Review Article

Dietary Immunomodulators - An Organic Boom in the Management of Chronic Diseases

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ABSTRACT:

Immunology involves all the defence mechanisms occurring in the body after the invasion of any infectious agent and the ability to resist this infection. The micronutrients like essential proteins, essential amino acids, vitamins (A, B6, B12, C, D, E and folic acid), fatty acids, minerals (iron, selenium, zinc and copper) and certain phytochemicals are of prime importance towards healthy immune system. In addition to these nutritional components, intestinal microflora and certain bacteria (probiotic bacteria) also play an important role in the modulation of healthy immune system. There is an ongoing trend of usage of immunomodulators to combat various chronic diseases like viral diseases, cancers, inflammatory and autoimmune diseases. This review focuses on various immunomodulators available in daily dietary meals, its positive and negative effects on immune system and its role in management of chronic illness as an adjunct to other modalities to achieve positive health benefits with minimal side effects.

KEY WORDS: cancer; immunity; immunomodulator; organic food; probiotics; vitamins

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INTRODUCTION:

Nutrition plays an important role in modulating immune functions. The immune system needs adequate supply of nutrients to function properly. Immune functions are indispensable for defending the body against attack by pathogens or cancer cells, and therefore it plays a pivotal role in the maintenance of health. The immune functions are disturbed by malnutrition, aging, physical and mental stress or undesirable lifestyle. Therefore, the ingestion of foods with immune-modulating activities is considered an efficient way to prevent immune functions from declining and reduce the risk of infection or malignancy. Food-derived substances can modulate either innate or acquired immunity.

Several studies have shown that the improvement of depressed immune functions by ingesting foods reduced infection rates and mitigated the severity of infectious disease.[1] Therefore; food substances that are capable of enhancing the immune responses of cancer patients with disturbed/ compromised immune functions are valuable. The proliferation and metastasis of cancer cells accelerate when immune functions are disturbed. It has been found that patients with malignancy have lower Natural Killer (NK) cell activity than healthy controls and such persons are subject to higher rates of cancer incidence, metastasis and aggravation of cancer.[2]

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Mechanism of action of dietary immunomodulators on immune functions:

1. Basic nutrients-

***Fatty acids*:** Polyunsaturated fatty acids (PUFA), are important regulators of several cellular functions, including those related to inflammation and immunity.[3] Maternal fish oil supplement modifies the balance between cellular n-3 and n-6 PUFAs within the foetus and has the capacity to influence neonatal immune function. It also has potential clinical benefits in reducing the risk of allergic disease.[4] Dietary supplementation with fish oil in anti-inflammatory doses inhibits prostaglandin E2 (PGE2) synthesis by stimulating peripheral blood monocytes.[5] This provides a mechanistic basis for the reduction in take of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). The onset of action of fish oil is being evident at 12 weeks after commencement. There is no direct dose-by-dose effect as with the analgesic action of NSAIDs. Clinical benefits have been observed to last up to 6 weeks after discontinuing therapy.[6] There is evidence that PUFAs regulate the expression of genes for cytokines, adhesion molecules, inducible nitric oxide synthase and other inflammatory proteins.[7] Since the expression of many of these genes is regulated by the transcription factor, nuclear factor kappa B (NFkB), these observations suggest that PUFAs might affect the activity of this transcription factor.[8]

Aminoacids:

Arginine is a semi-essential amino acid in mammals. While dietary arginine is not an absolute requirement under normal conditions, it can become essential at times of growth and metabolic stress, such as following trauma, sepsis or burn injuries.[9] Arginine is required for the normal growth and proliferation of lymphocytes in vitro.[10] Supplemental arginine also benefits the innate immune response, with increase in macrophage and natural killer cell cytotoxicity.[11] In the setting of protein-calorie malnutrition and tumour inoculation, supplemental arginine (1% by weight) reduced the growth rate of the immunogenic neuroblastoma C1300 and improved host survival compared with glycine-supplemented controls.[12] Glutamine is another amino acid having high rate of utilization by neutrophils, macrophages and lymphocytes and its levels get elevated in cellular challenging situations suggesting its importance for functioning of these cells to mount an efficient immune response.[3]

Carbohydrates:

Dietary monosaccharides like glucose and fructose and disaccharides like sucrose and lactose[13] and lectins have capacity to interfere with bacterial and viral attachment to epithelial cell surfaces within the alimentary canal, as they contain mucosal immunoglobulin, secretory IgA. Thus within the alimentary canal, IgA, lectins, bacteria, viruses and mucous membrane exist within a delicate equilibrium which potentially may be perturbed by dietary saccharides.[14]

2. Micronutrients-Vitamins

Vitamin A:

Vitamin A plays a role in the maintenance of mucosal surfaces, in the generation of antibody responses, in haematopoiesis and in the function of T and B lymphocytes, NK cells and neutrophils.[15] The influence of vitamin A and its metabolites on different aspects of immune function is attributed to its actions as modulators of gene transcription.[16] Vitamin A supplementation reduces the morbidity and mortality from measles and diarrhoeal diseases in infants and children in developing countries.[17,18] Periodic high-dose vitamin A supplementation seems to reduce both morbidity among children born to HIV-infected mothers[19] and diarrhoeal disease morbidity in HIV infected children.[20]

Role of Vitamin A in oral diseases:

Vitamin A plays an important role in management of oral leukoplakia and oral submucous fibrosis. It also maintains immune defence responses, oral epithelial integrity, bone growth, normal cell development, avoids keratinisation of mucous forming cells, allows cell differentiation, stimulates osteoclasts and permits normal tooth spacing.[21]

Vitamin C:

It has an inhibitory effect on the expression of pro-inflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor alpha (TNF-α) in adult whole blood cells. It has been postulated that vitamin C might be an interesting compound for modulation of an overexuberant immune response.[22]

Role of Vitamin C in oral diseases:

Study conducted by R. Guruprasad et. al in 2014 evaluated the correlation between Serum Vitamin C and Iron levels in OSMF patients. The level of Serum Vitamin-C and Iron was significantly decreased in OSMF patients when compared to controls. They concluded, that the chemical, thermal and/or mechanical factors associated with the use of areca nut may act in conjunction with the Vitamin C and Iron

deficiency leading to the development of OSMF. Therapeutic substitution of Vitamin C and Iron may be recommended in the management of OSMF.[23]

A study conducted by Supriya Bhat et al, in 2017 aimed to estimate the detoxification status of serum and saliva by assessing the serum and salivary Vitamin C in oral potentially malignant disorders and oral cancer. A total of 90 subjects, 30 subjects with oral potentially malignant disorders, 30 subjects with oral cancer, and 30 healthy subjects (controls) were included in the study. The study concluded that the mean serum and salivary Vitamin C levels were decreased significantly in potentially malignant disorders and oral cancer when compared to healthy subjects.[24]

Vitamin E:

It is the most effective chain breaking, lipid-soluble antioxidant in cell membranes and plays a major role in maintaining cell membrane integrity by limiting lipid peroxidation by reactive oxygen species (ROS).[25] It can influence a variety of inflammatory processes by inhibiting the activity of NFk B, required for maximal transcription of many proteins involved in inflammatory responses, including several cytokines, such as IL-1B, IL-2 and TNF-α.[26] Vitamin E supplementation in diet enhances antibody production, lymphocyte proliferation, NK-cell activity, and macrophage phagocytosis.[27]

Carotenoids:

The bright red, yellow and orange pigments in various fruits and vegetables are attributed to Carotenoids. The prevalent ones in the human diet include beta-carotene, alpha-carotene, beta cryptoxanthin, lycopene, lutein, and zeaxanthin, having provitamin A activity, and are converted to retinol, the active form of vitamin A, in the body.[22] Lycopene has been shown to have high singlet oxygen quenching capability and has been associated with anti-tumour promoting activities in various tissues in animal studies. Association between lycopene intake, primarily from tomato products is associated with reduced risk for cancers at all sites.[28] Epidemiological studies have found significant associations between higher plasma beta cryptoxanthin and a reduced risk for gastric adenocarcinomas and lung cancer in men.[29,30] Consuming a carotenoid-rich diet may be one of the ways for reducing the risk of cancer.[22]

Role of Carotene in oral diseases:

Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. Dosage of 4.8 mg/day orally for 3 months leads to the reversal of dysplastic changes in leukoplakia and dosage of 16 mg/day leads to substantial increase in the mouth opening in oral submucous fibrosis. In vitro studies have shown lycopene to be twice as potent as β-carotene and ten times that of α-tocopherol in terms of its singlet oxygen quenching ability.

Thiamine:

Thiamine is a water-soluble Vitamin B.[22] Several case control studies have reported significant associations between thiamine intake and reduced risk of several cancers including colon, and colorectal.[31,32]

Folate:

Folate is a water-soluble vitamin B found naturally in certain citrus foods called food folate, and the synthetic form added to fortified foods and supplements, called folic acid. Several studies hypothesized that folate supplementation is associated with a decreased rate of infection, positive effects on blastogenic response and proliferation of T lymphocytes, enhanced delayed-type hypersensitivity response, enhanced phagocytosis, and immunoglobulin production. It appears to have no effect on NK cell function. Immunologically folate deficiency are likely caused by defects in DNA and RNA synthesis or methyl metabolism.[22]

Vitamin B-6:

It affects immune function as it plays a role in the formation of the amino acid cysteine, an important precursor in glutathione, which is closely associated with lymphocyte proliferation.[33] Its potential mechanism to reduce cancer risk includes reducing the disruption of DNA synthesis, repair, and methylation associated with inadequate intake.[25] Also it may reduce cancer cell proliferation and oxidative stress, suppress nitric oxide, or have antiangiogenic properties.[34]

Minerals:

Zinc-

High content of Zinc (Zn) is present in animal protein food.[35] Zn plays a role in T lymphocyte activation and signal transduction. Zn has been implicated in the non-covalent interaction of the cytoplasmic tails of CD4 and CD8 with the tyrosine kinase p56lck, an essential process in the early steps of T-cell activation.[36] Zn stimulates autophosphorylation of tyrosine residues by p56lck and subsequent

phosphorylation of the T-cell receptor complex involving CD45.[37] Zn-deficient children with acrodermatitis enteropathica (AE) have reduced numbers of lymphocytes, particularly T-cells, in the blood and peripheral lymphoid tissues. Decreased CD4+/ CD8+ cell ratios are also seen. T-cell responses, such as proliferation in response to mitogens, cytotoxicity and delayed-type hypersensitivity (DTH), natural killer cell activity and chemotactic response of the monocytes are suppressed.[38,39] Controlled trials of Zn supplementation demonstrated a reduction in the incidence and duration of acute and chronic diarrhoea by 25-30 %, and in the incidence of pneumonia by up to 50%.[40]

Role of Zinc in SARS-CoV 2:

It is known that zinc (Zn) possesses a variety of direct and indirect antiviral properties. Administration of Zn supplement has a potential to enhance antiviral immunity, both innate and humoral, and to restore depleted immune cell function or to improve normal immune cell function, particularly in immuno-compromised or elderly patients. Zn may also act in a synergistic manner when co-administered with the standard antiviral therapy, as was demonstrated in patients with hepatitis C, HIV, and SARS-CoV-1. Zn may also protect or stabilize the cell membrane that blocks the virus entry into the cell. It also inhibits viral replication by alteration of the proteolytic processing of replicase polyproteins and RNA-dependent RNA polymerase (RdRp) in rhinoviruses, HCV, and influenza virus, and diminish the RNA-synthesizing activity of nidoviruses, that belongs to SARS-CoV-2. Therefore, it has been hypothesized that Zn supplements may have potential benefit in prophylaxis and treatment of COVID-19.[41]

Iron:

It is an essential nutrient for cells because of its role as a cofactor for enzymes in the mitochondrial respiratory chain and oxidative phosphorylation, in the citric acid cycle (aconitase), and in DNA synthesis (ribonucleotide reductase).[42] Iron interferes with cytokine activities and the cell-mediated immune effector mechanisms of macrophages, thus altering the immune response toward invading pathogens.[43] One central mechanism responsible for this is a direct inhibitory effect of iron on IFN-γ activity. Iron loading of macrophages results in an inhibition of IFN-mediated pathways in macrophages, such as formation of the pro-inflammatory cytokine, TNF-α and expression of MHC class II antigen.[44] Part of this effect results from the reduced formation of nitric oxide (NO) in the presence of iron. This is important, because NO is an essential effector molecule produced by macrophages to fight infectious pathogens and tumour cells.[45] Iron blocks the transcription of inducible NO-synthase (iNOS or NOSII), the enzyme responsible for cytokine inducible high-output formation of NO by hepatocytes or macrophages.[46] The inhibitory effect of iron toward IFN-γ activity also affects the Th1/Th2 balance, with Th1 effector function being weakened, whereas Th2- mediated cytokine production and function, such as IL-4 activityis increased which is unfavourable during a malignant disease or an acute infection. B cells are not prominently affected by iron homeostatic changes, while NK cells are sensitive to iron homeostatic imbalances with impaired proliferation in iron deficiency and overload.[44]

Selenium:

Various milled wheat and corn products may contain 70% or more of selenium. Cooking appears to result in little significant loss of selenium in most foods, but dry heating of cereals may result in significant reductions in their original selenium content.[47] A major immune stimulatory effect of Selenium is by up-regulation of expression of the α and ß subunits of the IL-2 receptor, which are expressed on many immune cells and notably on T and B lymphocytes. This increases the ability of these cells to respond to IL-2. Stimulation with IL-2 from activated CD4+ T-helper cells potentiates the cytotoxicity of killer cells, increases numbers of lymphocytes, promotes antibody production by B lymphocytes and improves the responsiveness of immature bone marrow cells to other cytokines in order to produce immune-cell precursors.[48] Supplementation with Selenium appears to reverse the age-related decline in NK cell function in elderly individuals. The loss of NK-cell activity is a means by which cancer cells may evade immune-mediated destruction.[49]

Role of Selenium in oral diseases:

Oral lichen planus (OLP) is a chronic disease with immune mediated pathogenesis. Selenium (Se), an antioxidant, plays a role in modulating immunity. Passant O. Qataya et al, in January, 2020 conducted a randomized control clinical trial to evaluate two forms of Selenium (*novel* topical hydrogel and oral capsules), solely, in treating erosive OLP based on clinical evaluation and salivary oxidative stress markers. Patients were allocated into one of three groups: group I, topical corticosteroids; group II, topical Selenium; and group III, systemic Selenium.

Treatment lasted for 6 weeks; patients were clinically evaluated at baseline, 6 and 12 weeks. Patients in all the groups showed significant reduction in symptoms after the treatment. However, group II had significantly lower pain scores at the end of 12 weeks compared to the other groups.[50]

Probiotics:

Under normal circumstances, the resident gut bacteria cause neither pathogenicity nor inflammation in the host, but instead contribute to health maintenance, forming a barrier layer against colonization by pathogens and aiding in nutrient digestion and assimilation.[51] The resident intestinal microflora plays important physiological roles like deconjugating potentially damaging oxidative metabolites and toxins in the gut; degrading potentially allergenic food proteins; regulating cholesterol and triglyceride uptake; increasing vitamin biosynthesis and providing immunosurveillance signals to limit intestinal-tract inflammation. Thus, a stable, properly functioning and active intestinal tract microflora is essential to the continuance of human health. Among the most predominant microbes in the human intestinal tract are the Gram positive lactic acid-producing genera Lactobacillus and Bifidobacterium. Lactobacilli and bifidobacteria are also common fermentative microbes in yoghurt and cheese.[52] Certain strains of probiotic lactic acid bacteria (LAB) can prime peritoneal macrophage populations for enhanced phagocytosis, lysosomal enzyme production and free radical oxidant production.[53] In human studies, consumption of Lactobacillus rhamnosus (strain HN001) or Bifidobacterium lactis (strain HN019) has been demonstrated to up-regulate peripheral blood NKcell-mediated cytotoxicity against tumour cells.[54] In addition to anti-allergy immunoregulation, probiotics also combat inflammatorydiseases. Evidences demonstrate that dietary consumption of immunoregulating LAB might assist in combating autoimmune diseases, including juvenile chronic arthritis.[55] The potential use of probiotics to augment the routine immune signalling events of the gut microflora, as a means of restoring vital anti-inflammatory immunoregulatory control mechanisms is a promising means of combating inflammatory bowel disease.[56]

Prebiotics:

These are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon.[57] Unlike probiotics, that introduce exogenous bacteria into the human colon, prebiotics stimulate the preferential growth of a limited number of health-promoting commensal flora already residing in the colon.[58] Dietary raffinose suppresses serum immunoglobulin E response through suppression of Th2-type immune response against oral antigen in the lymphoid organs located in or near the intestine.[59]

Food beneficial to the immune system:

Epidemiological and experimental studies have demonstrated a negative correlation between the deficinency of diets rich in fruits, and vegetables and the risks for chronic diseases, such as chronic inflammation and cancers.[60] Therefore, adequate supplementation with fruits and vegetables might play an important role in the control of acute and chronic diseases via immuno-modulation. Dark coloured fruits and vegetables have potential in stimulating Th1/Th2 cytokine secretions.[61]

Strawberries, red onions, peppers and spinach:

Strawberry and red onions demonstrate an immunomodulatory potential via stimulating splenocyte proliferation.The immuno-modulatory components in these fruits are correlated with phenolics, including flavonoids.[61]

Apples:

It one of the main sources of dietary flavonoids. Apple extracts can significantly inhibit the TNF-alpha-induced NF-kappa B activation at a dose of 5 mg/ml.[62]

Carrots, celery and parsley:

Non-toxic doses (20 μg/ml) of these foods and their related ingredients might act to affect health as immune-stimulating agents, i.e. directly enhancing lymphocyte activation and/or secreting multipotent cytokine IFN-γ.[63]

Cruciferous vegetables:

Increased intake of cabbage, cauliflower, broccoli, Brussels sprouts, watercress, and mustard greens, is associated with a decreased risk of several cancers in human population.[64] This is achieved by alterations in the activities of metabolic enzymes that result in reduced carcinogenicity of dietary or environmental carcinogens, reduction of oxidative DNA damage levels in human lymphocytes in increased oxidative stress conditions.[65,66,67]

Tomato:

Epidemiological and experimental data suggest that an increased intake of tomato products can reduce the risk of cancers, especially prostate, colon, and oral cancer. Several evidence suggest that tomato constituents, such as lycopene, affect immune functions modulation and antioxidant activity.[68]

Garlic:

Allicin is the active ingredient of freshly crushed garlic. It significantly inhibits the secretion of IL-8, INF-γ-inducible protein of 10 kD (IP-10), monokine induced by INF- γ (MIG) and IL-1b from intestinal epithelial cells. These cyto-and chemokines play an important role in the pathogenesis of inflammatory bowel diseases. Therefore, local application of allicin may serve as a potential immune-mediating therapy in inflammatory bowel diseases.[69] Meta-analyses revealed that increased garlic consumption diminished the risk of stomach and colorectal cancers.[70]

Soybeans:

It possesses several traditional phytonutrients and several bioactive phytochemicals including flavonoids and saponins, with variety of potential health benefits, like anti-inflammatory, anti-oxidative, anti-mutagenicand anticarcinogenic effects.[71-74]

Cereals (rice and wheat):

Lipopolysaccharide (LPS) or LPS-like components associated with cereal grains play a major role in IL-10 production from Peripheral Blood Mononuclear Cells. The ability of various food products to induce IL-10 production did not always correlate with the concentrations of LPS in their extracts. Therefore LPS or LPS mimicking molecules likely work in concert with other immune stimulatory or immune regulatory molecules in the cereals, such as carbohydrate polymers or lectins, to induce robust IL-10 production. This immune modulatory effect might explain why most individuals who are at genetic risk for celiac disease do not acquire celiac disease or inflammatory bowel disease. [75]

Mushrooms:

Mushroom proteins are potent immune activators and tumour cell growth inhibitors, mediating their effects by regulating cytokine secretion and proliferation, and are mitogens and immune modulators with therapeutic potential.[76]

Honey:

The most promising bioactive compounds found in honey products are the proteins of royal jelly.[77] These proteins may have physiological functions as suppressors of allergic reactions, as well.[78]

Dairy products:

Yogurt is one of the best-known foods that contain probiotics. In human studies, cytokine production, phagocytic activity, antibody production, T cell function, and NK cell activity were shown to increase with yogurt consumption or when cells were exposed to LAB in vitro. There is evidence that yogurt-induced immune enhancement is associated with a lowered incidence of cancer, GI disorders, and allergic symptoms.[79]Denatured and native whey protein, both of which have remarkably higher cysteine contents than do other common edible proteins, may contribute to the immunostimulatory effects of yogurt. Cysteine is a rate-limiting component in the biosynthesis of glutathione. Glutathione is important for detoxification of endogenous and exogenous carcinogens and free radicals and in regulation of immune functions.[80]

Cheese constitutes another family of milk derived fermented products and its consumption exerts a stimulatory effect on immune system functions.[81] In addition to the bacterial cell components, the immunomodulatory effect of cheese could also result from non-bacterial components such as peptides which in a lyophilized extract of Gouda cheese suppresses proliferation of cultured human peripheral blood lymphocytes in vitro and induces apoptosis of human promyelocytic leukaemia cells.[82]

Detrimental effects of food on the immune system:

Food allergies are caused by immunologic pathways that include activation of effector cells (mast cells and basophils) through food specific immunoglobulin E (IgE) antibodies (IgE-mediated food allergy), cell-mediated reactions resulting in subacute or chronic inflammation (non-IgE mediated food allergies), or combined pathways. IgE-mediated reactions occur rapidly (within seconds to minutes) after ingestion of the offending foods. Rarely, reactions take up to two hours and beyond to occur.[83]Manifestations of IgE-mediated food allergy includeacute urticaria and angioedema, rhino-conjunctivitis, asthma, nausea, vomiting abdominal cramps and diarrhoea. However, generalized urticaria and anaphylaxis can also occur.[84] The oral allergy syndrome is an IgE mediated hypersensitivity is

considered as a form of contact allergy to certain (usually fresh) fruits, nuts and vegetables and seen in up to 50% of patients with allergic rhinitis to pollen.[85] Symptoms are mainly confined to oropharynx, and include the rapid onset of pruritus involving the lips, mouth and/or pharynx. Mild swelling of the lips is common. Symptoms generally subside within minutes after ingestion ceases. However, progression to systemic symptoms is thought to occur in approximately 10% of patients.[83] Over-activation of the immune system can lead to harmful effects such as chronic inflammation or autoimmune diseases. Sometimes, the body begins to manufacture T cells and antibodies directed against its own cells and organs. Some individuals develop an exaggerated immune response to food through developing food allergy which may be IgE mediated, non-IgE mediated, or mixed.

CONCLUSION:

Nutrition plays an important role in the modulation of immune function and the various food components like proteins, vitamins, fatty acids, minerals, phytochemicals and probiotics play an important role in the modulation of immune function which is directly associated with immunological tolerance toward diseases.Supplementation with single or multiple micronutrients may enhance immune functions even in healthy individuals. On the other hand, excess amounts of some nutrients may impair immune functions.

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