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Immunomodulatory effects of potent bioactive compounds derived from plants

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ABSTRACT

Plants are able to produce diverse group of bioactive components. Components of several plants have been reported to possess immunomodulatory activity and can help improving immunity as well as potential source of drug in various diseases. Various alkaloids, flavonoids, terpenoids, polysaccharides, lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties, which can modulate immune system in a specific or nonspecific manner influence any constituent. The scientific community is devoting efforts towards traditional medicine and plant-based therapeutics, due to tremendous potential of the plants and their derived drugs. This review focuses on the immunomodulatory potential of common fruiting plants.

Keywords:Immunomodulators, immunity, bioactive compounds, anti-inflammatory, plant-derived

Introduction:

Immune system is a defence system within vertebrates, to protect them from disease causing pathogens. It iscapable to produce varieties of cells and molecules proficient of recognizing and eliminating foreign agents. Immunomodulation is a process that alters the immune system of the host by interfering with its functions, resulting in either immunostimulation or immunosuppression **(Belapurkar, P.,2014, Naved, T.,2005)**. An immunomodulator is a substance that helps to normalizeand optimize the immune system by improving host defence mechanism **(Nagarathna, P. K. M., 2013, Agrawal, S. S.,2010)**.Naturally occurring or synthetic compounds can alterthose mechanisms leads to immune responses modulation**(Singh, N., 2016)**.

Immunomodulatory drugs are used as immunosuppressive andimmunostimulative agents have various side effects such as pulmonary toxicity, myelosuppression, increased risk of infection, hepatic fibrosis, lymphoma (Epstein–Barr virus associated), Nephrotoxicity, headache, motor disturbances, GI complaints, hypertension, hyperkalemia, hyperglycemia, diabetes, renal dysfunction, tremor, hypertension, gum hyperplasia, hyperuricemia, hyper cholesterolemia, etc.and also generalized effect throughout the immune system (**Naved, T.,2005, Singh, N., 2016)**.

About three-quarters of the world population relies upon traditional medicine for the healthcare according to the World Health Organization. All over the world, researchers are

attracted towards traditional medicine and plant-based therapeutics. And wide research activities on several plants and their therapeutic properties have explored by scientist**(Sethi, J., 2015, Kumar, D., 2012)**.Traditional medicinal systems havesuggested plant resources to increase the body's natural immunity. Various plants and their compounds are known to have immunomodulatory activity(**Naved, T.,2005**).

Plant derived immunomodulator are better alternatives to conventional chemotherapeutics and antibiotics **(Muthulakshmi, M., 2015)**.The immunomodulatory activities shown by the plant extracts are due to the compounds present in them. They are several types of flavonoids such as including apigenin, oligomeric proanthocyanidins, isoflavonoids, flavones, and anthocyanidins, alkaloids, terpenoids, polysaccharides, lactones, saponins and glycoside**(Sharma, P., 2017)**.

Methods for Testing Immunological Factors (Singh, N., 2016, Joseph, M. M., 2012):

The single ingredient or single distilled fraction extracted from herbal remedies is screened by the classic pharmacological means, to determine its bioactivity. The aspect of medicine evaluation, whole animal model is the most classic pharmacological screening model used,since it can respond to the effectiveness, side effect and toxicity of medicines in in-vivosurroundings.

***In vitro and In vivo* methods:**

Various *in-vitro*and *in-vivo* methods for pharmacological screening of medicinal plants extracts possess immunomodulatory activity have been listed:

1. Inhibition of histamine release from mast cells
2. Mitogen induced lymphocyte proliferation
3. Inhibition of T cell proliferation
4. Chemiluminescence in macrophages
5. Inhibition of dihydro-orotate dehydrogenase
6. Spontaneous autoimmune diseases in animals
7. Acute systemic anaphylaxis in rats
8. Anti-anaphylactic activity (Schultz-Dale reaction)
9. Passive cutaneous anaphylaxis
10. Arthus type immediate hypersensitivity
11. Delayed type hypersensitivity
12. Reversed passive arthus reaction
13. Adjuvant arthritis in rats
14. Collagen type II induced arthritis in rats
15. Proteoglycans - induced progressive Polyarthritic in mice
16. Experimental autoimmune thyroiditis
17. Coxsackievirus B3-induced myocarditis

18. Porcine cardiac myosin-induced autoimmune myocarditis in rats
19. Experimental allergic encephalomyelitis
20. Acute graft versus host disease (GVHD) in rats
21. Influence on SLE-like disorder in MRL/lpr mice
22. Prevention of experimentally induced myasthenia gravis in rats
23. Glomerulonephritis induced by antibasement membrane antibody in rats
24. Auto-immune uveitis in rats
25. Inhibition of allogenic transplant rejection.
26. Antitumor activity by in vitro proliferation assay.

Immunomodulation by Plants:

The bioactive components of various plants can regulate the immune system and can enhance resistance towards various diseases**(Belapurkar, P.,2014)**.Plant extracts used in traditional therapy are being studied for their Immunomodulatory activities. They have shown direct anti-proliferative effect on tumour cells and also have the ability to enhance tolerance of host cell from toxic chemicals used to destroy cancer which can cause damage healthy cells**(Singh, N., 2016)**. The biological substances present in plants that can stimulate suppress or modulate of the immune system effects both adaptive and innate effector mechanism by interacting with various immunocytes and regulating their effector mechanism throughcytokines and their receptors**(Kumar, D., 2012).**

Common fruiting Plants as Immunomodulator:

Several medicinal plants used in the Indian traditional system known as Rasayana, exhibit wide range of therapeutic properties such as antioxidant, antiasthmatic, antiarrhythmic, antiinflammatory, hepatoprotective, hypocholesterolemic, antifungal, cardiotonic, diuretic, immunomodulatory activity and other medicinal activities**(Kumar, D., 2012, Singh, N., 2016).**

Punica granatum:

Punica granatum (Pomegranate)belongs to the family of Punicaceae and mainly grown in the Near East, India, Spain, Israel and the United States **(Joseph, M. M., 2012).**Pomegranate fruit extract (PE) contains mixture of various phytochemicals, including the punicalagins, a class of tannins unique to pomegranates, polyphenols, anthocyanins, flavonoids, ellagitannins and hydrolysable tannins **(N Syed, D., 2013, Hajleh, M. A., 2016).**Pomegranate fruit juice is known for the source of fructose, sucrose, and glucose and also contains ascorbic acid, citric acid, fumaric acid, and malic acid. In addition, it contains small amounts of all amino acids, specifically proline, methionine, and valine. High amount of polyphenols are found in its fruit juice and peel **(Zarfeshany, A., 2014).**

The different extracts of *Punica granatum* (Pomegranate) have been reported for several activities such as antitumor, antibacterial, antidiarrhoeal, antifungal, antiulcer, antioxidant and can also induces apoptosis, anti-proliferative, anti-invasive, and anti-metastatic effects **(Zarfeshany, A., 2014,Joseph, M. M., 2012).**

Several studies shows therapeutic potential pomegranate extracts against cancer, as pomegranate extracts can inhibit the growth of prostate cancer cells in culture and also inhibit cell proliferation and induce apoptosis in human breast cancer cells (MCF-7), human pancreatic cancer cells, colon cancer (CACO) and in Hepato-cellular carcinoma (HepGII) cell lines **(Hajleh, M. A., 2016, Joseph, M. M., 2012)**

Thus, Pomegranate can be used in the prevention and treatment of numerous types of cancer, cardiovascular disease, osteoarthritis, rheumatoid arthritis, and other diseases and in wound healing. Its various constituents can induce its beneficial effects through influencing gene expressions**(Zarfeshany, A., 2014, Mahmoud, S. H., 2015).**

Vaccinium corymbosum L.:

Vaccinium corymbosum L. **(**Blueberry) are rich in polyphenols, anthocyanins and phenolic acids.Polyphenols such as 3-glucoside, arabinoside, galactoside-based polymers of delphinidins, petunidins, peonidins, malvidins and anthocyanins, are found in large amounts in blueberries. Anthocyanins and phenolic acids found in Blueberry shows anti-proliferative, antiapoptotic, anti-obesity,anticancer, anti-inflammation , antidiabetic, antibacterial,prevention of degenerative diseases, protective effect on vision and liver, prevention of heart disease, enhanced immune function, prevention of cardiovascular diseases, and improved cognitive and reduced the risks of cancer recurrence**(Ma, L., Sun, Z., 2018, 28).**

Study investigated the anti-inflammatory activity of blueberry by mediating and modulating the balances in pro-inflammatory cytokines of IL-1β, IL-6, and IL-12. Blueberries were found to exhibit anti-inflammatory activity, due to the presence of a wide range of anthocyanins as well as polyphenols. Increased obesity is often due to by adipose tissue inflammation andincrease in inflammatory proteins,includes tumor necrosis factor-α (TNF-α), interleukin- 6, monocyte chemoattractant protein-1 (MCP-1), and nitric oxide (NO). Inflammatory proteins may accumulate causing inflammatory macrophages leads to increase in the adipose tissue. 28Blueberry juice acts a methylation suppressor for methylenete trahydrofolate reductase and DNA methyltransferase 1 in human **(Ma, L., Sun, Z., 2018).**

The anti-inflammatory properties and antidiabetic effect of polyphenols are mediated by the regulation of the pro-inflammatory cytokine balance and suppression of genes, controlling the inflammatory pathway by inhibition of -amylase and-glucosidase, promoting the expression of GLUT-2 and PPARg. Polyphenols prevents of cardiovascular diseases by the inhibiting soluble angiotensin-converting enzyme activity **(Ma, L., Sun, Z., 2018).**

Mangifera indica:

Mangifera indica (Mangoes) belong to family Anacardiaceae. It is worldwide cultivated on an area of approximately 3.7 million ha. It has been well recognised that mango fruits are an important source of micronutrients, vitamins and other phytochemicals, dietary fibre, carbohydrates, proteins, fats and phenolic compounds.Mangiferin (1, 3, 6, 7 tetrahydroxy xanthone 2-glucopyranoside) has found to be present in leaves, fruits, stem bark, heartwood, roots of mangoes andconsidered as immunoregulator**(Parvez, G. M., 2016).**

According to Ayurveda *Mangifera indica* claimed to possess number of therapeutic uses, are attributed to different parts of mango tree.From various studies it is found that mango possesses anti-diabetic, anti-oxidant, anti-viral, anticancer, antimicrobial, anti-inflammatory properties.

The alcoholic extracts of *Mangifera indica*showed increased circulating antibodies production, establishes presences of the cellular and humoral immunomodulatory property. In vivo study of alcoholic extract showed significant increased the production of circulating antibodies, establishing the cellular and humoral immunomodulatory property**(Naved, T., 2005).** The cytotoxicity of mango extracts are found against the breast cancer cell lines MCF 7, MDA-MB-435, MDA-N; colon cancer cell line (SW-620); renal cancer cell line (786-0) and K562 leukemia cells**(Parvez, G. M., 2016).**

Momordica charantia:

Momordica charantia (Bitter melon) is an herbaceous plant with tendril-bearing vines and an edible fruit, cultivated in multiple regions across the world.In ancient literature, various parts of this plant, such as fruit, leave seed, etc. has been shown to possess medicinal properties.A Bitter melon fruit is arich source of carbohydrates, proteins, vitamins, fibers and minerals and the pulp of mature ripe fruit is a major source of the carotenoid lycopene **(Rao, C. V., 2018)**.

Medicinal properties of bitter melon aredue to presence of phenols, alkanoids, flavonoids, terpenes, anthroquinones, and glucosinolates **(Joseph, B., 2013).** Variousbitter melonproperties has been studied includes antioxidant, antidiabetic, anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, antimalarial activity, anti-HIV, anthelmintic, hypotensive, anti-obesity, immuno-modulatory, antihyperlipidemic, hepato-protective, and neuro-protective activities **(Rao, C. V., 2018, Kwatra, D., 2016)**

Fang et al. have isolated and characterized a 14-kDa ribonuclease (RNase MC2) from MC seeds. RNase MC2 showed both cytostatic and cytotoxic properties against MCF-7 breast cancer (BC) cells causing nuclear damage, leading to either early or late apoptosis. The treatment resulted in inhibition of cancer cell proliferation and inhibition of HER2 gene expression in vitro**(Kwatra, D., 2016).**

Conclusion:

The researches collectively show that specific food components, plays an important role in preventing diseases or manage disease symptoms and boost immunity. The fruits and vegetables consumptionin daily foodhas been linked with various health benefits, due to theirmedicinal properties and great nutritional value. Increasing interest in the use of plant extracts as therapeutic agents, because plants are rich in bioactive compounds which can be used to generate potential drugs for several disease. However, manyin-vitro as well as in-vivo clinical trials of bioactive compounds is need before evaluated for clinical use, to find their efficiency and side effects.

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