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REPORTED HERBAL IMMUNOMODULATORS FOR BETTER HEALTH : AN OVERVIEW

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ABSTRACT

Currently there is much growing interest in the use of various medicinal plants as modulators of the complex immune system. A wide range of health-care practices is required to exploit the beneficial effects of Ayurveda, which is the most ancient system of medicines. Being the essence of herbal medicines, Indian medicinal plants manifest miraculous effects in curing a vast range of diseases and disorders among humans and can be better called as "elixirs of life. Through a number of vast researches conducted in the area, it is being explored that many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides, lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties. Keeping in mind, the tremendous potential of the medicinal plants and their derived drugs, herewith introducing this review with a purpose to globally popularize the Indian herbal medicinal plants as immunomodulatory action.

KEYWORDS: Immunomodulators; Herbal Plants; Immunosuppressor.

INTRODUCTION

Biological products of animals and plants sources have been used by human for thousands of years either in the pure forms or crude extracts to treat many diseases. Herbs are used as bases of medicine in many ways in human beings in their life. Research interest has focused on various herbs that possess immune-stimulating properties as a useful feature in helping

diminish the risk of cancer. In different herbs, a wide-ranging of phytochemicals, have been identified such as the flavonoids, lignans, terpenoids, polyphenolics, sulfides, saponins, carotenoids, curcumins, plant sterols and phthalides. Several of these phytochemicals either inhibit nitrosation or the formation of DNA stimulate the activity of protective enzymes such as the phase II enzyme glutathione transferase. Many of plants contain potent antioxidant compounds that provide significant protection against chronic diseases. These compounds may defend LDL cholesterol from oxidation, inhibit cyclooxygenase and lipoxygenase enzymes, prevent lipid peroxidation, or have antitumor activity.[1-3]

It is an evident from the human history that medicinal plants have been the treatment regimen to cure a variety of diseases, including diseases caused by insects, fungi, bacteria, and viruses. The effects shown by the plants are due to the chemicals present in them and they work in the same manner as the conventional drugs. However, there are equally chances for these plants to have some potential harmful and toxic effects also. These undesired side effects can be reduced by processing of the plant's crude product. Ethnobotany is the study of traditional plants for their medicinal properties and is an effective method to discover future medicines. According to 2015-16 data, more than 300 plants have been identified to have therapeutic potential.[4]

Around 122 chemicals derived from plants have been identified as therapeutic substances which are also used in commercial drugs, for example, bark of willow tree is very rich in salicylic acid, which is also an active metabolite of aspirin, and this bark has been used from ancient times as a pain killer and antipyretic substance.[5] Some of the drugs which are frequently used by the physicians are also derived from plant sources, for example, aspirin, digoxin, quinine and opium, etc.[5] They have a long history of use as herbal drug. Currently, there is much growing interest to use these medicinal plants as modulators of the complex immune system. Through a number of researches conducted in the area have explored that many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides,[6] lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties.[6]

IMMUNITY

The term immunity defines body's natural defense system against a vast array of diseases and disorders. Remarkably sophisticated and advanced among vertebrates, the complex immune system is capable to generate a limitless variety of cells and molecules to arrest enormous

spectrum of infections and undesirable substances. Immunomodulators refer to those substances capable of inducing, amplifying, and inhibiting any component or phase of the immune system. Immunostimulators and immunosuppressant are two types of immunomodulators are known for use. In fact, immunopharmacology is a newer branch of pharmacology concerned with immunomodulators.[7] Administration of immunostimulators as in the case of AIDS and use of immunosuppressor in cases of an exaggerated response of an immune system is appreciating to reconstitute the normal immune system and increase the longevity of life. Immunomodulator intake along with antigen, the process is meant to boost the immune system, and the modulator is known as immune adjuvant.[8] The two ways of defense of an immune mechanism involving short-term mechanism which is the first line of defense and the other highly advanced adaptive immune response marked by complexity, diversity, and memory.[9] An adaptive immune response also consists of two subtypes of immune responses, humoral immune response concerned with β-lymphocytes and cell-mediated cytotoxic response mediated by T-cells.[9] Well, all the component cells of the immune system originate from bone marrow through hematopoiesis from bone marrow-derived stem cells. They are either develop into mature cells or migrate to other peripheral sites for migration.[9] Besides a vast range of specialized cells of immune cells, certain molecules called cytokines which are one of the important mediators of the immune system mediate the cross talk between the specialized cells of the immune system, thereby completely integrating the behavior and action responses of the cells.[10]

CYTOKINE MODULATION CAUSED BY HERBAL PLANTS

Through a number of in vitro and in vivo studies conducted to see the effect of the herbal medicine on cytokines have shown that they influence a large number of multiple cytokines. By nature, cytokines are a group of soluble extracellular proteins or glycoproteins in the form of interleukins (ILs), interferons, chemokines, etc., and are crucial to both innate and acquired types of immunity. These cytokines through intermolecular cross talks maintain physiological stability through their secretions in all nucleated cells through inducible response to some injury.[10] In fact, it is evident from knowledge of the medical literature of various diseases that these disease conditions are in connect with cytokine secretions. In diseases of the central nervous system, these cytokines have a predominant role as in the variety of psychiatric disorders, and abnormal secretions of these chemicals have been demonstrated. Various neurochemicals, neuroendocrine, and neuroimmune substances have appeared at the command of cytokines. Their role has been marked in cases of depression,[11] Alzheimer's

disease,[12] and schizophrenia;[13] various behavioral shifts, positive and negative emotions, stress, infection, etc., have all been demonstrated to stimulate cytokine secretion.[14]

All these hurdles in the way of therapeutic protocol make a challenge for cytokines. Adverse effects produced and experienced among the patients made us consider phytotherapy in modifying the cytokine expression. Plants such as Astragalus membranaceus also known as "spleen chi tonic" is a Chinese plant used in various diseases and wasting state of the body. The root extract of the plant was found to lower IL-6 in in vitro human model.[15] IL-6 is inflammatory and impending deterioration marker.[17] Very well-known plant of garlic or Allium sativum used in most of the Indian houses is found to lower IL-1 and IL-6, acting as anti-inflammatory, hypocholesterolemic, antioxidant, and also angiotensin-converting enzyme inhibitor.[16] It has great potential as anti-inflammatory due to an inhibitory effect on IL-1, IL-6, TNF, IL-8 and boosting effect on IL-10 which is an antagonist to pro-inflammatory cytokines.[16] Besides anti-inflammatory, it also manifests antimicrobial potential. Garlic use has been suggested in inflammatory bowel diseases. Its use is also indicated in Alzheimer's disease due to IL-10 modulation. Spelman et al. have reported in his review, immunomodulatory activity of more than 18 herbal plants including Acanthopanax gracilistylus, A. sativum, Ananas comosus, Cissampelos sympodials, Coriolus versicolor, Curcuma longa, Tinospora cordifolia, and Withania somnifera.[17] Aloe vera, a very popular plant which grows in arid climate, is claimed to have wound and burn healing properties due to its anti-inflammatory nature. It has been found to reduce TNF-α and IL-6 in various animal models.[18]

EFFECT OF MEDICINAL PLANTS ON INNATE AND ACQUIRED IMMUNE COMPONENTS

Various herbal medicines have been found to modulate various components of innate and acquired immune system. In fact, based on proper understanding of various immunomodulatory activities of herbal plants, plants derived the secondary metabolites in natural products can be the lead molecules for the future development of immunomodulators for therapeutic use. Various immunomodulators have been suggested in various allergic diseases including asthma, allergic rhinitis, and eosinophilic esophagitis on the basis of experiments performed on various animal models.

EFFECT ON ACQUIRED IMMUNE SYSTEM

Patil et al. explained that ethanolic extract of Ficus carica produces stimulatory effect on humoral and cell-mediated immune response in experimental animals and suggested its therapeutic use in immunological disorders.[19] Chlorophytum borivilianum root extract, an effective immunomodulatory, not only potentiates non-specific immune response but also improves humoral as well as cell-mediated immunity. It may use in infection condition, enhancement of immunological response against foreign particles or antigens, and improving defensive response under normal circumstances.[20] Ethanoic extract and aqueous extract of Picrorhiza kurroa have the ability to stimulate humoral response by acting various level of immune mechanism such as antibody production, release of mediators of hypersensitivity reactions, and tissue responses to these mediators in the target organs.[21]

1. Reishi (*Ganoderma tsugae*, *G. lucidum*, *G. curtisii*, *G. martinicense*, Ganodermataceae)

Parts Used: Mushroom fruiting body.

Preparations: Long decoction, syrup, preserved concoction.

Herbal Actions: Immune tonic, Immunomodulator, Antiviral, Antibacterial, Adaptogen, Anti-inflammatory, Antioxidant, Anti-anxiety, Cardiotonic, Hepatic.

Known as the ‘mushroom of immortality’, reishi is an herbal immune tonic and *immunomodulator*. Taken regularly, it can enhance and fine-tune the body’s immune response. It’s especially helpful as a daily remedy for those who have weak lungs or who frequently succumb to respiratory infections. It strengthens the circulatory system and is a legendary adaptogen, making it a supreme ally for increasing overall resilience. Reishi is also a traditional tonic for anxiety and can help impart calmness in a slow and sustained manner.

Reishi is better prepared as a tea than a tincture, as some of its medicinal properties are destroyed by high percentages of alcohol. Simmer the mushrooms for a few hours to fully extract its polysaccharide compounds, which are the active immunomodulation compounds. Its flavor is slightly bitter, so I like combining it with pleasant-tasting herbs like astragalus (*Astragalus propinquus*), licorice (*Glycyrrhiza glabra*)*, and cinnamon (*Cinnamomum verum*) —it's particularly delicious in herbal chai blends. I also add a handful or two of dried reishi slices to bone or vegetable broth when I have a pot simmering. Reishi can be purchased online or at local health food stores, cultivated at home, or gathered from the wild. There are a number of medicinal species in the genus. We use our local hemlock reishi (*Ganoderma tsugae*) and artist's conk (*Ganoderma applanatum*). If you'd like to try foraging this mushroom, please research which *Ganoderma* species grows near you—and if they've been used medicinally—along with referencing a good mushroom field guide or reliable online source.[21-25]

2. Elderberry (*Sambucus nigra* var. *canadensis* and *S. nigra*, Adoxaceae)

Parts Used: Berries and flowers

Preparations: Syrup, tincture, infusion (flowers), decoction (berries), infused honey

Herbal Actions:

Berries: Immune stimulant, Immune tonic, Antibacterial, Antiviral, Antioxidant, Diaphoretic, Anticatarrhal Anti-inflammatory.

Flowers: Immune tonic, Antiviral Anti-inflammatory, Diaphoretic, Anticatarrhal (decongestant), Astringent.

The berries of elder are one of our most treasured immune tonics—they are effective, nourishing, and delicious when prepared as a dark purple syrup. Taken daily throughout the fall and winter, elderberry offers us protection against colds, flu, and other viral infections.

One *study* demonstrated elderberry's antimicrobial effects against two strains of the influenza virus and several bacteria that are commonly responsible for secondary, or concomitant, sinus infections with the flu.

And in the case of an illness, elderberry is immune stimulating, diaphoretic (helps to break a fever), and anticatarrhal (decreases mucus in the respiratory passages). Studies show a lessening in the duration and severity of cold *symptoms* as well as the *flu*.

I prepare elderberry syrup by combining equal parts elderberry tincture, elderberry tea, and elderberry-infused honey. Children love this remedy, which can be made alcohol-free if you prefer (you can substitute a vinegar extraction for the alcohol-based tincture). Doses can be liberal (by the tablespoon), several times per day. Do not give elderberry honey or syrup containing the honey to babies younger than one-year-old.

Elder flowers also demonstrate strong antiviral activity against influenza, and can be integrated into your elderberry syrup along with other immune-boosting herbs like cinnamon (*Cinnamomum verum*) and ginger (*Zingiber officinale*). Curious to see a step-by-step demonstration on making herbal syrups? Visit our *video tutorial* and download our *syrup guide*!

Dried elderberries can be purchased online from sources like *Mountain Rose Herbs*, and fresh, frozen elderberries can be purchased from organic farms (you'll need to do an online search for these). However, elder is also a classic garden-grown medicinal and forageable herb. If you plan to forage elder from the wild, you will need to do some serious botanical detective work. There are several deadly poisonous look-alikes, including water hemlock (*Cicuta* spp.).[26-27]

3.Garlic (*Allium sativum*, Amaryllidaceae)
Parts Used: Bulb
Preparations: Raw, tincture, fire cider and other infused vinegars, honey
Herbal Actions: Immune tonic, Immune stimulant, Antimicrobial, Diaphoretic, Hypotensive (lowers blood pressure) Anticatarrhal (decongestant).

This beloved spice has been used medicinally for over 5,000 years; one of the first accounts of its use was to sustain the health of the Egyptian laborers who built the pyramids.[1] Later, it

was a powerful field remedy in World War I, saving thousands of lives and limbs through its infection-fighting capabilities.[2]

Garlic is an essential staple in my kitchen as a potent immune system tonic and antimicrobial herb. It can be highly effective in preventing infections such as the common cold and flu, as well as infections of the digestive tract. The volatile oils in garlic are excreted through the lungs, making it especially beneficial for infections of the respiratory system. One randomized controlled *study* showed that garlic reduced the incidence of common cold. Here's a *review* of garlic's demonstrated activity against various pathogenic bacteria, fungi, and protozoans.

Our family prepares a special garlic sauce every week made of raw garlic, extra-virgin olive oil, sea salt, and nutritional yeast. The sauce goes on avocado toast, eggs, pasta, chili, soup, baked potatoes, you name it. We keep it in the refrigerator (important, as garlic oil can harbor botulism and has made people sick) and literally pull it out at every meal. Our family of three goes through a quart a week and we rarely catch colds.

Garlic is easy to add to the diet as a culinary herb, and I always save my garlic skins to toss into broths. The suggested daily dosage is one clove per day, added to food. My favorite garlicky preparation is fire cider—a sweet and spicy tonic made with apple cider vinegar. I recommend trying our ruby-red recipe for *Hibiscus Pomegranate Fire Cider*. To fully capitalize on garlic's antimicrobial and blood thinning qualities, it should be eaten raw.

Contraindications: Garlic can aggravate heartburn and gas, especially if ingested raw or in large quantities. It can also aggravate peptic ulcers. Coating garlic with olive oil or preparing it in an oil-based sauce helps minimize these effects. Avoid high doses of raw garlic one week before surgery due to its blood-thinning qualities. If taking blood thinners, consult a cardiologist before taking high doses of raw garlic.

Garlic is a superfood, used to treat numerous health-related issues. The pungent-smelling herb, found in almost every kitchen has antimicrobial, antibiotic, and anti-inflammatory properties. Ginger contains compounds that increase the number of white blood cells in the body, which kills foreign bacteria and virus. You can increase the amount of garlic in your food to uplift your immune system.[28-29]

4.Astragalus (*Astragalus propinquus*, Fabaceae [formerly *Astragalus membranaceus*])

Parts Used: Root.

Preparations: Decoction, powder, soup and stew stock, goo balls

Herbal Action: Immunetonic, Immunomodulator, Antiviral, Antibacterial, Adaptogen, Antioxidant, Cardiotonic Hepatic, Astragalus has become a renowned tonic in Western herbalism over the past two decades, primarily for its adaptogenic and tonic immune qualities. Scientific studies.

because demonstrate that astragalus regulates white blood cell (immune cell) activity and stimulates our natural killer cells (NK cells) to present a strong front against pathogens. Astragalus has also demonstrated increased interferon production (an antiviral and immune-signaling agent produced by the body).

Astragalus is best used as a daily remedy to build immune strength—its medicine is slow and sustained, with full benefits reached after weeks of daily ingestion. In Traditional Chinese Medicine, astragalus augments the *Wei Qi*, which can be likened to a protective sphere, shielding the body from harmful external pathogens.

Because astragalus is a food herb, it's safe to take relatively large amounts regularly. I love adding a handful to broth, integrating the fine-flavored root into herbal chai, and mixing the powder into goo balls, cookies, and other treats. Tincture is not recommended because alcohol doesn't optimally extract astragalus' immune-enhancing polysaccharides. These polysaccharides are water soluble and more readily extracted with prolonged decoctions or simmering.

Astragalus root has a sweet, beany flavor (it is in the legume, or bean, family, after all), making it easy to sneak into the diets of picky eaters, including kids. Toss a few of the pressed roots (these look like tongue depressors, and are pictured above) into any simmering stew, soup, or sauce, and it will impart only the tiniest of flavor imprints! The roots can be pulled out of the dish, much as you would pull out a bay leaf, right before serving.

Contraindications: Because astragalus stimulates immune activity, it could potentially weaken the effects of immunosuppressive pharmaceuticals, such as cyclosporine and corticosteroids. This adverse reaction is theoretical in humans but has been verified in animal studies. In high doses (30 grams or more) and via injection, astragalus has caused itching and allergic skin reactions. Symptoms of overdose may include headaches, insomnia, dizziness, hot flashes, and hypertension.[30-31]

5. Turkey Tail (Trametes versicolor, Polyporaceae)

Parts Used: Mushroom fruiting body.

Preparations: Long decoction, soup stock.

Herbal Actions: Immune tonic, Immune stimulant, Antiviral, Antitumor, Antioxidant.

Turkey tail is a medicinal mushroom and immune tonic par excellence, with significant antiviral and immune-balancing qualities.[5] It's beneficial for anyone who wants to prime their immune system, but especially for those who experience general immune weakness or frequent upper respiratory infections. In addition to boosting immunity, some herbalists believe turkey tail enhances the effects of antimicrobial herbs.[6] Turkey tail is a foundational herb for supporting the immune system in alternative cancer therapy and prevention.[7]

Like other medicinal mushrooms, turkey tail is best taken as a decoction or added to broth blends. Again, this is a perfect time to incorporate the warming flavors of chai. Turkey tail is mildly bitter—combine it with other medicinal mushrooms that are pleasant in flavor, such as shiitake (Lentinula edodes), maitake (Grifola frondosa), or lion's mane (Hericium erinaceus).

I make an herbal broth over the winter that contains astragalus, reishi (just a little, so it's not too bitter), shiitake, turkey tail, calendula (Calendula officinalis), and seaweed. We add the broth to soups, stews, and marinades, and my picky daughter doesn't notice the herbal flavor.

However, her immune system certainly takes note!

Turkey tail is one of the most common woodland mushrooms in the world—it's likely growing near you! It can be found exclusively on dead hardwood trees, stumps, and branches (and sometimes on dead conifers).

Turkey tail does have some look-alikes, and proper identification is essential. That being said, many people successfully learn to know and recognize turkey tail. Its fruiting body is fan-shaped—bearing a likeness to a turkey's opened tail feathers—with colored bands of blue, brown, red, gray, and white. Its undersides are white or tan in color and spotted with tiny pores (NOT gills). False turkey tail mushrooms (Stereum spp.) have a matte, tawny underside with no visible pores.[32-33]

6.Giloy

Giloy is a versatile herb used to make Ayurvedic medicines for a long time. It helps to remove toxins from the body, purifies the blood and fights disease-causing bacteria. Giloy contains anti-oxidant properties that improve health, boosts immunity and digestion. Mix 15-30 ml of Giloy juice in a glass of water and consume it on an empty stomach in the morning.[34-35]

7. Chia Seeds

The small chia seeds are rich in antioxidants and omega-3 fatty acids, which is beneficial for enhancing immunity. It also reduces inflammation and regulates inflammatory responses in the body. You can make chia seeds pudding to increase your intake.

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8.Pumpkin seeds

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Loaded with zinc, iron and vitamin E, pumpkin seeds are good for boosting the immune function. Pumpkin seeds also have anti-fungal and anti-viral properties. It helps in cell growth, improves your mood and is even better for quality sleep. Sprinkle some pumpkin seeds on your salad to reap its amazing health benefits.[38-39]

9.Sunflower seeds

Sunflower seeds are a rich source of vitamin E and nutrients. The small crunchy seeds contain selenium which helps to body fight certain type of cancer and helps to build your immunity. The antioxidant and vitamin E in the sunflower seeds fight free radicals and are even good for your skin. Add it in your salad or oatmeal.[40-41]

10.Turmeric

The bright yellow-spice is common in Indian cuisine as well as treating numerous health ailments. Curcumin, which is the main compound of turmeric has immunity-boosting potential. The compound activates white blood cells in the body, which in turn enhances its an antibody response[42-43]

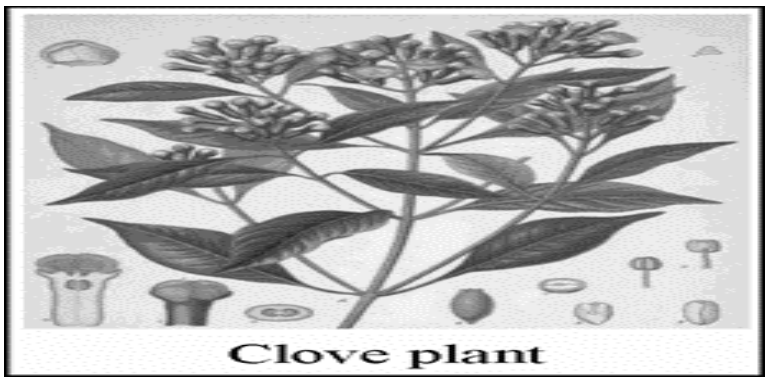
11.Cinnamon

Cinnamon has also been used for its medicinal properties for thousands of years. It fights inflammation, ward of infection and heals damaged tissues. Cinnamon is high in immune-boosting antioxidants, have anti-diabetic effects and even help to cut the risk of heart disease.[44-45]

12.Clove

Cloves (Syzygium aromaticum) are one of the most loved and well-utilized spices in the entire world. Its distinct sweet and spicy aroma lends dishes and pastries a unique depth in flavor that you can pinpoint once you take a bite.

But while cloves are usually relished for their taste and fragrance, they are also packed with vitamins, minerals and other nutrients that are absolutely essential for the body.



Cloves are the dried flower buds of the Syzygium aromaticum tree, an evergreen that grows up to about 30 feet. Its name originates from the Latin word “clavus,” which means “nail,” because of the shaft and head that it closely resembles. Syzygium aromaticum trees usually grow in warm and humid climates, typically in Indonesia, Sri Lanka and Brazil. In the current

trade of cloves, Tanzania leads the market, producing about 80 percent of the world's clove supply.

Like other spices, the story of how cloves were distributed throughout the world spans over hundreds of years, starting with the establishment of the trade routes. Together with pepper, cinnamon and hazelnut, cloves were one of the spices that were highly sought-after in both Europe and the Americas, especially by noblemen. These four spices were known to be the "Big Four" because of their rarity and value.

In the Moluccas, or the Spice Islands, clove spice trees were used to represent the lives of each child born into a family, an important symbolism that reflected their children's survival. When the Portuguese and the Dutch learned of the existence of spices, they sought to control the monopoly of the trade. This led to the Dutch burning down clove trees to raise its price, which then triggered to numerous wars and battles against the locals.

However, the high demand for the spice eventually died down once the spices were successfully cultivated in other parts of the world.5While cloves are now easily available in the market and doesn't require the thousand-mile journey to reach our shores, it remains to be one of the most expensive spices in the world, placing fourth behind saffron, vanilla and cardamom. Because of its numerous health benefits and medicinal uses, it's a wise decision to invest in a small container of cloves to use for your food and in your home.[46-47]

13- Tulsi

Tulsi is an aromatic shrub in the basil family Lamiaceae (tribe ocimeae) that is thought to have originated in north central India and now grows native throughout the eastern world tropics.[48] Within Ayurveda, tulsi is known as "The Incomparable One," "Mother Medicine of Nature" and "The Queen of Herbs," and is revered as an "elixir of life" that is without equal for both its medicinal and spiritual properties.[49] Within India, tulsi has been adopted into spiritual rituals and lifestyle practices that provide a vast array of health benefits that are just beginning to be confirmed by modern science. This emerging science on tulsi, which reinforces ancient Ayurvedic wisdom, suggests that tulsi is a tonic for the body, mind and spirit that offers solutions to many modern day health problems.

Tulsi is perhaps one of the best examples of Ayurveda's holistic lifestyle approach to health. Tulsi tastes hot and bitter and is said to penetrate the deep tissues, dry tissue secretions and

normalize kapha and vata. Daily consumption of tulsi is said to prevent disease, promote general health, wellbeing and longevity and assist in dealing with the stresses of daily life. Tulsi is also credited with giving luster to the complexion, sweetness to the voice and fostering beauty, intelligence, stamina and a calm emotional disposition.[49-52] In addition to these health-promoting properties, tulsi is recommended as a treatment for a range of conditions including anxiety, cough, asthma, diarrhea, fever, dysentery, arthritis, eye diseases, otalgia, indigestion, hiccups, vomiting, gastric, cardiac and genitourinary disorders, back pain, skin diseases.

Considered as a potent adaptogen, tulsi has a unique combination of pharmacological actions that promote wellbeing and resilience. While the concept of an "adaptogen," or herb that helps with the adaptation to stress and the promotion of homeostasis, is not widely used in Western medicine, Western science has revealed that tulsi does indeed possess many pharmacological actions that fulfill this purpose.

The medicinal properties of tulsi have been studied in hundreds of scientific studies including *in vitro*, animal and human experiments. These studies reveal that tulsi has a unique combination of actions that include: Antimicrobial (including antibacterial, antiviral, antifungal, antiprotozoal, antimalarial, anthelmintic), mosquito repellent, anti-diarrheal, anti-oxidant, anti-cataract, anti-inflammatory, chemopreventive, radioprotective, hepato-protective, neuro-protective, cardio-protective, anti-diabetic, anti-hypercholesterolemia, anti-hypertensive, anti-carcinogenic, analgesic, anti-pyretic, anti-allergic, immunomodulatory,

central nervous system depressant, memory enhancement, anti-asthmatic, anti-tussive, diaphoretic, anti-thyroid, anti-fertility, anti-ulcer, anti-emetic, anti-spasmodic, anti-arthritic, adaptogenic, anti-stress, anti-cataract, anti-leukodermal and anti-coagulant activities.[50-53] These pharmacological actions help the body and mind cope with a wide range of chemical, physical, infectious and emotional stresses and restore physiological and psychological function.

14.Honey

Nutritional and nonnutritional components of honey

Today, approximately 300 types of honey have been recognized.[54] These varieties are related to the different types of nectar that are collected by the honeybees. The main composition of honey is carbohydrates that contribute 95–97% of its dry weight. Furthermore, honey includes main compounds, such as proteins, vitamins, amino acids, minerals, and organic acids.[55-56] Pure honey also consists of flavonoids, polyphenols, reducing compounds, alkaloids, glycosides, cardiac glycosides, anthraquinone, and volatile compounds.[57-59] Monosaccharides (fructose and glucose) are the most important sugars of honey and may be contributed to the most of the nutritional and physical effects of honey.[60] In addition to monosaccharides, smaller quantities of disaccharides (sucrose, galactose, alpha, beta-trehalose, gentiobiose, and laminaribiose), trisaccharides (melezitose, maltotriose, 1-ketose, panose, isomaltose glucose, erlose, isomaltotriose, theanderose, centose, isopanose, and maltopentaose), and oligosaccharides are present in honey.[61-62] Many of these sugars are formed during the honey ripening and maturation times. Gluconic acid, a product of glucose oxidation, is the main organic acid that is present in honey; in addition, small amounts of acetic, formic, and citric have been found.[63] These organic acids are responsible for the acidic (pH between 3.2 and 4.5) property of honey.[64] Honey also consists of some important amino acids, such as all nine essential amino acids and all nonessential amino acids except for asparagine and glutamine. Proline was reported as the primary amino acid in honey, followed by other types of amino acids.[65] Enzymes (diastase, invertases, glucose oxidase, catalase, and acid phosphatase) constitute the main protein ingredients of honey.[66] The vitamin level in honey is low and does not close to the recommended daily intake. All of the water-soluble vitamins exist in honey, with Vitamin C being the most frequent. Approximately 31 variable minerals have been found in honey, including all of the major minerals, such as phosphorus, sodium, calcium, potassium, sulfur, magnesium, and chlorine. Many essential trace components are detected in honey, such as silicon (Si), rubidium (RB),

vanadium (V), zirconium (Zr), lithium (Li), and strontium (Sr). However, some heavy metals such as lead (Pb), cadmium (Cd), and arsenic (As) are present as pollutants.[67] Previous studies have detected the approximately 600 volatile compositions in honey that contribute to its potential biomedical effects.[68]

The volatile compounds of honey are generally low but include aldehydes, alcohols, hydrocarbons, ketones, acid esters, benzene and its derivatives, pyran, terpene and its derivatives, norisoprenoids, as well as sulfur, furan, and cyclic compounds.[69-70] Flavonoids and polyphenols, which act as antioxidants, are two main bioactive molecules present in honey. Recent evidence has shown the presence of nearly thirty types of polyphenols in honey.[71-72] The existence and levels of these polyphenols in honey can vary depending on the floral source, the climatic and geographical conditions. Some bioactive compounds, including galangin, quercetin, kaempferol, luteolin, and isorhamnetin, are present in all types of honey whereas naringenin and hesperetin are found only in specific varieties. In general, the most phenolic and flavonoid compounds in honey consist of gallic acid, syringic acid, ellagic acid, benzoic acid, cinnamic acid, chlorogenic acid, caffeic acid, isorhamnetin, ferulic acids, myricetin, chrysin, coumaric acid, apigenin, quercetin, kaempferol, hesperetin, galangin, catechin, luteolin, and naringenin.[71-72] The ingredients of honey have been reported to exert antioxidant, antimicrobial, anti-inflammatory, antiproliferative, anticancer, and antimetastatic effects.

15. Orange peel

Citrus fruits are good sources of nutrition with an ample amount of vitamin C. Besides, the fruits are abundant in other macronutrients, including sugars, dietary fiber, potassium, folate, calcium, thiamin, niacin, vitamin B6, phosphorus, magnesium, copper, riboflavin and

pantothenic acid.[73] However, secondary metabolites are an especially popular topic in the present research. These constituents, also known as phytochemicals, are small molecules that are not strictly necessarily for the survival of the plants but represent pharmacological activity. *Citrus* fruits contain a number of secondary metabolites, such as flavonoids, alkaloids, coumarins, limonoids, carotenoids, phenol acids and essential oils. These active secondary metabolites show several bioactivities of vital importance to human health, including anti-oxidative, anti-inflammatory, anti-cancer, as well as cardiovascular protective effects, neuroprotective effects, etc. In addition, *Citrus* fruits have been used as traditional medicinal herbs in several Asian countries, such as China, Japan and Korea. Nine traditional Chinese medicines have been recorded in the Chinese Pharmacopoeia for appropriate medical use from six *Citrus* species[74] *C.reticulata* Blanco, *C.medica* L. var., *C.medica* L., *C.wilsonii* Tanaka, *Citrusaurantium* L. and *C.sinensis* Osbeck. These peels or whole fruits (mature or immature) are known to treat indigestion, cough, skin inflammation, muscle pain, and ringworm infections, as well as to lower blood pressure.

CONCLUSION

As reported from the ancient time herbal properties are responsible for the immunomodulatory action. Many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides, lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties.

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