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Herbal Immunomodulators: A Powerful Preventive Weapon for COVID-19

Shobhit Prakash Srivastava [1], Saurav Yadav [1], Ratnesh Chaubey [1], Smriti Ojha [2], Ayush Chandra Mishra [1], Shalini Yadav [1], Sudhanshu Mishra [2,*]

[1] Dr. M. C. Saxena College of Pharmacy, Lucknow, Uttar Pradesh, India
[2] Department of Pharmaceutical Science & Technology Madan Mohan Malaviya University of Technology Gorakhpur, Uttar Pradesh, India
* Correspondence: msudhanshu22@gmail.com (S.M.);

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Abstract: The Corona Virus Disease of 2019 is characterized by a serious epidemic (COVID-19). The acute respiratory syndrome is caused by the coronavirus, which is followed by an inflammatory response in the host. Systemic inflammatory response syndrome (SIRS) is a condition in which the body causes acute breathing problems, multiple organ impairment disorder, and even in the early stages of multiple organ failure extreme COVID-19. Increased development of anti-inflammatory cytokines in the late stages of serious disease causes the immune system's reaction to becoming controlled, resulting in immune fatigue. Pandemics have wreaked havoc on humanity's strata, wiped out whole nations, and strengthening immunity is long overdue. A strong immune system is needed to fight a viral infection. Multivitamin-rich diets improve pathogen immunity by triggering immune responses in several immune cells, as an example. Various immune-stimulating herbs, plants, and spices like chicory, *Tinospora cordifolia*, *Withania somnifera*, myrrh, ginger, etc., must be included to counteract the pathogens.

Keywords: coronavirus; immunity; immune system; immune-modulatory; immune cells.

1. Introduction

Traditional systems of medicines have always played an essential role in meeting global needs. Ayurveda is one of the significant medicinal systems for curing health in the medieval period. Ayurveda has always played a vital role in pandemic situations for preventive care. In this pandemic situation, due to covid, immunomodulators have played an important role in preventative care. Herbal immunomodulators are products or derivatives that enhance the components of the immune system. The modulation of the immune system by various medicinal plant products has become the subject of scientific investigations currently worldwide [1]. COVID-19 is a kind of coronavirus disease belonging to the family Coronaviridae. A woman first reported the disease in Wuhan, China. The condition is spread by inhalation or close interaction with infected droplets that have an incubation period of a week to 15 days [2]. The initial infection of individuals was mostly linked to exposure to the seafood market in Wuhan. The Coronaviruses are enveloped, belonging to the category of positive-strand RNA viruses with the largest known RNA genomes. The coronaviruses are mostly spherical shaped, but being pleomorphic, they can change or modify themselves

according to environmental factors [3]. The Diagrammatic explanation of the pathogenesis of COVID-19 is depicted in figure 1, and its clinical presentation is depicted in figure 2.

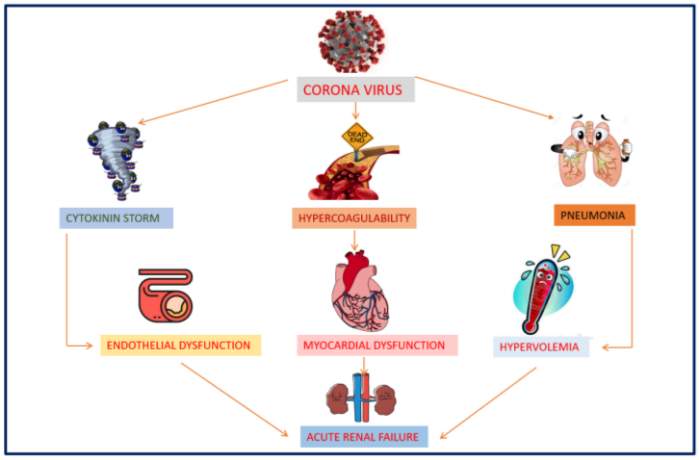

Figure 1. Diagrammatic explanation of pathogenesis of COVID-19.

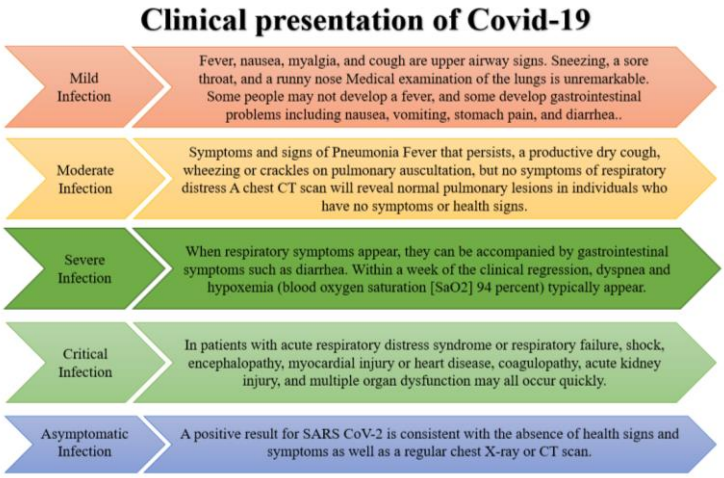

Figure 2. Clinical Representation Of COVID-19.

1.1. Immunity.

Immunity Can be defined as the power of the human body to resist any disturbance-causing element which may affect the body's integrity. The Immune system (Figure 3) is a collection of cells mediator chemical processing that has to occur to prevent the body from foreign antigens [4].

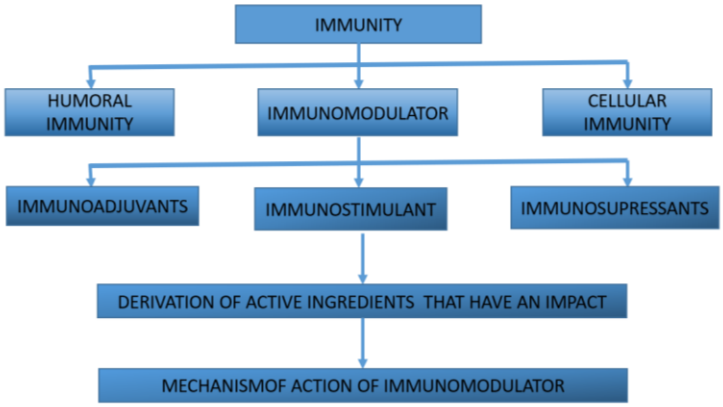

Figure 3. Diagrammatic representation of immunity and immunomodulator.

1.1.1. Innate Immune response.

It is the first-line defense mechanism against any external cellular, biochemical, physical component, or foreign matter [5].

1.1.2. Adaptive immune response.

It is developed due to the action of the innate immune system; it remembers the antibody released by the Innate immunity system against particular foreign material; it uses this information for future interaction [6].

1.1.3. Humoral immunity.

It is an antibody-induced response that occurs only when there is ingression of any foreign body. This is driven by ß cells lymphocytes [7].

1.1.4. Cell-mediated immunity.

It is an immune system that involves the activation of phagocytosis, antigen-specific cytotoxins, T-lymphocytes, and the release of cytokines [8]—figure 4 represents various types of immunity along with its mechanism of action.

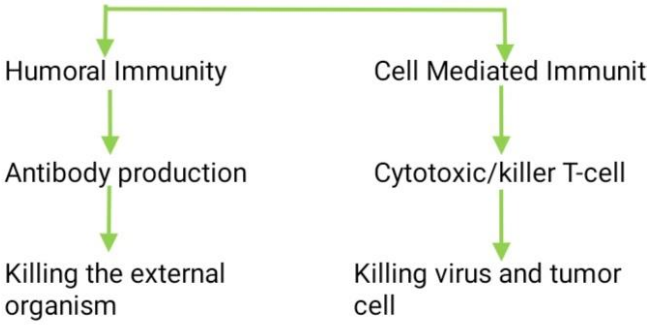

Figure 4. Immunity types and their mechanism.

1.2. Immunomodulators.

These biological substances can alter the various aspects of the immune system, including both adaptive and innate arms of the immune system (Figure 5) [9].

1.2.1. Immunosuppression.

These medicines can also be used to treat autoimmune diseases, graft rejection, graft versus host disease, hypersensitivity autoimmune diseases (both sudden and delayed), and immune pathology involved with infections [10].

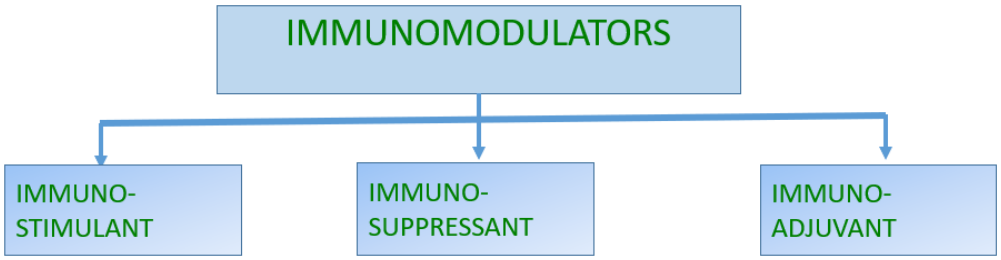

Figure 5. Types of Immunomodulators.

1.2.2. Immunostimulant.

The word immunostimulant refers to a prophylactic or therapeutic strategy for stimulating our non-specific immune system. This layer takes non-antigen-dependent stimulation of granulocytes, macrophages, complement, and natural killer (NK) cells' function and efficiency [10].

1.2.3. Immunoadjuvants.

Immunoadjuvants are used to improve the efficacy of vaccines and hence may be listed with basic immune stimulants. Immunoadjuvants can be genuine immune response modulators. They've been introduced as selectors between cellular and humoral helper T1 (Th1) and helper T2 (Th2) cells, immune-protective, immune-destructive, and regain [immunoglobulin E (IgE)] versus IgG type immune responses, pose a real challenge to vaccine designers [11].

2. Etiology of COVID-19

Coronavirus is named from the throne spikes on the virus's outer surface. Coronaviruses are tiny (65-125 nm in size) and contain single-stranded RNA with a length of 26 to 32 kilobases (kb) as their nucleic content [12]. The aim is to track down the intermediate host responsible for the coronavirus's transmission to humans. The virus's origins must be identified to aid in identifying the zoonotic propagation pattern. SARS-CoV-2 has high virulence factors and variability [13,14]. Attachment, penetration, biosynthesis, maturation, and release are the five steps in the virus's life cycle with the host. Viruses invade host cells via endocytosis or membrane fusion after linking to host receptors (attachment) (penetration). Viral RNA joins the nucleus for replication after the viral contents are released within the host cells. Viral proteins are made from viral mRNA (biosynthesis). Then, after maturation, new viral particles are created and distributed. Spike (S), membrane (M), envelop (E), and nucleocapsid (N) are the four structural proteins found in Coronaviruses (N) [15]. It could be passed from person to person through droplets and touch. The COVID-19 virus's dominant receptor is ACE2. Within the host cell, the spike protein (S protein) on COVID-19's surface is pinched and binds to the ACE2 receptor. Furin, absent in SARS-CoV, is present in the host cell and plays a critical role in allowing the virus to penetrate [16,17]. The virus then begins to spread with a small innate immune response, which can be identified using nasal swabs. The virus then spreads to the respiratory tract, which is met with a more powerful innate immune response. An endogenous response cytokine may be indicative of the eventual clinical path at this point when the condition is clinically manifest [18].

Since there is no authorized treatment or vaccine for COVID-19, the immune system is the first line of protection since it supports the body's innate capacity to fight pathogens (such as viruses, microbes, fungi, protozoa, and worms) and prevent infections. Infections like COVID-19 go untreated as long as the immune system functions normally [19].

3. Description of Various Herbal Approaches as an Immunomodulator

An herbal immunomodulator (Table 1) is a substance that promotes and demotes the components of the immune system, involving both humoral and cellular immune responses. The modulator potentiates your immune system's fighters by preparing them to fight against

any threat they may encounter. When our system is ready to fight, the attackers have no time to build strength against immunity.

3.1. Tinospora Cordifolia.

Research on natural immunomodulators and their consequences for curing various diseases linked to the immune system has been growing interest in the last few years. Among all the natural immunomodulators, *Tinospora Cordifolia* is well known in Hindi Giloy and commonly as Amrita and Guduchi is one plant with many characteristics. This GILOY is a member of the family *Menispermaceae*, rich in source of alkaloids and terpenes involving 70 genera and 450 species that are ground in tropical lowland regions. Individual body parts of plants have been utilized to isolate active components such as alkaloids, steroids, diterpenoids, lactones, aliphatic, and glycosides [20]. Apart from these constituents, it is also the inception of some micronutrients like copper, calcium, iron, zinc, phosphorus, and manganese [21]. Their active components like Cardifolioside-A, Magnoflorine, Tinocordiside, N-Methyl-Pyrrolidone, and Syringin have been recorded to have a potential immunomodulator action by the outcome of boosting the phagocytic activity of killing cells [22].

Table 1. Various plant parts with their pharmacological action.

S.NO.	Plant Parts	Pharmacological Action
1.	STEM	Stimulate bile juice, jaundice, urinary disease,
2.	BARK	Anti-spasmodic, Anti-pyretic. Anti-allergic, Anti-neoplastic.
3.	ROOT	Antioxidant.
4.	STEM JUICE	Diabetes, Dyspepsia, vaginal and urethral discharge.

3.2. Withania Somnifera.

Withania somnifera is a plant described in the indigenous system of medicine, namely Ayurveda Unani Siddha and Tibetan medicine. It belongs to a family called Solanaceae and is commonly known as ashwagandha means horse-like order. As a Rasayana herb, the decoction and extracts of the herb show excellent immunomodulatory activity by non-specific activation of macrophages, granulocytes, complement systems, natural killer cells, and lymphocytes [23]. It can also source the production of various effecter molecules generated by activated cells (para-immunity) and protects against different pathogens, including bacteria, fungi, viruses, etc. Withania extract opposes hypersensitivity reactions and enhances the phagocytic activity of macrophages. It also modulates cell-mediated immune responses by increasing the replication of lymphocytes and bone marrow cells in responses to mitogens [24].

3.3. Cichorium Intybus.

North-western Europe is home to a large population of the plant Cichorium Intybus, also known as chicory. Inulin, a water-soluble fiber found in abundance in chicory roots, has an immunomodulatory impact. In some processed and functional meals, chicory inulin, which cannot be digested, can be utilized in place of dietary fat or sugar. Food may have fewer calories if inulin is used instead of sugar or fat. In France and Japan, chicory root is also frequently used to make a bitter coffee substitute [25,26]. Chicory contains various nutrients, including carbohydrates, proteins, vitamins, minerals, soluble fiber, trace elements, and bioactive phenolic compounds, which are responsible for the plant's nutritional, prophylactic, and therapeutic properties. Chicory plants include inulin, coumarins, tannins, monomeric flavonoids, and sesquiterpene lactones, among other phytoconstituents. The phenolic extract

of the chicory plant has shown an increase in humoral and macrophage immunity components in the state of immunosuppression caused by an external agent, and dry chicory extract has a good effect on sending mediated immunity; it also increases phagocytic activity of peritoneal macrophages which plays an important role in immunity when administered in a ratio of 30 mg/kg [27].

3.4. Myristica Fragrans.

Myristica Fragrans, popularly known as "Nutmeg" is a seed or ground spice of several spices of the genus myristica. Acharyas have been used for the treatment of various disorders in that native eastern regions. Is obtained from seeds of the plant *Myristica fragransis* of the family Myristicaceaea. Its plant bears seeds, and said seeds are ground into a powder commonly referred to as Nutmeg. It is widely found in Sri Lanka and India. Nutmeg seeds have been used in traditional medicine systems as a general toxin and nervous system stimulant, but also for the treatment of paralysis, respiratory ailments, and sickness or for improving the libido, appetite, and blood circulation; it also bears the properties of being a stomachic and carminative agent [28].

The lignans present in fresh Nutmeg have immune-modulatory properties. These properties are found in cell-free systems and protect the PUC18 plasmid against radiation that induces DNA damage. In response to the polyclonal T cell, the mammalian spleen cells trigger the cell-mediated as well as humoral immunity. The increase in activation of induced cell death by mace lignans depended on the dosage. Mace lignans protect splenocytes against radiations and external pathogens. The increased internal activated immunity will fight against external factors [28].

3.5. Moringa Oleifera.

Herbal remedies have long been acknowledged as naturally occurring compounds with pharmacotherapy and nutritious properties that help prevent illness in humans [29]. *Moringa oleifera* a perennial tree well known as the miracle tree belongs to the Moringaceae family native to India and is popularly known as the "drumstick" or "horseradish" tree. *Moringa oleifera* is ingested for its nutritive benefits and healing properties [30]. Phytoconstituents in *Moringa oleifera* include glucosinolates, flavonoids, ellagic acid, and kaempferol, which have pharmacological and nutritional properties that help humans avoid and manage the disease [31]. The ethanolic *M. oleifera* leaf extract has enhanced cellular and humoral immunity, indicating that *Moringa oleifera* has immunomodulatory properties [32]. Apart from this immunomodulatory action, it also does possess anti-inflammatory, anti-oxidative, and anti-cancerous properties.

3.6. Panax Ginseng.

Ginseng is a plant belonging to the family Araliaceae and the genus Panax with the formal name of Panax ginseng C. A. Meyer, and it is also known as a gem of traditional herbal medicine resources as the "King of Herbs." Since the medieval period. Ginseng contains two significant compounds: ginsenosides and gintonin. Ginsenoside is the essential chemical found in ginseng herbs and is frequently employed in the pharmacological study of ginseng's effects, which range from its traditional role as a nourishing stimulant to its usage as an anticancer reagent [33]. The following factors help in modifying the immune system. 20-S-

protopanaxatriol, an intestinal metabolite of steroidal ginseng saponins, activates cell-mediated immunity against the external pathogen [34]. Ginsenoside Rh2 has been reported in several studies for anticancer power. It induces apoptosis through caspase-like proteases activation by using the Bcl-2-insensitive signaling pathway. Another factor is called Ginsenoside Rh1, and Rh2, isolated from ginseng's root, showed anti-proliferative action in the NIH 3T3 fibroblast cell lines through the inhibition of phospholipase [35].

3.7. Allium sativum.

The plants belonging to the family Allium are generally known for producing organosulfur compounds, which consist of various biological and pharmacological properties. The plants of the family Allium 'The Garlic (*Allium sativum*) are most widely used for their pharmacological action, such as beneficial effects against various microbial infections and cardioprotective, anticarcerfenic, and anti-inflammatory activity. Herbal plants like garlic and others are generally used as immunomodulators as health promoters are gaining increasing attention from consumers and scientific circles. Some plants exhibit immunomodulatory action like modulation of cytokine secretion, phagocytosis promotion, activating macrophages, production of immunoglobulin, allergic reaction, and lymphocyte proliferation. Garlic has been suggested as a promising agent for maintaining homeostasis and as an immunomodulating agent [36].

3.8. Zingiber Officinale.

The rhizome of Ginger that is *Zingiber Officinale* is one of the most used species of Zingiberaceae, also known as the ginger family. Ginger is commonly used for headaches, nausea, rheumatism, and colds. Ginger contains various active constituents and active ingredients. The steam distillation method extracts ginger oil with a high quantity of sesquiterpene hydrocarbon. The pungent compound is majorly active in gingerols, which are further converted into shagaols, zingerone, and paradol. The compound which is responsible for characteristic taste is 6-gingerol [37]. Ginger is one of the most effective herbal immunomodulators. In the study, it was found that ginger inhibits lymphocyte proliferation, it was due to a reduction in IL-2 and IL-10 production. The aqueous extract increased IL-2beta, IL-6, and TNF- alpha in macrophages, splenocyte proliferation, and cytokine production. On the consumption of the ginger diet for 12 weeks, it is observed that there is a significant increase in hematocrit, hemoglobin, erythrocyte, MCH, MHCH, WBC value, and neutrophils percentage in the body. Ginger also increased the humoral and cell-mediated immunity in suppressed mice [38]. The following table no 2.0 include various herbal plant with their pharmacological potential.

Table 2. Various herbal plants with their various active constituents along with their pharmacological actions.

S. No.	Herbal Plant And Spices	Botanical Plant Name	Family	Active Constituents	Pharmacological Property
1.	Gudhal	*Hibiscus rosa-sinensis L.*	Malvaceae	Citric acid, Ascorbic acid, Malic acid, Tartaric acid.	Anti-fertility, anti-diabetic, antipyretic, fibrinolytic.
2.	Satavari	*Asparagus racemsus wild.*	Liliaceae	Asparagamine, steroidal saponins, mucilage, flavones.	Anti-ulcer, antioxidant, anti-diabetic, anti-diarrhoeal.
3.	Musli safed	*Chlorophytum borivilianum.*	Asparagaceae	Saponins, sapogenins, carbohydrates.	Immunosuppressant, revitalizer, myelosuppression.

S. No.	Herbal Plant And Spices	Botanical Plant Name	Family	Active Constituents	Pharmacological Property
4.	Papita	*Carica papaya*	Caricaceae	Papain, tocopnerol,	Anti-fungal, anti-bacterial, anti-hypertensive.
5.	Gritkumari	*Aloe barbadensis.*	Asphodelaceae	Glucomannan, hemicellulose, pectins, polysaccharides.	Anti-fungal, anticancer, anti-inflammatory, moistening agent, anti-scar.
6.	Lotus	*Nelumbo nucifera.*	Nelumbonacea e	Ferulic acid, protocatechuic acid, p-coumaric acid, isoschaftoside.	Diuretic, Antipyretic, anti-ischemic, hypoglycemic.
7.	Genda	*Calendula officinalis.*	Asteraceae	Triterpendiol esters, saponins, flavonoids.	Bactericide, antiseptic, anti-inflammatory, anti-fungal, anthelmintic.
8.	Wolfs bane	*Arnica montana*	Asteraceae	2,5-dimethoxy-p-cymine, thymol-methyl- ether, cumene, decanal.	Anti-inflammatory, anti-aches, immunostimulants, anti-bruise.
9.	Coneflower	*Echinacea purpurea*	Asteraceae	Alkamide, chlorogenic acid, caffeic acid, caftaric acid.	anti-fungal, anti-bacterial, anti-oxidant.
10.	Jatamasi	*Nardostachys jatamasi*	Caprifoliaceae	Sesquiterpenes, coumarins, jatamansone, veraranone.	Anti-convulsant, hypotensive, anti-parkinsonism.
11.	Tulsi	*Ocimum tenuiflorum. tenuiflorum*	Lamiaceae	Eugenol, 1-hydroxy-2-methoxy-4-allylbenzene.	Antioxidant, anti-diabetic, gastric disorder, antibiotic, anti-malarial, auto-immunomodulatory.
12.	Clove	*Syzygium aromaticum*	Mirtaceae	Eugenol, Kaempferol, Quecertin, Galiic acid	Antioxidant, antimicrobial, lauricidal agents
13.	Fenugreek	*Trigonella foenum-graecum*	Leguminacea e	Sapogenins, Nicotinic acid, Mucilage	Antidiabetic, hypocholestrolemic,an ti-cancer
14.	Coriander	*Coriandrum sativum*	Umbillife-rae	Essential oil, Caffeic acid, Linalool	Hyperlipidemia, liver disease, antihypertensive, anti-fertility
15.	Fennel	*Foeniculum vulgare*	Aplaceae	Volatile oil, Flavonoid, phenolic compounds, fatty acid, amino acids	Anti-viral, antipyretic, anti-spasmodic, anti-tumor, memory-enhancing property
16.	Turmeric	*Curcuma longa*	Zingiberaceae	Curcuminoids, curcumin, bisdemethoxycurcum in	Heart disease, arthritis, Alzheimer's disease, gastrointestinal disorder
17.	Cinnamon	*Cinnamomum verum*	Lauraceae	Cinnamaldehyde, eugenol, camphor	Immunomodulator, Cardio-protective, Antioxidant
18.	Bay leaf	*Laurus nobilis*	Lauracea	Linalool, Methyl chavicol, Anthocyanins, Eugenols	Anti-oxidant, Immunostimulant, Anti-fungal, Analgesic
19.	Asafoetid a	*Ferula assa-foetida*	Umbilliferae	Glucuronic acid, Sesquiterpene, Coumarins, Fervlic acid	Diuretic, Asthma, Anti-diabetic, Anti-spasmodic
20.	Liquor ice	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizin, Glabra A and B, Isoflavones	Anti-bacterial, Anti-inflammatory, Anti-oxidant, Anti-diabetic
21.	Saffron	*Crocus sativus*	Iridaceae	Crocin, Safranal, Anthocyanins	Anti-depressant, Anti-obesity, Neuroprotective, Cardioprotective
22.	Nutmeg	Myristica fragrans	Myristicaceae	Terpinol, geraniol, and linalool	Antioxidant, Immuno-modulatory, Radio-protective, Anti-carcinogenic, hepatoprotective, Anti-inflammatory.
23.	Myrrh	Burseraceae	Torchwoods	Volatile oil (Myrrhol), Resin (Myrrhin), Gum	Antimicrobial, Antiseptic, Anti-heeling, Antithrombotic activity.

4. Conclusions

The article's central idea is to review the immunomodulatory action of specified traditional herbs, spices, or drugs that have been discussed and mentioned. Patients and their families can use these herbs or spices to boost their immunity power. The utilization of

numerous plant or spice extract and herbal additives in a particular dose while the vaccination may be supportive in obtaining greater therapeutic effect and preserving antibodies in opposition to various infection or infective agents, including manufacturing and developing a greater immune response for prevention from various ailments. Some botanical products have an application due to their greater therapeutic efficacy, low toxicity, and low economic input.

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Conflicts of Interest

The authors declare no conflict of interest.

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