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Review article

Immunomodulatory effects of food

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Abstract
There is a strong consensus that nutrition plays a role in modulating immune function and that the immune system needs adequate supply of nutrients to function properly. The complexity of the immune system supports this idea because its optimal functioning involves a variety of biological activities including cell division and proliferation, energy metabolism, and production of proteins. The micronutrients most often cited as being important to immune function include vitamins A, C, E, and B6, folate, iron, zinc, and selenium. Other nutrients mentioned as playing a role in immune function include beta-carotene (a precursor to vitamin A), vitamin B12, and vitamin D. On the other hand, over-activation of the immune system can lead to detrimental effects such as chronic inflammation or autoimmune diseases. In persons with allergies, a normally harmless material can be mistaken as an antigen. Some individuals develop an exaggerated immune response to food through developing food allergy which may be IgE mediated, non-IgE mediated, or mixed. This review will highlight the interaction between the immune system and some foods and food components in terms of modulation of immune functions by a variety of mechanisms.

Introduction
Immune functions are indispensable for defending the body against attack by pathogens or cancer cells, and thus play a pivotal role in the maintenance of health. However, the immune functions are disturbed by malnutrition, aging, physical and mental stress or undesirable lifestyle (Fig 1). 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 cancer[1].

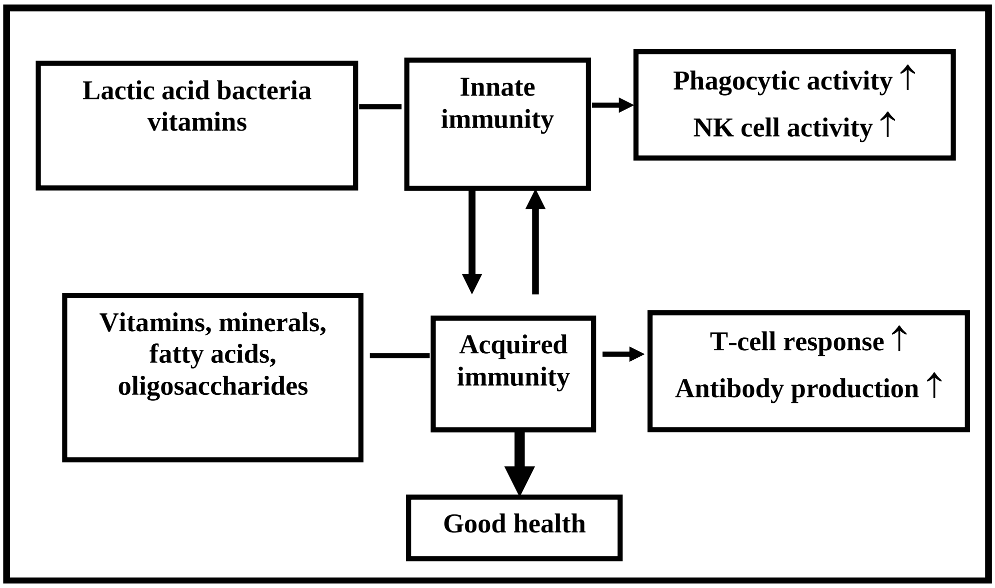

Figure 1. Modulation of immune functions by foods. The immune system is divided into innate immunity and acquired immunity, and food-derived substances can modulate either innate or acquired immunity. For example, probiotics such as lactic acid bacteria and some vitamins enhance phagocytic activity and natural killer (NK) cell activity (innate immunity), while vitamins, minerals, amino acids, fatty acids and oligosaccharides augment T cell responses and antibody production (acquired immunity). A balance of innate and acquired immunity is desirable for good health[1].

Hypersensitivity is mainly due to genetic causes, but environmental factors, including air pollution, dietary components and residential conditions, also play an important role. As clinical condition and immune parameters change concomitantly in allergic patients, it is possible to observe the effects of foods by measuring the immune parameters associated with allergic reactions[1]. An allergic reaction is a sequential immune response involving the processing and presentation of the allergen, activation of allergen-specific T and B cells, production of IgE against the allergen, and activation of mast cells and eosinophils triggered by the allergen. Therefore, food-derived materials could prevent allergy by counteracting at least one step in the cascade of allergic reactions. It has been reported that a variety of foods contain substances are able to prevent an allergic reaction[2].

Several reports have shown that the improvement of depressed immune functions by ingesting foods reduced infection rates and mitigated the severity of infectious disease[3]. Therefore, foods capable of enhancing the immune responses of cancer patients with disturbed immune functions are valuable[1]. Moreover, the proliferation and metastasis of cancer cells accelerate when immune functions are disturbed. It has been found that cancer patients have lower NK cell activity than healthy controls and persons with lower NK cell activity are subject to higher rates of cancer incidence, metastasis and aggravation of cancer[4].

Mechanisms by which foods influence immune functions:

I- Basic nutrients:

- **Fatty acids:**

Fatty acids, especially polyunsaturated long-chain fatty acids (PUFA), are important regulators of numerous cellular functions, including those related to inflammation and immunity[5]. Maternal fish oil supplementation modifies the balance between cellular n-3 and n-6 PUFAs within the fetus and has the capacity to influence neonatal immune function. It also provides preliminary evidence that fish oil might offer potential clinical benefits in reducing the risk of allergic disease[6].

Also, Dietary supplementation with fish oil in anti-inflammatory doses inhibits prostaglandin E2 (PGE2) synthesis by stimulated peripheral blood monocytes[7]. This provides a mechanistic basis for the reduction in non-steroidal anti-inflammatory drugs (NSAID) requirements in patients taking anti-inflammatory doses of fish oil. The onset of action of fish oil is delayed with effects being evident at 12 weeks after commencement. In addition, 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[8].

There is evidence that PUFAs regulate the expression of genes for cytokines, adhesion molecules, inducible nitric oxide synthase and other inflammatory proteins[9]. Since the expression of many of these genes is regulated by the transcription factor nuclear factor kappa B (NF_kB), these observations suggest that PUFAs might somehow affect the activity of this transcription factor[10].

- **Amino Acids:**

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[11].

Arginine is required for the normal growth and proliferation of lymphocytes in vitro[12]. Also, supplemental *arginine* also benefits the innate immune response, with increases in macrophage and natural killer cell cytotoxicity[13].

Additionally, the anti-tumour activity of *arginine* has been studied in a number of models, with variable results. 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 while a similar effect was not seen in mice bearing a poorly immunogenic neuroblastoma[14].

Glutamine is another amino acid whose high rate of utilization by neutrophils, macrophages and lymphocytes and its increase when these cells are challenged suggests that provision of glutamine might be important to the function of these cells and so to the ability to mount an efficient immune response[5].

- **Carbohydrates:**

Dietary monosaccharides are represented by glucose and fructose. The commonest disaccharides are sucrose and lactose, but maltose and trehalose may also be present[15]. Both saccharides and lectins have the capacity to interfere with bacterial and viral attachment to epithelial cell surfaces within the alimentary canal, as has the major mucosal immunoglobulin, secretory IgA. All of a small group of lectins were found by immunoblotting to bind to secretory IgA via the secretory component. 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[16].

II- Micronutrients:

- **Vitamins:**

- Vitamin A:

Vitamin A deficiency is a leading cause of morbidity and mortality worldwide, especially among infants, children and women in developing countries. An estimated 253 million children are at risk of immunodeficiency due to Vitamin A deficiency in developing countries[17].

Vitamin A plays a role in the maintenance of mucosal surfaces, in the generation of antibody responses, in hematopoiesis and in the function of T and B lymphocytes, NK cells and neutrophils[18]. The influence of vitamin A on different aspects of immune function is attributed to the action of vitamin A and related metabolites as modulators of gene transcription[19].

Vitamin A supplementation reduces the morbidity and mortality from measles and diarrhoeal diseases in infants and children in developing countries[20,21]. Also, periodic high-dose vitamin A supplementation seems to reduce both morbidity among children born to HIV-infected mothers[22] and diarrhoeal disease morbidity in HIV-infected children after discharge from the hospital for acute lower respiratory tract infection[23].

- Vitamin C:

Vitamin C is an essential water-soluble antioxidant in cells and plasma. Besides metabolic functions, vitamin C is also known to contribute to immune homeostasis. Recently, it has been demonstrated that vitamin C has an inhibitory effect on the expression of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) in adult whole blood cells in vitro. It has been postulated that vitamin C might be an interesting compound for modulation of an over-exuberant immune response, e.g., in patient cohorts susceptible for the development of systemic inflammatory response syndrome such as neonates[24].

- Vitamin E:

Vitamin E is found in many dietary fats and oils, especially those containing PUFA .Thus, the dietary intake of vitamin E is related to the intake of PUFA. Since vitamin E is the most effective chain-breaking, lipid-soluble antioxidant present in cell membranes, it is considered likely that it plays a major role in maintaining cell membrane integrity by limiting lipid peroxidation by reactive oxygen species (ROS)[25].

Vitamin E and other antioxidant nutrients can influence a variety of inflammatory processes by inhibiting the activity of NF_k B, which is required for maximal transcription of many proteins that are involved in inflammatory responses, including several cytokines, such as IL-1B, IL-2 and TNF-α[26]. Also Vitamin E supplementation of the diet of laboratory animals enhances antibody production, lymphocyte proliferation, NK-cell activity, and macrophage phagocytosis[27].

- Carotenoids:

Carotenoids are natural fat-soluble pigments found in plants that help with photosynthesis reactions. They provide the bright red, yellow and orange coloration of many fruits and vegetables. The prevalent carotenoids in the human diet include beta-carotene, alpha-carotene, betacryptoxanthin, lycopene, lutein, and zeaxanthin. All have provitamin A activity, that is, they are converted to retinol, the active form of vitamin A, in the body[24].

Lycopene has been shown to have high singlet oxygen quenching capability and has been associated with anti-tumor promoting activities in various tissues in animal studies. There is also an association between lycopene intake, primarily from tomato products, and reduced risk for cancers at all sites and in the digestive tract and prostate[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]. This supports the idea that consuming a carotenoid-rich diet consisting of a variety of fruits and vegetables may be the best way for reducing the risk of cancer[24].

- Thiamine:

Thiamine is a water-soluble vitamin B also known as vitamin B1. Thiamine functions as a coenzyme in carbohydrate and branched-chain amino acid metabolism[24]. 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 that includes the form of the vitamin found naturally in certain foods (including citrus fruits and juices), called food folate, and the synthetic form of the vitamin that is added to fortified foods and supplements, called folic acid. Based on the results of human, in vitro and animal studies, it can be 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. Folate appears to have no effect on NK cell function. Some of the deleterious effects of folate deficiency on immune function are likely caused by defects in DNA and RNA synthesis or methyl metabolism, both of which may be significantly influenced by folate availability[24].

- *Vitamin B6:*

Low vitamin B6 concentrations could result in a reduced number of one carbon compounds, which may impair DNA and RNA synthesis and therefore cell proliferation and protein synthesis. Vitamin B6 may also affect immune function because it is necessary for the formation of the amino acid cysteine, an important precursor in glutathione, which is closely associated with lymphocyte proliferation[33].

Potential mechanisms by which vitamin B6 reduces cancer risk include reducing the disruption of DNA synthesis, repair, and methylation associated with inadequate vitamin B6 intake[25]**.** Also it may reduce cancer cell proliferation, reduce oxidative stress, suppress nitric oxide, or have antiangiogenic properties[34].

Table 1. Dietary reference intake (DRI) of some vitamins recommended for infants and children[35].

Age group	Vitamin A μg/day	Vitamin C mg/day	Thiamine mg/day	Vitamin B6 mg/day	Folate μg/day
0-6 mo	400	40	0.2	0.1	65
7-12 mo	500	50	0.3	0.3	80
1-3 yr	300	15	0.5	0.5	150
4-8 yr	400	25	0.6	0.6	200
Males 9-13 yr	600	45	0.9	1.0	300
Females 9-13 yr	600	45	0.9	1.0	600
Males 14-18 yr	800	75	1.2	1.3	400
Females 14-18 yr	700	85	1.0	1.2	600

Minerals:

- *Zinc:*

Zinc (Zn) is highly correlated with the protein content of foods, especially in animal protein foods[36]. Zn plays a role in multiple aspects of 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 $p56^{lck}$, an essential process in the early steps of T-cell activation[37]. Through this and possibly other pathways, Zn stimulates autophosphorylation of tyrosine residues by $p56^{lck}$ and subsequent phosphorylation of the T-cell-receptor complex involving CD45[38].

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. Also, T-cell responses, such as proliferation in response to mitogens, cytotoxicity and delayed-type hypersensitivity (DTH), are suppressed in those patients[39]. In addition to suppressed natural killer cell activity and chemotactic response of the monocytes[39,40].

A number of studies have demonstrated the benefits of Zn supplementation in regard to infectious diseases in human populations[40]. Controlled trials of Zn supplementation demonstrated a reduction in the incidence and duration of acute and chronic diarrhea by 25-30 %, and in the incidence of pneumonia by up to 50%[41]. Decreased Schistosoma mansoni egg counts were observed among children given Zn supplements versus those given a placebo[42].

- *Iron:*

Iron is the fourth most abundant element in the world; this points to the general importance of this metal for life. It is an essential nutrient for cells because of its role as a cofactor for enzymes in the mitochondrial respiration chain and oxidative phosphorylation, in the citric acid cycle (aconitase), and in DNA synthesis (ribonucleotide reductase)[43].

Iron interferes with cytokine activities and the cell-mediated immune effector mechanisms of macrophages, thus altering the immune response toward invading pathogens[44]. 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-γ-mediated pathways in macrophages, such as formation of the proinflammatory cytokine, TNF-α and expression of MHC class II antigen[45].

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 tumor cells[46]. 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[47].

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 activity, is increased; a condition that is rather unfavorable during a malignant disease or an acute infection. B cells are not prominently affected by iron homeostasis changes, while NK cells are sensitive to iron homeostasis imbalances with impaired proliferation in iron deficiency and overload[44].

- *Selenium:*

Selenium (Se) is present in most foods and human daily intake reveals a relatively wide range. Available data indicate that various milled wheat and corn products may contain 70% or more of selenium in the original crop. 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[48].

A major immunostimulatory effect of Se 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 then 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[49]. Also, Se supplementation appears to reverse the age-related decline in NK-cell function in elderly humans. The loss of NK-cell activity is one means by which cancer cells may evade immune-mediated destruction[50].

- *Probiotics:*

Microorganisms represent an essential functioning component of the mammalian intestinal lumen. While the stomach is sparsely populated by acid-tolerant microbes, post-gastric sites support an increasing microbial popular density. Under normal circumstances, these 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 such as maintenance: 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, feeding of *Lactobacillus rhamnosus* (strain HN001) or *Bifidobacterium lactis* (strain HN019) has been demonstrated to up-regulate peripheral blood NK-cell-mediated cytotoxicity against tumor cells[54]. Clinical studies have demonstrated that the orally delivered *L. rhamnosus* GG can also increase the frequency of pathogen-specific and total antibody-secreting cells in children during convalescence from *rotavirus* diarrhoea[55].

Supplementing the diets of newborn babies with the probiotic *Lactobacillus rhamnosus* (strain GG) can effectively reduce the incidence of atopic eczema during infancy and early childhood, suggesting that augmentation of the neonatal intestinal microflora with exogenous bacteria can provide the bacterial signals necessary to combat allergic sensitization[56].

In addition to anti-allergy immunoregulation, several studies have suggested that probiotics could be used to combat inflammatory-type diseases. There is some evidence that dietary consumption of immunoregulating LAB might assist in combating autoimmune diseases, including juvenile chronic arthritis[57]. The potential use of probiotics to augment the routine immune signaling events of the gut microflora, as a means of restoring vital anti-inflammatory immunoregulatory control mechanisms, has recently gained a great deal of attention as a promising means of combating inflammatory bowel disease[58].

- *Prebiotics:*

Prebiotics are defined as 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[59]. Compared with probiotics, which 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[60].

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[2]. In addition, a study among young children attending day care showed that prebiotic-supplemented cereal was associated with fewer episodes of diarrhea with fever than was control cereal, although the overall rate of diarrhea episodes was not different between the groups[61].

Examples of foods beneficial to the immune system:

Epidemiological and experimental studies demonstrate a negative correlation between the consumption of diets rich in fruits, and vegetables and the risks for chronic diseases, such as chronic inflammation and cancers[62]. Therefore, adequate supplementation with fruits and vegetables might play an important role in the control of acute and chronic diseases via immuno-modulation. Deep-colored fruits and vegetables have potential in stimulating Th1/Th2 cytokine secretions[63].

- ***Strawberries, red onions, peppers and spinach:***

Strawberry and red onions demonstrate an immuno-modulatory potential via stimulating splenocyte proliferation. The immuno-modulatory components in these fruits are highly correlated with phenolics, including flavonoids[63].

- ***Apples:***

Apples are one of the main sources of dietary flavonoids and showed the strongest associations with decreased mortality[64]. They have been found to have a potent antioxidant activity and can greatly inhibit the growth of liver cancer and colon cancer cells and may have higher bioactivity than the apple flesh[65]. Apple extracts significantly inhibited the TNF-alpha-induced NF-kappaB activation at a dose of 5 mg/ml. Inhibition of NF-kappaB activation in cancer cells is advantageous in cancer therapy by lowering the resistance to chemotherapy[66].

- ***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 secretion multipotent cytokine IFN-γ[67].

- ***Cruciferous vegetables:***

Increased intake, of cruciferous vegetables (CVs) such as cabbage, cauliflower, broccoli, Brussels sprouts, watercress, and mustard greens, is associated with a decreased risk of several cancers in human population studies[68] These foods are found to display several anti-carcinogenic properties in vivo including alterations in the activities of metabolic enzymes resulting in reduced carcinogenicity of dietary or environmental carcinogens in vivo, reduction of oxidative DNA damage levels in humans after supplementation with Brussels sprouts, and reduced DNA damage in human lymphocytes in conditions of increased oxidative stress after supplementation with cruciferous and leguminous sprouts[69-71].

- ***Tomato:***

Epidemiological and experimental data suggest that an increased intake of tomato products can reduce the risk of cancers, especially prostate and colon cancer. Several lines of evidence suggest that tomato constituents, such as lycopene, affect biological mechanisms such as modulation of immune functions and of antioxidant status[72].

- ***Garlic:***

Allicin is the active substance of fresh crushed garlic Allicin significantly inhibited 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. Thus local application of allicin may serve as a potential immune-mediating therapy in inflammatory bowel diseases[73].

Moreover, meta-analyses revealed that increased garlic consumption diminished the risk of stomach and colorectal cancers, but efficacy against developing other types of cancers was either equivocal or required additional study[74].

- ***Soybeans:***

Soybean possesses many traditional phytonutrients and several bioactive phytochemicals including flavonoids and saponins, which have a variety of potential health benefits, such as anti-inflammatory, anti-oxidative, anti-mutagenic, and anti-carcinogenic effects[75-78].

- ***Cereals (Rice and wheat):***

Lipopolysaccharide (LPS) or LPS-like components associated with cereal grains likely play a major role in IL-10 production from PBMCs. 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 immunostimulatory or immunoregulatory molecules in the cereals, such as carbohydrate polymers or lectins, to induce robust IL-10 production. This immunomodulatory effect might explain why most individuals who are at genetic risk for celiac disease do not have celiac disease or inflammatory bowel disease[79].

- ***Mushrooms:***

Mushroom proteins are potent immune activators and tumor cell growth inhibitors, mediating their effects by regulating cytokine secretion and proliferation, and seem to be mitogens and immunomodulators with therapeutic potential[80].

- ***Honey:***

The most promising bioactive compounds found in honey products are the proteins of royal jelly (RJ)[81]. The discovery that RJ-proteins may have physiological functions as suppressors of allergic reactions, as well as their proliferation stimulatory properties, opened a new era in application of RJ and honey[82].

- ***Dairy products (Yoghurt and cheese):***

Yogurt is one of the best-known foods that contain probiotics. To meet the National Yogurt Association's criteria for "live and active culture yogurt," the finished yogurt product must contain live lactic acid bacteria (LAB) in amounts $>10^8$ organisms/g at the time of manufacture, and the cultures must remain active at the end of the stated shelf life, as ascertained with the use of a specific activity test[83].

In human studies, cytokine production, phagocytic activity, antibody production, T cell function, and natural killer (NK) cell activity were shown to increase with yogurt consumption or when cells were exposed to LAB in vitro. There is some evidence that yogurt-induced immune enhancement is associated with a lowered incidence of cancer, GI disorders, and allergic symptoms[84].

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 function[85].

Cheese constitutes another family of milk-derived fermented products. Consumption of cheese is also believed to exert a stimulatory effect on immune system functions, but studies dealing with the immunomodulatory effect of cheese and its components are scarce[86]. In addition to the bacterial cell components, the immunomodulatory effect of cheese could also result from non-bacterial components such as peptides: the peptides present in a lyophilized extract of Gouda cheese suppressed proliferation of cultured human peripheral blood lymphocytes in vitro and induced apoptosis of human promyelocytic leukaemia cells[87].

How foods can be harmful to 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 up to two hours and beyond can occur[87]. Manifestations of IgE-mediated food allergy include any of the following: acute urticaria and angioedema, rhinoconjunctivitis, asthma, nausea, vomiting abdominal cramps and diarrhea. However, generalized urticaria and anaphylaxis can also occur. IgE-mediated food allergy occurs most often in association with certain foods. In young American children, cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish account for approximately 90% of IgE-mediated allergies. However, any food has the potential to cause allergy[88].

The oral allergy syndrome is another IgE-mediated hypersensitivity and considered as a form of contact allergy to certain (usually fresh) fruits, nuts and vegetables that is seen in up to 50% of patients with allergic rhinitis to pollen[89]. Symptoms are mainly confined to the oropharynx, and include the rapid onset of pruritus involving the lips, mouth and/or pharynx. Mild swelling of the lips is not uncommon. Symptoms generally subside within minutes after ingestion ceases. However, progression to systemic symptoms is thought to occur in approximately 10% of patients[87].

The non-IgE mediated food allergy or the combined pathways primarily affect the gastrointestinal tract in the form of diarrhea, nausea, vomiting, gastroesophageal reflux, and dysphagia. Poor weight gain and failure to thrive are common. Celiac disease is an extensive enteropathy leading to malabsorption. It is associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat, rye and barley. The age distribution of patients with celiac disease is bimodal, the first at

8-12 months and the second in the third to fourth decade. Celiac disease is associated with 2 class II histocompatibility antigens, HLA-DR3 and HLA-DQw2, in most populations tested[89].

In conclusion, supplementation with single or multiple micronutrients may enhance some immune functions even in healthy individuals. On the other hand, excess amounts of some nutrients may impair immune functions. Additionally, over-activation of the immune system can lead to detrimental 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. Knowledge in this field will indeed enable physicians to design proper nutritional regimens for children with vulnerable immune systems.

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