulating inflammation and immunity in obese adults, increasing production of NK and T cells, serum antioxidant concentration, and reducing inflammatory cytokine levels. Garlic was encouraged during the COVID-19 Pandemic as a preventative tactic to strengthen the immune system against COVID-19.

Clove

The dried flower buds known as cloves (*Syzygium aromaticum*) have a rich brown color, a powerful smell, and a bitter taste. They are part of the Myrtaceae family. In both savory and sweet cuisines in India, whole or ground clove is employed. Clove is largely recognized for its medicinal effects against various disease-causing parasites and bacteria because of its antiseptic and antibacterial qualities.

Clove extracts have been demonstrated to enhance humoral immune responses while inhibiting T cell cellular immunity. According to experimental data, clove causes immune induction reactions to shift in favour of modulatory and Th2 responses as well as cytokines that speed up humoral immunity. The primary bioactive component of cloves is eugenol, coupled with a number of other phenolic chemicals found in nature, including flavonoids (quercetin and kaempferol), hydroxybenzoic acids, hydroxycinnamic acids, and hydroxyphenyl propens.

According to an *in-vitro* research using the human dermal fibroblast system, clove essential oil's main active ingredient, eugenol, has anti-inflammatory qualities. Additionally, a research done *in-vivo* on BALB/c mice revealed that clove extract decreased macrophage production of IL-1 and IL-6, and the findings of this study were refuted in a study done *in vitro*. In addition, another ingredient, eugenin, which inhibited the viral DNA polymerase to prevent the viral DNA from being synthesized, was found to have antiviral efficacy against the herpes simplex virus. Because of this, making tea with two to three clove buds, cinnamon, and ground ginger has long been used in Indian homes as a natural cure to relieve cold, flu, and congestion symptoms.

Cinnamon

One of the most popular spices used as a flavoring agent worldwide is cinnamon bark, which is a member of the Lauraceae family of plants. Cinnamon is known to have anti-inflammatory qualities in addition to its traditional use as a spice. Chemically, cinnamon is made up of several

resinous substances, including cinnamaldehyde, eugenol, cinnamate, cinnamic acid, and a number of essential oils. Numerous tests, such as the carbon clearance test, cyclophosphamide-induced neutropenia, neutrophil adhesion test, influence on serum immunoglobulins, mice lethality test, and indirect hemagglutination test, were used to investigate the immunomodulatory effects of cinnamon bark. The findings demonstrated that cinnamon [5,6]. Bark reduced the death rate from *Pasteurella multocida* infection by 17% at a dosage of 100 mg/kg p.o. in a study.

increased the carbon clearance test's phagocytic index, improved neutrophil adhesion, and elevated serum immunoglobulin levels and antibody titers. In many inflammatory disorders, including asthma and probably in the severe phase of COVID-19 infection, the transcription factor NF- κ B, which is involved in the control of genes responsible for inflammation, is chronically active.

Cardamom

Natural killer cells' cytotoxic activity is markedly increased by cardamom extracts, suggesting they could possess anti-cancer qualities. Cardamom essential oil (EO) has a component that shows promise in treating acute campylobacteriosis and maybe preventing post-infectious morbidities.

Red chili powder

The high potassium content of red chilies aids in maintaining the flexibility of the blood vessels. They contain a unique chemical compound known as capsaicin. It promotes the release of vasodilators, which helps to maintain blood pressure stability. Improving blood flow and preserving cardiovascular health as a result. The main component of red chilies, capsaicin, has anti-inflammatory properties. If your joints or muscles are hurting, consume red chilly. Both pain and inflammation may be reduced by it. Red chilies are a strong source of vitamin C, which helps boost the body's defenses against infection.

Mustard seed

The small mustard seeds may help treat psoriasis, an autoimmune disease with a history of persistent inflammation. Studies carried out by a group of Chinese experts have demonstrated the effectiveness of mustard seed as a potential anti-inflammatory agent and as a component of psoriasis therapies in the future.

Turmeric

The ancient Ayurvedic root which is native to Southeast Asia and also called "Indian saffron" for its beautiful golden color. Turmeric contains a large number of bioactive compounds called curcuminoids that help deliver the revered botanical's vast health benefits-and its vibrant hue. Curcumin, the main and most well-known curcuminoid, has been utilized for its anti-inflammatory and antioxidant

properties. Turmeric supports immunological support, cognitive function, and heart health in particular by boosting antioxidant capacity and battling oxidative stress. By lowering pro-inflammatory indicators (such as ESR and CRP), curcumin's advantages for a healthy inflammatory response can support joint health and mobility. Through inactivating the transcription factor NF- κ B, curcumin can also suppress the production of a number of proinflammatory cytokines, including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines. Curiously, low doses of curcumin can boost antibody levels as well. Curcumin has been shown to have immunomodulatory properties in recent preclinical and clinical investigations. These properties are the consequence of curcumin's effects on immune cells and immune response mediators such as different T-lymphocyte subsets, dendritic cells, and multiple inflammatory cytokines. Autoantibodies [7]. Immune complexes deposited in various organs, the activation of autoreactive and inflammatory T cells, and elevated plasma proinflammatory cytokine levels are all characteristics of the inflammatory, chronic, autoimmune disease known as systemic lupus erythematosus (SLE). Dendritic cell numbers and activity, as well as T cell subsets including regulatory and T helper 1 (Th1) and Th17, have been reported to be considerably changed in SLE. Results from in vitro, experimental (pre-clinical), and clinical studies on the modulatory effects of curcumin on the number and function of dendritic cells and T cell subsets, as well as relevant cytokines involved in SLE responses.

Saffron

It is the purported immunoregulatory properties of saffron and its active derivatives, including crocin, crocetin, and safranal, have led to the use of *Crocus sativus* [8]. for a very long time as a food coloring, flavoring, and medicinal ingredient. Recent research has shown the effectiveness of saffron's active ingredients, which include the spice's anti-inflammatory and molecular mechanisms on the defensive qualities of the immune system as well. Additionally, saffron was shown to have favorable impacts on serum concentrations of the nuclear transcription factor B (NF- κ B) p65 unit, tumor necrosis factor alpha (TNF- α), interferon gamma (IFN- γ), and various interleukin (IL) molecules such as IL-1, IL-12, IL-6, and IL-17A. More than 150 volatile chemicals may be found in saffron stigmas, but crocin (C₄₄H₆₄O₂₄), picrocrocin (C₁₆H₂₆O₇), and safranal (C₁₀H₁₄O) are the main bioactive components that give saffron its distinctive colors, flavors, and aromas. The powerful antioxidant and radical-scavenging properties of saffron, which appear to primarily be attributed to crocetin and crocins, are undoubtedly connected to its anti-inflammatory potential. Saffron has been recommended as a medicinal herb to prevent the harm caused by neutrophil cells, which act as the main cells in acute inflammatory processes. Neutrophil numbers, motility, longevity, tissue

influx capability, and phagocytic activity all rise during inflammatory processes.

Tradition treatment by immune modulation principles

Numerous plant-based compounds that may have immunomodulatory effects have been discovered [9]. which can both explain and support their historical application in traditional medicine and serve as the foundation for future research. This review's objective is to highlight findings from investigations into the immunomodulators found in spices. Various plants identified in the Indian Ayurvedic system of medicine display a wealth of pharmacological properties. One of the oldest medical systems, ayurveda encompasses a number of ethnopharmacological practices, including adaptogenic, immunostimulating, tonic, neurostimulating, anti-aging, antibacterial, antiviral, anti-rheumatic, and anticancer treatments. Spices added in food not only increase the taste and flavor of food it also improves the immune status of the consumer where food also serve as medicine. These are natural compounds or combination of compounds in food that alters or modify both the CMI and HMI either adaptive or innate response.

Modern era of immune modulation

The immune system of the human body is capable of battling a variety of possible infections. Only when the host and the pathogen interact in a way that causes enough damage to throw off equilibrium does infection turn into disease. Immune modulation can be efficient and secure, as demonstrated by experience with passive antibody and cytokine therapy as well as immunization. One of the most well-known new cancer treatment options in the past ten years has been immunotherapy, which uses the patient's own immune system to eradicate tumor cells. Finding tumor- and patient-specific antigens to include in the vaccine is the key challenge for conventional cancer vaccines. The most active area of biomedical research now is cancer immunotherapy, with thoracic immuno-oncology as a pioneer. For both non-small-cell lung cancer and small-cell lung cancer, PD-(L)1 inhibitor is already a staple of first-line therapy. For an infection to be successfully resolved, immunological pathways must be stimulated in the proper way. It is equally crucial to stop the immune reaction once an illness has been treated because an overactive immune system might cause unchecked inflammation [10-12]. As immunomodulators, TLR agonists have already demonstrated promise. On the other hand, cationic-host defense (antimicrobial) peptides can control innate immunity and guard against infection without causing inflammation or even while decreasing it. Depending on whether they reduce or enhance the natural response brought on by the contact between the host and the microbe, substances that affect innate immunity may have unexpected or even contradictory effects on the host response. It is difficult to anticipate the behavior of innate immune modulators because of the myriad interconnected regulatory systems that make sure the immune response is

enough to eradicate the disease-causing bacteria and is then quickly shut off. According to past experience, innate immune manipulation can result in undesirable outcomes. TLR antagonists can cause autoimmune disorders in genetically susceptible animals.

Medicinal plants are abundant sources of bioactive phytochemicals, which have a variety of and frequently pleiotropic properties. These compounds can be used both therapeutically and as preventative nutraceuticals. Immunomodulators are plant-based nutraceuticals that have been identified as being of interest as immune system boosters, to combat infectious or exogenous injuries, immunosuppressors, to control the abnormal immune response occurring during autoimmune ailments, or as adjuvants that help by modifying nonimmune targets.

CONCLUSION

Evidence of foods' health benefits is accumulating quickly. Foods can regulate immunological processes that show up as either acquired immunity (T cell response, production of antibodies) or innate immunity (phagocytic activity, NK cell activity) This conclusion is considering the systematic nature of the findings that were presented earlier. Foods that boost immune system activity can help allergy or cancer sufferers feel more normal physically, as well as lower disease risk in healthy people. As a result, evaluating foods' capacity to modulate immunity and gauging innate vs acquired immunity are important.

REFERENCES

1. Chi X, Zhang H, Zhang S, Ma K (2020) Chinese herbal medicine for gout: A review of the clinical evidence and pharmacological mechanisms. *Chin Med* 15: 17.
2. Han X, Parker TL (2017) Anti-inflammatory activity of clove *Eugenia caryophyllata* essential oil in human dermal fibroblasts. *Pharm Biol* 55: 1619-1622.
3. Ishida M, Miyagawa F, Nishi K, Sugahara T (2022) Aqueous Extract from *Cuminum cyminum* L. Seed Alleviates Ovalbumin Induced Allergic Rhinitis in Mouse via Balancing of Helper T Cells. *Foods* 11: 3224.
4. Das S, Pradhan C, Pillai D (2023) Dietary coriander *Coriandrum sativum* L oil improves antioxidant and anti-inflammatory activity innate immune responses and resistance to *Aeromonas hydrophila* in *Nile tilapia* *Oreochromis niloticus*. *Fish Shellfish Immunol* 132: 108486.
5. Niphade SR, Asad M, Chandrakala GK, Toppo E, Deshmukh P (2009) Immunomodulatory activity of *Cinnamomum zeylanicum* bark. *Pharm Biol* 47: 1168-1173.
6. Ghasemi G, Fattahi M, Alirezalu A, Ghosta Y (2018) Antioxidant and antifungal activities of a new

- chemovar of cumin *Cuminum cyminum* L. Food Sci Biotechnol 28: 669-677.
7. Di Sotto A, Vitalone A, Di Giacomo S (2020) Plant-Derived Nutraceuticals and Immune System Modulation an Evidence Based Overview. Vaccines 8: 468.
 8. Khorasany AR, Hosseinzadeh H (2016) Therapeutic effects of saffron *Crocus sativus* L in digestive disorders: A review. Iran J Basic Med Sci 19: 455-469.
 9. Momtazi-Borojeni AA, Haftcheshmeh SM, Esmaeili SA, Johnston TP, Abdollahi E, et al (2018) Curcumin A natural modulator of immune cells in systemic lupus erythematosus. Autoimmun Rev 17: 125-135.
 10. Actor JK, Hwang SA, Kruzel ML (2009) Lactoferrin as a natural immune modulator. Curr Pharm Des 15: 1956-1973.
 11. Carr AC, Maggini S (2017) Vitamin C and Immune Function. Nutrients 9: 1211.
 12. Kaczanowska S, Joseph AM, Davila E (2013) TLR agonists: Our best frenemy in cancer immunotherapy. J Leukoc Biol 93: 847-863.