IMMUNOPROPHYLACTIC PLANT BASED MEDICINES AS NATURAL ALTERNATIVES FOR PREVENTION OF COVID-19

Ms Kritika Sachan[1], Dr Anupam Sachan[2], Dr Sachin Tyagi [3]

1. Assistant Professor, Institute of Pharmacy, PSIT, Kanpur.

2. Professor & Director, Dayanand Dinanath College, Institute of Pharmacy, Ramaipur, Kanpur

3. Professor & Director, Bharat Institute of Technology, School of Pharmacy Meerut.

Abstract:

COVID-19 has been declared pandemic, globally, it is clear that none of food or dietary supplement is more important than social distancing and practicing good hygiene practices, to get ourselves protected from COVID-19. Natural herbal immune-boosters carrying the potential to fight viral infections in the form of herbal supplements are known for their immune-boosting potential. Some of the major herbal immune-boosters are need to be discussed at this point of time. Some herbs can act well in strengthening the immunity on prolonged and regular use. Some formulations have been found to alter some modules of immune function; their inclusion in any form in daily life can play vital role to enhance immunity to the point where we are better protected against diseases. A review has been done on the herbs carrying immune-promoter prospective.

Keywords: COVID 19, HERBAL, IMMUNOPROPHYLACTIC, IMMUNOBOOSTERS, ALTERNATES, DIET.

INTRODUCTION:

With the onset of COVID-19 pandemic, globally, it is clear that none of food or dietary supplement is more important than practicing good hygiene practices, following social distancing to get ourselves safe from COVID-19. Strong immune system decreases chances of viral infection and flu, and can lessen the frequency of pandemic infections. Taking a diet containing leafy vegetables and fruits, regular exercise, proper sleep are some of the important factors to

strengthen up immunity. Coronaviruses are a family of viruses that interact at multiple levels with host cells, using its some of the cellular machineries for replication. By consuming nutritious foods and other supplements, it is possible to boosten up the immunity of body. Our immunity comprises assortment of cells,that protects our body against microbes, like viruses, bacteria etc. [1] Keeping immune system active, by adopting healthy lifestyle choices by wise intake of nutritious foods, getting ample amount of sleep and exercise. Certain vitamins, enzymes, botanicals can surge immune response and can work against various infective agents. These supplements should be selected carefully, as they are matter of concern for people with certain health issues. A viral disease produces acute respiratory distress syndrome as different disorders. [2]. Pandemic viruses are the most common viruses as Influenza viruses and coronaviruses *e.g*., H5N1, H1N1, severe acute respiratory coronavirus, which are potentially lethal pathogens, viable for lung injury and death due to mild to moderate respiratory illness. The coronavirus particles are organized with long RNA polymers tightly packed into the center of the particle, and surrounded by a protective capsid, which is a lattice of repeated protein molecules referred to as coat or capsid proteins. In coronavirus, these proteins are called nucleocapsid (N).[3] To date, four protein receptors have been characterized as main receptor for coronavirus binding to host cells: several members of the Alpha corona virus genus are known to bind to amino peptidase N (APN, CD13) of their respective host species, using an RBD located in the CTD of the S protein.[4] The symptoms are Cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache, loss of taste or smell, Sore throat, Congestion or runny nose, Nausea or vomiting, Diarrhea etc. [5]COVID-19 virus spreads in form of cough, sneeze or droplets of saliva. People with medical problems or co-morbidities like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more prone to develop illness, as in that case, immunity already I weakened. It is posing a big threat to public health on International level. [6] Almost all virus infections cause the recruitment and activation of inflammatory cell types — particularly macrophages and, in some infections, neutrophils — that in turn release a range of molecules that induce tissue damage or malfunction. These include cytotoxic cytokines, cationic proteins, lipid mediators, metalloproteinase and components of the oxygen burst. The reactive oxygen species that accumulate in the mitochondria may further contribute to tissue damage. [7] Studies have shown that vitamin C may avert the vulnerability of respiratory tract infections [8], while COVID-19 may cause respiratory infection of lower tract. Therefore,

vitamin C inclusion in moderate amount may be a way to prevent COVID-19. [9, 10] Antioxidants present in foodstuffs play important role as health-promoters. Herbal immunoboosters carry the potential to fight viral infections in the form of supplements, are known for their immunogenic potential, some of the major herbal immunoboosters as in figure 1, and are discussed in this mini-review.

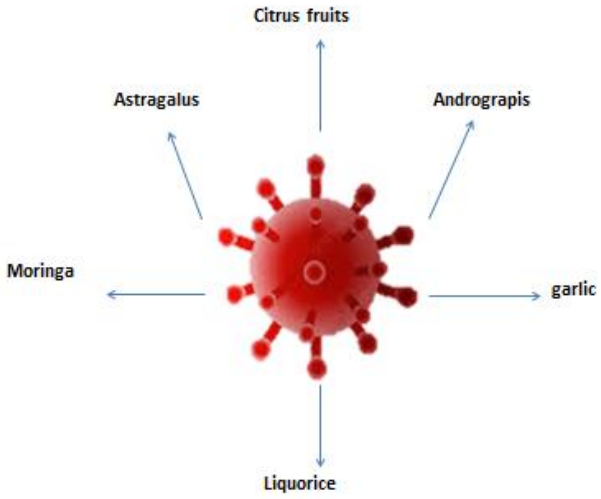

Figure 1 commonly used Herbal Immunoboosters

Material & Methods:

A review is attempted to pertain significant knowledge about Natural herbal immune-boosters, commonly available, carrying the power to fight viral infections in the form of herbal dietary supplements are known for their immune-boosting potential, with the help of data bases or Academic libraries as PubMed, Scopus, Web of Science, Medline, etc , with the help of keywords as COVID 19, HERBAL, IMMUNOPROPHYLACTIC, IMMUNOBOOSTERS, ALTERNATES, DIET from a time-period range of 2000-2020.Some of the major herbal immune-boosters need to be discussed at this point of time. An inclusion of these herbs in any form in our daily life can make a difference.

Citrus fruits: Vitamin C, an essential vitamin, obtained from citrus fruits, as in figure 2 is an essential vitamin , perform many roles for impressive health benefits. It is water-soluble vitamin

present in oranges, strawberries, kiwi fruit etc. [11] the recommended daily intake for vitamin C is 75 mg for women and 90 mg for men. Its deficiency lowers immunity against certain microbes while an adequate amount endows it. Vitamin C acts as a powerful antioxidant by protecting against oxidative stress, caused by free radicals.[12]Vitamin C is a cofactor, required by many enzymes, it also reduces the common cold, duration and severity caused in upper respiratory tract infections, as main indications of COVID-19.[13] Intravenous vitamin C treatment improves viral infections generated sepsis and acute respiratory distress syndrome.[14,15]Vitamin C supports cellular functions of both the innate and adaptive immune system.[16] It accumulates in phagocytic cells and increases chemo taxis, phagocytosis. By enhancing immunity, it causes multiple benefits as:

- Sinks dangers of chronic disease.
- Lowers elevated blood pressure.
- Decreases probability of heart disease.
- Reduces levels of uric acid in blood.
- Prevent gout attacks.
- Helps to cure iron deficiency.
- Enhances immunogenicity.
- Shields memory.[17,18]

Many marketed preparations like Fasten up, Vitamin C with citrus fruits, Doctor's Best, Vitamin C with Q-C and Natural Orange Flavor are available with active extracts of Citrus fruits.

Astragalus: Astragalus is a herb commonly used since ancient ages in form of traditional medicine. Animal researches have proved about its extract efficiency in immune-related responses. It is rich in polysaccharides as APS, the main active extract from *Astragalus membranaceus*, used as an immunomodulatory as provides immune-boosting effects. It is used to treat a wide variety of ailments as allergies and the common cold. It plays pivotal role in the enhancement of innate immune response and the production of cytokines. Four active flavonoids like calycosin-7-O-β-d-glucoside, ononin, calycosin and formononetin provide good effects. Many marketed preparations like Nature's Answer, Astragalus, 500 mg, Now Foods, Astragalus extract, 500 mg are available with extracts of Astragalus [19,20,21]

Garlic: Garlic has powerful anti-inflammatory and antiviral properties. Garlic is a healthy food that may have some antimicrobial properties. It supports the functioning of the immune system by stimulating certain cell types as macrophages, lymphocytes, and eosinophils by modulation of phagocytosis, and macrophage activation. It enhances immune health by stimulating white blood cells like NK cells and macrophages. γ-glutamyl cysteine derivatives are initial precursors of allin and allyl methyl cysteine, which are precursors of many sulphur rich compounds as asajoene, dithiin and fructans.[22,23] It enhances anti-SRBC and anti-BA antibody production.[24,25,26,27,28]

Andrographis: This herb possesses andrographolide, a terpenoid with anti-viral properties against respiratory disease, caused by viruses as enterovirus D68 and influenza A. They are rich in immunoregulatory activities. In autoimmune cases, it produces antigen-specific tolerance and thus prevents detrimental autoimmune responses. It proves that andrographolide can have various effects in different immune disease models.[29,30,31,32]

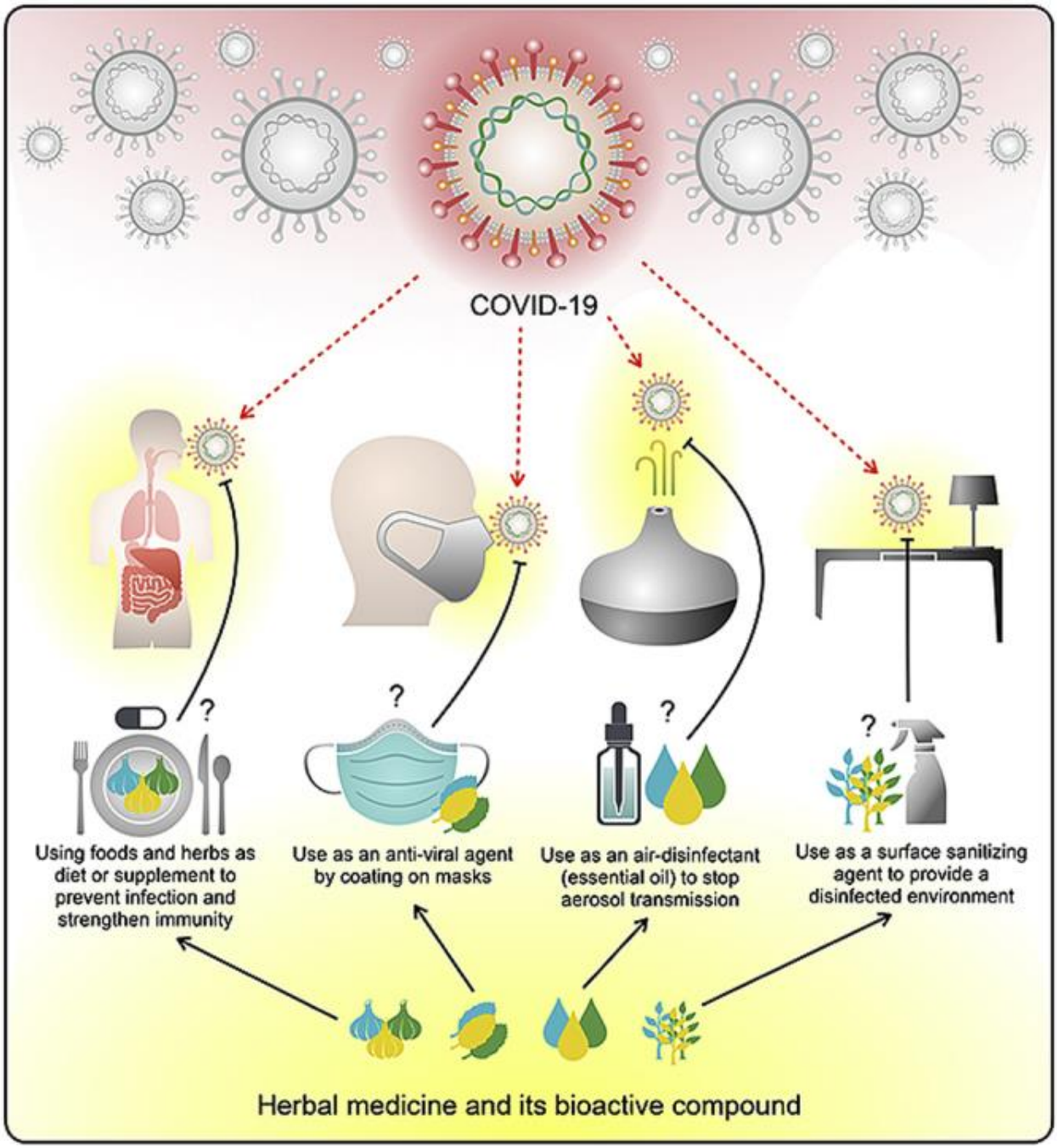

Figure:2 Illustrating herbal medicines and its bioactive compounds.

Liquorice: Liquorice constitutes glycyrrhizin, that may help protect against viral infections. According to test-tube research, glycyrrhizin is active against severe acute respiratory syndrome-related coronavirus. As per study published in Lancet, licorice contains many substances, including glycyrrhizin, a saponins based derivative that may help against viral infections.

Glycyrrhizin, an active component present in roots of Liquorice , is effective in inhibition of replication of SARS-associated Coronavirus. [33]Isoflavones like glabridin, hispaglabridin A and 4-O-methylglabridin present as active phytoconstituents present in Glycyrrhiza glabra were found to have antioxidant activity. Recently,α-dihydro- 3,5,4-trihydroxy-4,5-diiodopentenylstilbene, in form of dehydrostilbene derivatives have been isolated as free radical scavengers.[34,35]

Pelargonium sidoides: Its extract is used for treatment of symptoms of acute viral respiratory infections, as of common cold and bronchitis. It prevents bacterial adherence to cells, helps fight viruses and stimulates the immune system against invaders. Secretory immunoglobulin A production in saliva by and interleukin-15 in the nasal mucosa by its extract is observed. Gallic acid and other phenolic compounds are the active constituents responsible for the antiviral effects of it. Phenolic compounds and coumarins exert immunomodulatory effects due to a combination of umckalin and its derivatives. [35,36,37]

Curcumin: Curcumin is the main resin in turmeric. It is a combination of three molecules, together called curcuminoids, is present in major amount in form of curcumin as 60–70%, demethoxycurcumin, 20–27% and bisdemethoxycurcumin is 10–15%. Other active components of turmeric are resin based sesquiterpenes, diterpenes and triterpenoids.[38]It is potent immunomodulator that can modulate the activation of T cells, B cells, macrophages and neutrophils. It also down regulate the expression of various proinflammatory cytokines including TNF, IL-1, IL-2.α-turmerone and ar-turmerone,are two compounds isolated from the lipid based fraction of *Curcuma longa*, used to initiate cytokine production.[39,40]
Curcumin exhibits antiviral properties against dengue and hepatitis C virus. It prohibits proliferation of B-cell lymphoma cells via down-regulation of c-MYC and modulate the activation of T cells, B cells, macrophages, neutrophils.[41,42,43]. It prohibits proliferation of B-cell lymphoma cells via down-regulation of c-MYC. [44,45,46,47]

Echinacea: Echinacea, is a genus of plants of daisy family. Certain species have been shown to improve immune health and may have antiviral effects against several respiratory viruses as respiratory syncytial virus and rhinoviruses. Research shows that its extract increases the number of white blood cells, which fight infections and shortens the duration and severity of colds and

other upper respiratory infections. It reduces the severity and duration of the symptoms in Common cold and upper respiratory tract infections.[48,49,50,51]

Tulsi: It not only works on improving immunity but even improve the rate of formation of new blood cells. Its drops, mainly containing some important terpenes are used to fight with various kinds of infections, fever, cold, cough, flu and for detoxification of body. Tulsi , exhibit broad-spectrum antimicrobial activity, which include activity against a wide range of pathogens, suggests that it can be used as a hand sanitizer, mouthwash and water purifier. The ability of its extract to protect against the damaging effects of various toxic substances has been documented in numerous earlier works.[52,53,54]

Withania: Fayaz Malik et al.investigated the effects of graded doses of aqueous alcoholic (1:1) root extract of Withania somnifera, on the immune system of mice. Mice were administrated its extract orally for 15 days, which stimulated cell mediated immunity, revealing IgM and IgG titers reaching peak value with 30 mg/kg.The extract, induced type 1 immunity because it guided enhanced expression of T helper cells, cytokines interferon and interleukin. Withanolides-A, a major constituent significantly increased the levels of Th1 cytokines. The studies suggested that it supports predominantly Th1 immunity with increase in macrophage functions. [55,56,57]

Cinnamon: A study on rats reported that the administration of the bark powder of Cinnamon for 90 days produced antioxidant activities with respect to cardiac and hepatic antioxidant enzymes, lipid conjugate dienes. A research stated that cinnamon oil potentially exhibits superoxide-dismutase like activity as indicated by the inhibition of pyrogallol autoxidation. Different flavonoids isolated from cinnamon possess free-radical-scavenging activities and antioxidant properties. A study of the inhibitory effects of cinnamaldehyde and other compounds of cinnamon revealed that it possesses anti-oxidant potential. Various extracts of cinnamon, such as ether, aqueous, and methanolic extracts exert antioxidant activities.[58,59,60]

Asparagus: shatavarin, an active constituent of Asparagus stimulated immune cell proliferation and IgG secretion. It stimulated interleukin production and inhibited production of IL-6. It also had strong modulatory effects on Th1/Th2 cytokine profile, indicating its potential suitability for treatments as immunotherapies. [61, 62, 63]

Tinospora:. Commonly known as Guduchi or Giloy, has been a part for centuries in the Ayurvedic and Unani systems of the medicine. T. cordifolia extract contains many constituents such as alkaloids, steroids, glycosides, and polysaccharides . It has been shown to possess immunomodulatory properties. [64,65] Dry stem crude extract of it contains a polyclonal B cell mitogen, G1-4A. In order to explore the possibility of using partially purified immunomodulatory to modulate radiation induced immunosuppression, the antioxidant effect of constituents from this plant was examined against reactive oxygen and nitrogen species generated by photosensitization or by peroxynitrite.[66,67]

Emblica: E. officinalis fruit, contains emblicanin, glycosides, proanthocyanidins,Vitamin C, tannins and flavonoids. Amla have very powerful immunomodulatory, antioxidant activities. Poly-herbal formulation, "ProImmu" which also contains E. officinalis including Ocimum sanctum, Tinospora cordifolia and Withania somnifera, has been reported as immunomodulatory drug. It inhibits chromium-induced free radical production, and restored the antioxidant status back to control level. It even restored the IL-2 and gamma-IFN production.[68]

Moringa: Moringa peregrine , its leaves ethanolic extracts possess potent compounds effects on T cell-mediated immunity and possess potent compounds effects on the cellular and humoral immunity.[69]

In the worldwide search for a response to the COVID-19 pandemic, news about "alternative remedies against COVID" have been disseminated. [71]

Laurus nobilis L. – Lauraceae (Berries/Leaves)

Indications in the context of respiratory conditions. Laurus nobilis is used to treat respiratory infections. Chemical composition. Berries: essential oil (β-ocimene and 1,8-cineole as the main components); sterols (e.g., β-sitosterol); flavonoids (cyanidin 3-O-glucoside and cyanidin 3-O-rutinoside, as the major anthocyanins) Leaves: essential oil (1,8-cineole and a-terpinyl acetate as the major compounds) Further phytochemical investigations of laurel leaves led to the isolation of sesquiterpene lactones, alkaloids, glycosylated flavonoids, and monoterpene and germacrane alcohols. [72]

Posology (based on traditional uses). The only dosage information on L. nobilis is given by the American Pharmaceutical Association: 1–2 tablespoons leaf/cup water and 3 times/day or 1–2 drops of essential oil added to honey, or tea. Preclinical evidence. This species has not been experimentally proven for respiratory disease. The closest experiment is an in vitro study examining SARS-CoV and the effect of several essential oils. The authors reported that a distilled oil extracted from Laurus nobilis berries was an effective virucidal against SARS-CoV. This essential oil also contained eremanthin and dehydrocostus lactone as minor constituents at 3.65% and 7.57%, respectively. These compounds are somewhat unusual in essential oils, but at least one in vitro study found that dehydrocostus lactone had activity against the hepatitis B virus, an enveloped DNA virus. [73] The essential oil of L. nobilis has also been evaluated for its antinociceptive and anti-inflammatory activities in mice and rats. The essential oil exhibited a significant analgesic effect in tail-flick and formalin tests, a dose-dependent anti-inflammatory effect in formalin-induced edema, and a moderate sedative effect at the anti-inflammatory doses.[74]

Clinical evidence. This species has not been trialed clinically for respiratory disease. Overall, the clinical evidence is Low.

Safety. There is not enough reliable information about the safety of taking L. nobilis leaves and berries. As L. nobilis has been used as food since ancient times, overall, it can be considered safe in the recommended doses. Therefore, safety is High.

Overall assessment. Laurus nobilis profile and chemistry fit as an anti-inflammatory therapy in the context of upper respiratory affections. Therefore, this herbal medicine could be useful in the relief of respiratory symptoms through exerting anti-viral and anti-inflammatory effects on the respiratory tract. The clinical evidence is Low. This herbal medicine is considered presenting High safety.

Silybum marianum L. Gaertn. - Asteraceae (Fruits)
Indications in the context of respiratory conditions. *Silybum marianum* is indicated for symptoms of respiratory disease, namely fever, and catarrh. [75]
Chemical composition. Flavonolignans such as silymarin, silybin, isosilybin and taxifolin (1.5–3.0%) are the main components reported for *S. marianum*

Posology (based on traditional uses). It is preferable to use a commercial preparation with a defined composition and an adequate dose.

Preclinical evidence. *Silybum marianum* has not been experimentally proven for symptoms of respiratory disease. Silybin, the main flavonolignan from the seed of *S. marianum*, has demonstrated an anti-inflammatory activity by inhibiting the spontaneous and LPS-stimulated NF-kB activation as well as the production of inflammatory cytokines. [76]
Clinical evidence. *Silybum marianum* has not been trialed clinically for respiratory diseases. Overall, the clinical evidence is Low.
Safety. At high doses, mild laxative effect, as well as mild allergic reactions, have been reported [77], besides dry mouth, nausea, upset stomach, gastric irritation or headache. A preparation containing 7%–8% silymarin appeared to be safe for up to 41 months of use . Overall, safety is High.
Specific warnings and precautions of use. None.

Overall assessment. Although *S. marianum* is not clinically proven to provide symptomatic relief of flu symptoms, it could be useful in the relief of respiratory symptoms by exerting a systemic anti-inflammatory effect. The clinical evidence is Low. This herbal medicine is considered presenting High safety. [78]
Pimpinella anisum preparations have been trialed clinically for asthma. The bronchodilator activity of *P. anisum* was evaluated in a study involving 50 patients presenting bronchial asthma. The patients ingested tea (2 g in 200 ml of water), twice a day for 40 days. All patients presented a reduction of cough episodes after 21 days of treatment (from more than 6 episodes/day to none), as well as dyspnea and wheezing. Also, an improvement in the breath-holding time and respiratory rate was observed. Overall, the clinical evidence is High for asthma-related cough and Low for cough and fever.[79]
Safety. In the traditional doses, there is no report about the toxicity of *P. anisum*. However, allergic reactions can occur, for example, rhinoconjunctivitis). Overall, safety is High. [80]
Many foods and herbs are known to display antiviral and immunomodulatory activities. Aloe vera, Angelica gigas (Korean angelica), Astragalus membranaceus (Mongolian milkvetch), Ganoderma lucidum (lingzhi mushroom), Panax ginseng (ginseng), and Scutellaria baicalensis (Chinese skullcap) have been reported to exhibit immunomodulatory properties. [81] Their

activities are based on selectively stimulating cytokines, activating lymphocytes, increasing natural killer cell counts, and enhancing macrophage actions. Rice bran, wheat bran, Lawsonia alba (hina), Echinacea purpurea (eastern purple coneflower), Plumbago zeylanica (Ceylon leadwort), and Cissampelos pareira Linn (velvetleaf) also exhibit immunomodulatory properties by stimulating phagocytosis. Eucalyptus essential oil is reported to improve the innate cell-mediated immune response that can be used as an immunoregulatory agent against infectious diseases. [82] Collectively, using these immunomodulatory foods and herbs could enhance the immune system and protect the body against COVID-19. However, these observations must be verified through scientific or clinical studies.

Conclusion:

Coronavirus can be treated using nutrition; for instance, treating influenza with very large amounts of vitamin C has been practiced for decades. The common cold, SARS-CoV-1, and SARS-CoV-2 fall under the same coronavirus family; hence, are regarded as the same viral type. By including these natural alternatives in our diet we can have an immunoprophylactic effect and this will help in achieving a healthy immune system. Many people are concerned about maintaining a healthy immune system. Doing so can benefit our body and boost our defenses against viruses, bacteria, and other microbes. The immune system is precisely about a system. To function well, it requires balance and harmony among it. Our first line of defense is to choose a healthy lifestyle with good-health guidelines in order for naturally keeping immune system strong and healthy. Every part of body, including immune system, functions better when protected from environmental assaults. Some preparations have been found to modulate immune function, their prolonged use can booster immunity and we are better protected against infectious diseases. An inclusion of above discussed herbs can play an important role in strengthening the immunity on prolonged and regular use. Some preparations have been found to alter some components of immune function, their prolonged use can booster immunity to the point where we are better protected against infection and diseases. Various formulations are being developed globally from these natural substances, for instance a natural immune boosters developed from licorice having anti oxidant activity and being used as a natural Sweetener under the trade name DIABMAG was developed, patented and marketed by a start up Diabport Healthcare private

limited. They have assessed the efficacy of this natural formulations in large group of people through a trial in park, and from the feedback obtained in the form of questionnaire, it was observed that according to 78% people preferred the taste of this powder formulation developed named DiabMag was sweet and smoothing, also these kind of formulations are found to have immune stimulant action as well. [83] Immunomodulators may both stimulate or suppress the immune system by inhibiting and/or increasing the synthesis and release of pro-inflammatory mediators, including cytokines and eicosanoids. There is preclinical evidence of increased IL-1B and/or IL-18 production in infected immune cells by the use of Sambucus nigra L., polysaccharide-rich extracts from medicinal mushrooms, Echinacea angustifolia DC. and Echinacea purpurea L. arabinogalactans-rich extracts, and plant extracts or food supplements rich in Vitamin D. [84] Even though herbal remedies may seem harmless, if misused, they could increase a person's risk for COVID-19. We may find that certain herbs are effective in preventing and treating COVID-19 for some people, however, there currently is not enough data regarding the use of herbal remedies for the novel coronavirus. According to the World Health Organization, there are no medicines that have been shown to prevent or cure COVID-19. The abundance of plant species documented for the prevention and treatment of COVID-19 is a major indication of the potential that exists locally, so long as the scientific procedure is added to the indigenous knowledge. Furthermore, additional research on the sustainable use and conservation of medicinal species is highly suggested. Finally, pharmacological, phytochemical, and toxicological investigations on medicinal plant species with possible anti-COVID-19 effects are carried out for laboratory validation of the ancestral uses of these plants and to obtain the traditional medicines bios. A combination of natural products or herbal mixtures with validated anti-COVID-19 drugs may constitute a promising preventive and therapeutic alternative but should be assessed.

Future scope:

With the shadow of the COVID-19 pandemic, world ushered in the new decade. It has affected several business and has affected the entire economy. Focusing on the coronavirus pandemic and analysis of every aspect has become important. Human life is affected with significant impact on

the immune response involving reaction of mind and human body. Immunology in research, since its core area is the immune system, which is the main pathological basis of various diseases. The Immunodeficiency disorders are going to increase day by day and on the other due to urbanization the medicinal herbs are becoming endangered. Therefore it is need of the current as well as the future times to stay fit, fine and include all the natural immunity boosters in our daily life.

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