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REVIEW PAPER

Immunology and Its Relation with Food Components: An Overview

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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 is referred to as immunity. The early and later response towards the infection are termed as innate and adaptive immunity. The cells of immune system like neutrophils, macrophages, cytokines, lymphocytes etc. protect human body from various infectious agents like pathogenic micro-organisms, toxins, food borne allergens and other injuries or wounds. The origin of these cells is in the bone marrow from where they are distributed as circulating cells in the blood and lymph. Various food components have an immunomodulatory effect on the immune function and adequate nutrition is required for the proper functioning of immune system. The micronutrients like essential proteins, essential amino acids, vitamins (A, B_6, B_{12}, 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. However, over reaction of immune system leads towards the hypersensitivity reactions like autoimmunity which ultimately causes auto immune diseases and allergic reactions.

Keywords: Allergy, amino acids, immunity, immunomodulation, lymphocytes, probiotics

The term "immunity" has been derived from the Latin word "*immunitas*" which means protection from prosecution. Immune system involves various biological entities (cells, tissues and organs) and the processes (inflammation and immune tolerance) which are indispensable for defending the body from external and internal threats (Gershwin *et al.* 2000). The pathogenic micro-organisms, toxin compounds, air and food borne allergens are considered as external threats to the human body. Whereas, other factors like abnormal activity of gut microflora, abnormal cells (mutants) and tendency of immune system to attack itself (autoimmunity) are referred to as internal threats (Kussmann, 2010). The ability of an individual to resist these external and internal threats is referred to as immunity which is further classified as innate and acquired immunity. Both the components constitutes various blood borne factors (antibodies, complement, cytokines) and cells (leucocytes or white blood cells) which protect human body from various threats (Calder and Kew, 2002). The nutritional status and interaction of various food components with the immune system has an impact over the functioning of the immune system. Various components of foods like essential amino acids, fatty acids, vitamins and minerals along with intestinal microflora and certain bacteria (probiotic bacteria) have been reported to have immunomodulatory properties. So the studies on the effect of various food components on the immunity of an individual is important which might be helpful in preventing the declining activity of immune system and chronic diseases like cancer (El-Gamal *et al.* 2011). On the other hand, over activity of immune system leads to group of reactions called as hypersensitivity responses in which the immune system produce harmful response into the host (Silverstein, 2000). These hypersensitivity responses can be produced through endogenous self-antigens or exogenous antigens and lead to autoimmune diseases and allergic reactions which are characterized by variety of symptoms like itching, rash, fever, asthma and anaphylaxis (Basu and Banik, 2017 and Basu and Banik, 2018).

COMPONENTS OF IMMUNE SYSTEM (INNATE AND ADAPTIVE IMMUNITY)

Immune system defense mechanism has been characterized into 3 levels: (1) anatomic and physiologic barriers; (2) innate immunity; and (3) adaptive immunity. Anatomic and physiologic barriers prevent the entry of various pathogenic micro-organisms into the body. The various factors like intact skin, vigorous mucociliary clearance mechanisms, low stomach pH, and bacteriolytic lysozyme in tears, saliva, and other secretions act as anatomic and physiologic barriers (Turvey and Broide, 2010). The innate and adaptive immunity are the two important functional components of the immune system. The cells of the immune system (innate and adaptive immunity) arise from pluripotent hematopoeitic stem cells (HSC) which consists of myeloid and lymphoid lineage as depicted in the Fig. 1.

The first defensive mechanism or early response action after the attack of these threats is referred as innate immunity. It is also called as natural or native immunity and it is the first line of defence against any threat. Innate immunity mechanism is triggered within hours of the infection and is highly non-specific in nature (Marshall *et al.* 2018).

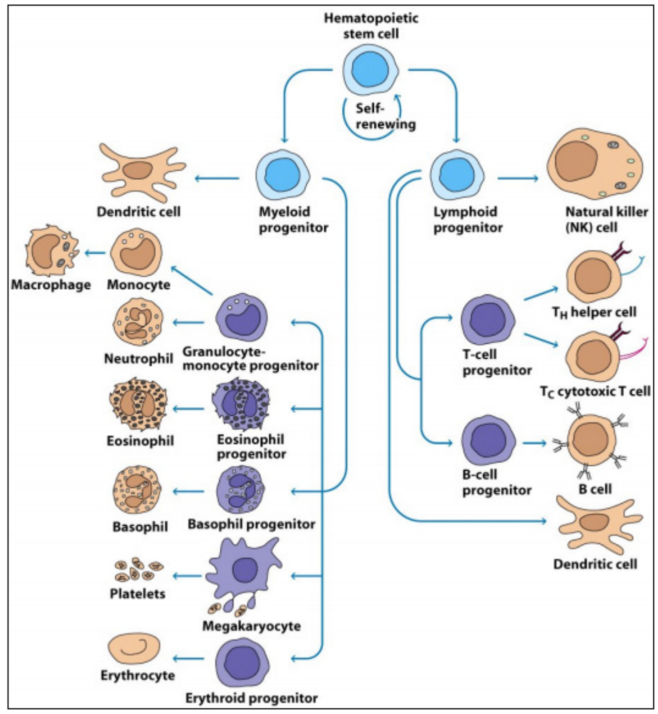

Fig. 1: Classification of cells of immune system (Source: Kindt *et al.* 2007; Kuby Immunology, 6th edition)

The innate immunity functioning process includes many cellular and biochemical events which prevent the entry of pathogenic micro-organisms and their products into the body. During the initial phase of innate immunity, there is production of cytokines which recruits the immune cells at the site of infection and inflammation (Warrington *et al.* 2011). These immune cells produce proteins and biochemical molecules which are termed as pattern recognition receptors. There is no immunological memory associated with the innate immune response and it is also unable to distinguish minute differences between the microbes as these responses are primarily produced against the molecules present over the pathogenic micro-organisms. The molecules found over the pathogenic micro-organisms like lipids and carbohydrates such as peptidoglycan, lipopolysaccharides, lipoteichoic acid and mannose-containing oligosaccharides are referred to pathogen associated molecular pattern (PAMP) and this pattern is recognised by specific proteins and biochemical molecules which are termed as pattern recognition receptors (Stewart, 2012). The foreign substances and dead cells present in organs, tissues, blood and lymph are removed by the innate immune response and it is also responsible for the activation of the adaptive immune response (Turvey and Broide, 2010 and Bonilla and Oettgen, 2010). The various cellular and soluble factors involved in innate immunity and their characteristic features have been mentioned depicted in Fig. 2 and Table 1. In addition to these cells, innate immune responsiveness is a property of the skin and the epithelial cells lining of the respiratory, gastrointestinal and genitourinary tracts (Turvey and Broide, 2010).

The ability of pathogens to mutate so as to avoid host detection and variation in antigenic structures, has led to the evolution of the adaptive (active) immune system (Cooper and Alder, 2006). Adaptive immunity function (host's second line of defence) can recognise small differences between micro-organisms so there is specific recognition of molecules (antigens) as a threat towards the human body. Due to this characteristic feature of adaptive immunity it is also termed as specific immunity. The adaptive immune system can also memorize the repetitive action of same pathogen towards the host. The adaptive immune response recognise the specific "non-self" antigens of the invading pathogen in the presence of "self" antigens and antibodies like immunoglobulins (Ig) which are produced by B lymphocytes and T lymphocytes. Further it leads towards the pathogen-specific immunologic effectors pathways which remove the invading micro-organisms and infected cells from the host. As it can memorize the pathogen, there is development of an immunologic memory which eliminate the specific pathogen during repetitive attack into the human body (Calder and Kew, 2002 and Bonilla and Oettgen, 2010). Lymphocytes are the major cells of adaptive immune system and are classified as B lymphocytes and T lymphocytes. B lymphocytes cells further get differentiated into these two subsets based on the strength of B cell receptor (BCR) signalling in individual cells. Follicular type I B cells are developed in the presence of stronger BCR signals whereas weaker signals favour the development of marginal zone B cells (Pillai and Cariappa, 2009). These follicular type I B cells and marginal zone B cells are further involved in the generation of antibodies in the host. T lymphocytes are subdivided into two classes namely CD4+ and CD8+ and this classification is on the basis of the expression of two different nonpolymorphic surface glycoproteins. The CD4+

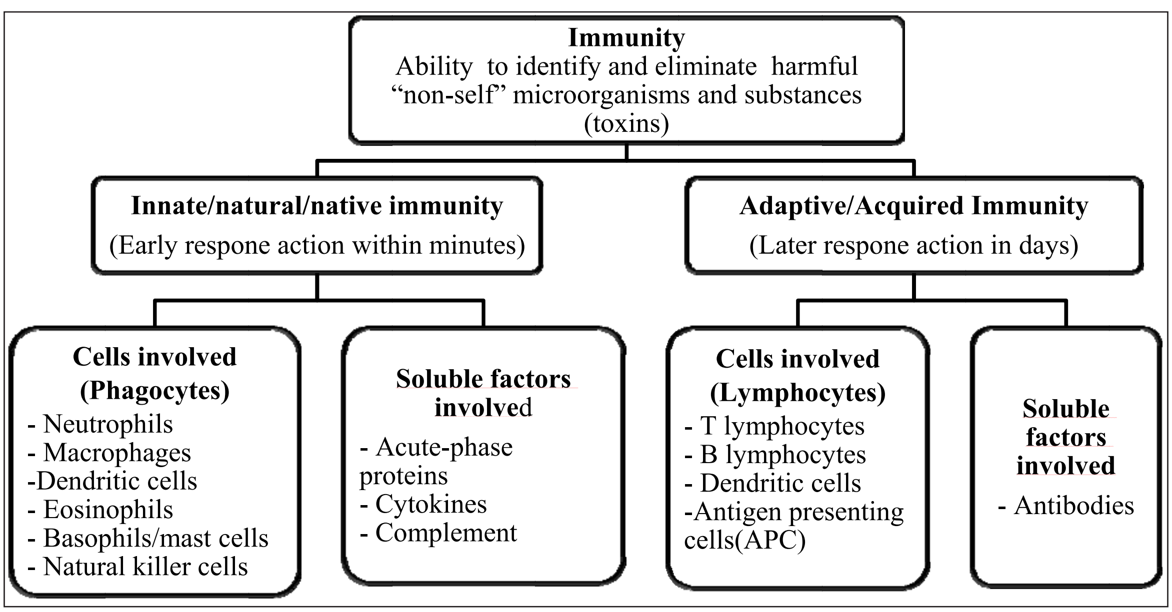

Fig. 2: Overview of immune system

Table 1: Characteristics of major cells of immune system

Cell	Origin	Size, shape and nucleus	Cell life	Role in immunity and functions
IgE	Lymph nodes and spleen	• Y-shaped structure	2 days	• Essential components of allergic inflammation • Elevated IgE levels are seen in patients with atopic diseases
Neutrophils	Bone marrow	• 12-15 μm • Projected • Multilobed nucleus	6 hours to few days	• Effector cells in the innate immune system • Phagocytosis and degranulation
Basophils	Originates in hematopoietic stem cells and mature in bone marrow	• 5-7 μm • Segmented • Bi- or tri-lobed nucleus	Few hours to few days	• Important in some allergic responses • Degranulation • Release of histamine and enzymes
Mast Cells	Undifferentiated cells from bone marrow and mature in tissues	• 6-12 μm • Oval or round • Single lobed nucleus	Months to years	• Wound healing in innate and adaptive immunity • Degranulation • Release of histamine, enzymes and cytokines
Eosinophils	Pluripotent hematopoietic stem cells differentiate into an eosinophil and develops in bone marrow	• 12-17 μm • Bi-lobed nucleus	8-12 days	• Release proinflammatory mediators • Degranulation of substances that kill parasites and worms • Release of enzymes, growth factors and cytokines
Monocytes	Bone marrow pluripotent stem cells	• 10-20 μm • Kidney/bean shaped nucleus	Hours to days	• Phagocytosis • Surface receptors for Abs (opsinized Ags)
Macrophages	Established during embryonic development	• 20-80 μm • Wide variability	Months to years	• Surface receptors for Abs (opsinized Ags) • Differentiate into dendritic cells to elicit an immune response
Dendritic cells	Bone marrow-derived cells	• 6-15 μm • Small round cells		• Best APC (Antigen presenting cells) for presenting to naïve T-cells
Lymphocytes (T cells and B cells)	Stem cells in the bone marrow and mature into T cells in thymus	• 6-20 μm • Eccentric nucleus	Weeks to years	• B lymphocytes: production of antibodies (Follicular B cells and marginal B cells) • T helper cells (CD4+): immune response mediators • Cytotoxic T cells (CD8+): cell destruction
Natural killer (NK) cells	Stem cells in the bone marrow	• Single-lobed nucleus	7-10 days	• Tumour rejection • Destruction of infected cells • Release of perforin and granzymes

S*ource: Kindt et al. 2007; Murphy et al. 2007; Turvey and Broide, 2010; Stone et al. 2010; Warrington et al. 2011; Zuidscherwoude and van-Spriel, 2012; Epelman et al. 2014; Marshall et al. 2018 and Sutton et al. 2019.*

cells possess a helper-inducer phenotype, while the CD8+ cells are having cytotoxic-suppressor functions and are responsible for the production of cellular immune response (Veillette *et al.* 1988). The T cell response is termed cell-mediated immunity whereas the B lymphocyte response towards the antigen is termed humoral immunity (Calder and Kew, 2002). Antigen presenting cells (APCs) and B cells activates the T cells of the adaptive immune system which differentiate into plasma cells to produce antibodies (Warrington *et al.* 2011). Specific immunity can be acquired or induced by overt clinical infection or inapparent clinical infection and deliberate artificial immunization (Stewart, 2012). The development of lymphocytes occurs in primary lymphoid organs (thymus and bone marrow) and then they pass into secondary lymphoid organs, including lymph nodes and the spleen where they target the circulating antigens from lymph and blood, respectively (Bonilla and Oettgen, 2010). The cells involved in innate and adaptive immunity along with their characteristic features have already been summarized in Fig. 2 and Table 1.

IMMUNOMODULATORY PROPERTIES OF FOOD COMPONENTSO

Immunomodulation refers to the ability of the immune system which protects the human body from various pathogenic micro-organisms and life threatening diseases like cancer, multiple sclerosis and aging (Naidoo *et al.* 2014; Havla *et al.* 2015; Routy *et al.* 2016 and Kang *et al.* 2019). The healthy immune system plays an important role in maintaining human health and nutrition plays an important role in the modulation of immune function. So various food components having immunomodulatory effect is a major concern of study as it is associated with improved immunological tolerance toward diseases leading to a better health of human being (Jedrychowski *et al.* 2009). The micronutrients like proteins and essential amino acids, vitamins (A, B_6, B_{12}, C, D, E and folic acid), fatty acids, minerals (iron, selenium, zinc and copper) are of prime importance towards healthy immune system. Immunomodulators can be classified into the following three categories: Immunoadjuvants, immunostimulants, and immunosuppresants. An adjuvant is an agent that stimulates the immune system, increasing the response to a vaccine, while not having any specific antigenic effect. Immunostimulants are envisaged to enhance body's resistance against infections (and may be against allergy, autoimmunity, and cancer as well), can act through both the innate and adaptive arms of the immune response. Immunosuppresants are used for the control of pathological immune response in autoimmune diseases, graft rejection, graft versus host disease, hypersensitivity (immediate or delayed type), and immune pathology associated with infections (Venkatalakshmi *et al.* 2016). The ability of immune system to fight with diseases is highly dependent on inadequate or deficient micronutrient status (Fig. 3).

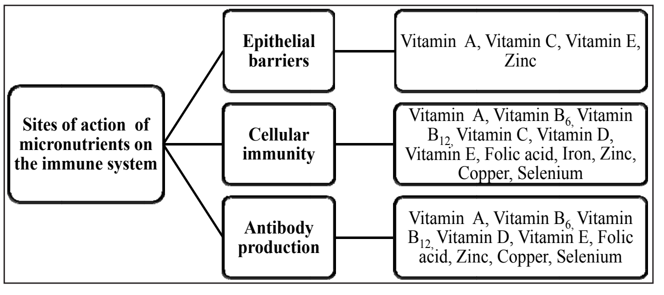

Fig. 3: Summary of the sites of action of micronutrients on the immune system (Adapted from Knight, 2000)

Proteins, amino acids and peptides

Proteins are the one of the main building material of human body and regarded as nutritious source of amino acids and biologically active peptides (Reyes-Diaz *et al.* 2018). The various protein compounds present in hemolymphs and hemocytes helps in preserving several immune components, such as metalloproteins, glycoprotein, amino sulfonic acid, antimicrobial peptides (AMPs), protease inhibitors, and coagulation factors. (Kang *et al.* 2019). The bioactive peptides which are released from proteins interact with specific receptors leading to stimulation/inhibition of immune system which ultimately have an impact on human health (Muro-Urista *et al.* 2011; Choi *et al.* 2012; De-Gobba *et al.* 2014; O'Keeffe and FitzGerald, 2015 and Reyes-

Diaz *et al.* 2018). Most of the most of the protein hydrolysates like soy, egg, wheat, casein etc increases the macrophage phagocytosis capacity and helps in preventing the wide variety of immune related disorders (Kazlauskaite *et al.* 2005; Kong *et al.* 2008; Wu *et al.* 2016; Meram and Wu, 2017 and Kiewiet *et al.* 2018). Reyes-Diaz *et al.* (2018) have reported effects on the modulation of the immune system with milk proteins in the presence of bacteria, like LAB. The hydrolysis of GMP (glycomacropeptide) by pepsin resulted in higher proliferative and phagocytic activities leading to enhanced immunostimulatory activities (Li and Mine, 2004). Whey proteins have been reported to enhance non-specific and specific immune responses through both *in vitro* and *in vivo* experiments and it also offers protection against colon and mammary tumours (Kumar *et al.* 2017). The isolated substances from mushroom (fungal proteins) such as polysaccharides, polysaccharo-peptides, polysaccharide-proteins and proteins exhibit *in vivo* and *in vitro* immunomodulatory activities like activation of immune effector cells such as human peripheral blood mononuclear cells (hPBMC) and differentiation of hematopoietic stem cells (Wasser, 2002; Berovic *et al*. 2003; Jin *et al*. 2003; Lull *et al*. 2005; Wang *et al.* 2012). Kang *et al.* (2019) have reported that marine-derived proteins, peptides, and protein hydrolysates exhibits antimicrobial, anticancer, antioxidant, antihypertensive and anti-inflammatory activities. The amino acid arginine has been reported to have anti-tumour activity whereas, glutamine has an ability to boost the efficiency of immune response (Calder and Field, 2002 and El-Gamal *et al.* 2011). Supplemental arginine helps in increasing the number of macrophages and NK cells which have beneficial effects in innate immunity response (Reynolds *et al.* 1988). Aspartate and glutamate have an important role in the proliferation, metabolism and function of leucocytes which are constituent cells of the immune system (Newsholme *et al.* 2003).

The low levels of protein intake by the body (Protein energy malnutrition) are associated with various respiratory and gastrointestinal infections and can be directly associated with several defects in the functioning of the immune system (Faria *et al.* 2013). It can lead to the reduction in total number of T and CD4 lymphocytes, weakens the production of antibodies, lowers the level of immunoglobulins, depresses IgA secretion and impairs synthesis of the complement system proteins (Szponar and Respondek, 1998). The various immunological effects of proteins, amino acids and peptides have been mentioned in Table 2.

Vitamins and anti-oxidants

Vitamins along with other anti-oxidants modulate immune cell function through regulation of redox-sensitive transcription factors and affect production of cytokines and prostaglandins along with counteracting the potential damage caused by reactive oxygen species to cellular tissues (Maggini *et al.* 2007). The compounds having antioxidative functions help to shape the immunological and modification of diet toward increased antioxidative potential with components that are characterized by high antioxidative property (Vitamin A, C, E, glutation, ubiquinon, and flavonoids) is used by sports people in order to maintain balance between oxygen reactive forms and antioxidants in the body cells (Jedrychowski *et al.* 2009).

Vitamin A has an important role in maintaining vision, promoting growth and development, and protecting epithelium and mucus integrity in the body. It plays a crucial role in enhancing immune function so it is also termed as anti-inflammation vitamin. It is also involved in the development of the immune system and plays regulatory roles in cellular and humoral immune responses or processes (Huang *et al.* 2018). Carotenoids compounds like α-carotene, β-carotene, betacryptoxanthin, lycopene, lutein and zeaxanthin have provitamin A activity, as they are converted to retinol (active form of vitamin A) in the human body. Various studies suggests hat the risk of cancer can be reduced by consuming a carotenoid-rich diet consisting of a variety of fruits and vegetables. The presence of B vitamins in diet helps in regulation of immune system by proper functioning of the methylation cycle, monoamine oxidase production, DNA synthesis, repair and

Table 2: Immunological effects of proteins, amino acids and peptides

Component	Immunomodulatory effects	Reference
Calorie-protein Excess	• Increased number of macrophages	Szponar and Respondek, 1998; Jedrychowski *et al.* 2009
Protein hydrolysates (Soy protein and wheat gluten)	• Increased macrophage phagocytosis • Ameliorate, delay and prevent onset of immune related conditions • IncreasedCD11b+ cells and CD56 • Increased NK cell activity	Horiguchi *et al.* 2005; Kong *et al.* 2008; Yimit *et al.* 2012; Wu *et al.* 2016; Meram and Wu, 2017; Kiewiet *et al.* 2018.
Milk proteins (*L. delbrueckii* subsp. *bulgaricus, S. thermophilus* and *L. casei* and *L. helveticus*)	• Increased IgA, macrophages and dendritic cells • Increased phagocytic activity	LeBlanc *et al.* 2002; Galdeano *et al.* 2007; Vinderola *et al*. 2007; Reyes-Diaz *et al.* 2018
Fungal proteins (Mushrooms)	• Differentiation of hematopoietic stem cells • Activation of immune effector cells (Human peripheral blood mononuclear cells)	Wasser, 2002; Berovic *et al*. 2003; Jin *et al.* 2003; Lull *et al*. 2005; Wang *et al.* 2012
Peptides/ Neuropeptides	• Modulators of immunoglobulin E synthesis	Aebischer *et al.* 1994; Jedrychowski *et al.* 2009
Amino acids (Arginine, cysteine, histidine, leucine, proline, tryptophan)	• Activation of T lymphocytes, B lymphocytes, natural killer cells and macrophages • Cellular redox state, gene expression and lymphocyte proliferation • Production of antibodies, cytokines and other cytotoxic substances • Regulation of immune responses • Inhibition of the production of inflammatory cytokines and superoxide	Newsholme *et al.* 2005; Calder and Yaqoob, 2004; Li *et al.* 2007
Calorie-protein undernourishment	• Disturbs cellular tolerance leading to increased infectious disease incidence and mortality	Szponar and Respondek, 1998; Jedrychowski *et al.* 2009

maintenance of phospholipids such as myelin (Mikkelsen *et al.*, 2017). Vitamin C has a role to play in maintenance of various cellular functions of both the innate and adaptive immune system. Vitamin C supports epithelial barrier function against pathogens and enhances chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. It is also involved in apoptosis and clearance of the spent neutrophils from sites of infection by macrophages (Carr and Maggini, 2017). Vitamin D also possesses immunomodulatory activities and various studies demonstrate the role of $1,25(OH)_2D_3$ in increasing the ability of the innate immune system to fight against pathogens by chemotaxis, autophagy and phagolysosomal fusion (Sassi *et al.* 2018). The incidence of various auto immune diseases like diabetes mellitus, multiple sclerosis, rheumatoid arthritis, fibromyalgia and others (tuberculosis and leprosy) can be lowered down by enhanced vitamin D intake (Radovic *et al.* 2012). Vitamin E can influence a variety of inflammatory processes by inhibiting the activity of NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), 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-α26 (Lavrovsky *et al.* 2000). Meydani and Beharka, (1998) have reported that supplementation of laboratory animals with vitamin E enhances antibody production, lymphocyte proliferation, NK-cell activity, and macrophage phagocytosis.

The antioxidants acts as bacteriostatic and bacteriocidal agents and its therapeutic applications can slow down or reverse various symptoms associated with neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) and spongiform encephalopathies (Brambilla *et al.* 2008 and Kashyap *et al.* 2017). The diet deficient in various vitamins and anti-oxidants can leads towards impaired body's natural defence system and poor immune system of the individual. The various immunological effects of vitamins and anti-oxidants present in human diet have been summarized in Table 3.

Fatty acids

Fats in the form of fatty acids (FA) are involved in the modulation of structural and functional properties at the cellular level which are selectively attributable to the long-chain polyunsaturated fatty acids (LC PUFA) of the n-6 and n-3 series (Galli and Calder, 2009). The consumption of long-chain n-3 fatty acids (fish oils) enhance certain immune functions, whereas high intakes induce lymphocyte apoptosis and are inhibitory on a wide range of functions, e.g., antigen presentation, adhesion molecule expression,

Table 3: Immunological effects of vitamins and anti-oxidants

Component	Immunomodulatory effects	Reference
Vitamin A	• Immunoglobulin production • Regulation of B cell activity • Treatment of infectious diseases like tuberculosis, AIDS, measles, diarrhoea and malaria	Bhandari *et al.* 1994; Mayo-Wilson *et al.* 2011; Elom *et al.* 2014; Huang *et al.* 2018
Carotenoids	• Reduced risk for cancers in digestive tract and prostate • Reduced risk of gastric adenocarcinomas and lung cancer	Nishino *et al.* 2002; Ito *et al.* 2005; Jeneb *et al.* 2006; El-Gamal *et al.* 2011
Vitamin B • B_6 • B_{12} • Folate	• Regulation of antibody DTH response, cytokines, NK cell activity and lymphocyte proliferation • Modulatory agent for cellular immunity (CD8+ and NK cells) • Improves overall immune function in elderly individuals	Trakatellis *et al.* 1997; Tamura *et al.* 1999; Troen *et al.* 2006
Vitamin C	• Enhance chemotaxis, phagocytosis, generation of reactive oxygen species and microbial killing. • Apoptosis and clearance of spent neutrophils • Modulates cytokine production and enhances antibody levels	Tanaka *et al.* 1994; Carr and Maggini, 2017; Gao *et al.* 2017; Portugal *et al.* 2017
Vitamin D	• Prevention of disorders due to deregulation of immune system • Increases the phagocytic activity (macrophages and NK cells) and microbicidal activity (phagocytes) • Active form of Vitamin D i.e. 1, $25(OH)_2D_3$ increases the ability of immune system to fight against pathogens	Radovic *et al.* 2012; Goldsmith, 2015; Sassi *et al.* 2018
Vitamin E	• Regulation of dendritic cells (DCs), macrophages, natural killer (NK) cells, T cells and B cells. • Lymphocyte proliferation • Lower incidence of presumptive clinical malaria	Meydani *et al.* 1990; Olofin *et al.* 2014; Lee and Han, 2018
Antioxidant supplements	• Reverses age associated immune deficiencies • Cytoprotection and prevention of free radical related disorders	Knight, 2000; Brambilla *et al.* 2008
Deficiency of various vitamins	• Disturbed immune system (retarded production of antibodies and cytokines or proliferation of lymphocytes	Jedrychowski *et al.* 2009

Th1 and Th2 responses, proinflammatory cytokine and eicosanoid production (Harbige *et al*. 2003). Calder (1994) have reported the importance of PUFAs (Polyunsaturated fatty acids) as it is highly required during generation of immune response in lymph nodes as lymphocytes preferentially incorporate n-6 fatty acids during growth and proliferation. PUFAs also help in regulating the expression of genes for cytokines, adhesion molecules, inducible nitric oxide synthase and inflammatory proteins (Wallace *et al.* 2001). The shortage of fatty acids can cause depression or considerable impairment of humoral and cellular tolerance response whereas low-fat diet with little omega-3 acids, causes elevated production of pro-inflammatory IL-1 and TNF-α cytokines. The diet poor in fat and rich in omega-3 can cause decrease in the number of T CD4 cells, IL-1, IL-6, and TNF-α while T CD8 cells are increased significantly (Erickson, 1998 and Jedrychowski *et al.* 2009). Cook and Pariza (1998) studied the effect of eicosonoids (prostaglandins, thromboxanes, leukotrienes) and reported their contribution to the maturation and differentiation of B and T lymphocytes, NK cells, macrophages and cytokines. The diet rich in cis-9, trans-11 CLA (Conjugated Linoleic Acid) isomer has an important role in the enhancement of $CD8^+$ T cells (Yamasaki *et al.* 2003). The CLA isomers are potent modulators of PPARs (Peroxisome proliferator-activated receptors) and these fatty acid receptors are involved in regulating expression of various genes involved in proliferation of lymphocytes and monocytes or macrophages, apoptosis, and inflammation (O'Shea *et al.* 2004). On the other hand Omega-3 and Omega-6 acids have a negative impact on the immune system as these decrease the number of lymphocytes, depress mitogenic response of T cells, depress the cytotoxic activity of macrophages and increase the incidence of cancer (Szponar and Respondek, 1998).

Minerals

The trace minerals like iron, zinc, selenium and copper are important for proteins and enzymes for their proper functioning and play a crucial role in biological processes, such as oxygen transport, cell growth and differentiation**,** and protection against oxidative stress. The intake of zinc has been found linked with immunological properties and is very essential for highly proliferating cells, specifically in the immune system (Alpert, 2017). Zinc is associated with the normal development and functioning of cell-mediating innate immunity, neutrophils, and natural killer cells (Prasad, 2009). Zinc acts as an essential cofactor for thymulin which modulates cytokine release and induces proliferation (Maggini *et al.* 2007). Iron is an essential component of human diet which maintains the proper functioning of macrophages especially macrophage listericidal mechanisms and helps in regulation of cytokine production, activation of protein kinase C and regulation of cell proliferation (Alford *et al.* 1991; Maggini *et al.* 2007 and Jedrychowski *et al.* 2009). Ferrucci *et al.* (2010) reported that after 65 years of age, anaemia and low iron status was one of major causes with elevated pro-inflammatory markers. The inhibition of IFN-γ mediated pathways in macrophages like formation of the proinflammatory cytokine, TNF-α and expression of MHC class II antigen is directly associated with iron loading of macrophages (Weiss *et al.* 1992). Selenium is an essential micronutrient which helps in up-regulation of expression of the α and ß subunits of the IL-2 receptor, which are expressed on many immune cells. Selenium boosts up the immune system by increasing the cytotoxicity of killer cells, numbers of lymphocytes and promotes antibody production by B lymphocytes (McKenzie *et al.* 2002). The supplementation of diet with selenium has an immuno-stimulatory effect, which includes T cell proliferation, NK cell activity, innate immune cell functions (Huang *et al.* 2012). Nelson *et al.* (2011) reported that selenium induces a phenotypic switch in macrophage activation from a classically activated, pro-inflammatory phenotype (M1) toward an alternatively activated, anti-inflammatory phenotype (M2) and selenium plays an important role in M2-mediated clearance of helminthic parasite infections. The increased levels of intake of selenium in the diet may protect neutrophils from endogenous oxidative stress (Kose and Naziroglu, 2014). The manipulation of individual selenoproteins (protein with selenocysteine amino acid) may enhance the immune system and is precise approach in mitigating chronic inflammation (Avery and Hoffmann, 2018). Copper is also having an important role in the development and maintenance of the immune system and its intake in diet alters several aspects of neutrophils, monocytes and superoxide dismutase (Maggini *et al.* 2007). Percival (1998) reported that diet poor in copper can lead to reduction in interleukin 2 which affects the T cell proliferation process and ultimately weakens the immune system. The diet poor in zinc, iron, selenium and copper can lead towards inhibited activity of NK cells, depressed secretion of cytokines, and lower number of B and T lymphocytes in peripheral blood (Jedrychowski *et al.* 2009). The various immunological effects of minerals have been summarized in Table 4.

Phytochemicals

Phytochemicals are naturally occurring compound with bioactive potentials, which posses immunostimulating activity. Antioxidant phytochemicals such as alkaloids, polysaccharides, lectins, glycosides, phenolic compounds, flavonoids, anthocyanins, tannins, saponins, terpenoids and sterols can be found in many foods and medicinal plants, which posses immune-modulating activity and play an important role in the prevention and treatment of chronic diseases caused by oxidative stress (Venkatalakshmi *et al.* 2016; Zhang *et al.* 2015). The various phytochemicals often possess strong antioxidant and free radical scavenging abilities, as well as anti-inflammatory action, which are also the basis of other bioactivities and health benefits, such as anticancer, anti-aging, and protective action for cardiovascular diseases, diabetes mellitus, obesity and neurodegenerative diseases (Zhang *et al.* 2015). Polyphenols can protect the cardiovascular system from oxidative stress and also have blood pressure reduction and inflammation decreasing action (He *et al.* 2012). The high lycopene intake diet and serum lycopene levels were inversely related to certain types of cancers whereas, β-carotene along with lycopene could inhibit cell proliferation, arrest cell cycle, increase apoptosis of human breast cancer cells (Gloria *et al.* 2014 and Tang *et al.* 2011). Alkaloids play an important role in enhancing the immune system

Table 4: Immunological effects of minerals

Component	Immunomodulatory effects	Reference
Zinc	• T lymphocyte activation and signal transduction • Reduction in acute and chronic diarrhoea • Stimulates immune system (increased B, T and CD4+ cell activity) and delayed hypersensitivity response	Ruel *et al.* 1997; Knight, 2000; Prasad, 2009; El-Gamal *et al.* 2011
Iron	• Apoptosis (programmed cell death) • Alteration of immune response towards invading pathogens • Activation of NF-Kb involved in innate immunity and inflammation	Weiss, 2004; Vallabhapurapu and Karin, 2009
Selenium	• Regulation of expression of the α and ß subunits of the IL-2 receptor involved in T and B lymphocytes • Improved potential of cytotoxicity of killer cells, increased numbers of lymphocytes, promotes antibody production by B lymphocytes • Control of age-related decline in NKcell function • Proliferation and differentiation of cluster of differentiation(CD)4^+ T helper (Th) cells.	Ravaglia *et al.* 2000; McKenzie *et al.* 2002; El-Gamal *et al.* 2011; Avery and Hoffmann, 2018
Copper	• Development and maintenance of the immune system	Maggini *et al.* 2007

and possess anti-tumor, antimicrobial and analgesic activity (Venkatalakshmi *et al.* 2016). The other phytochemicals like anthocyanins, curcumin and viniferin (resveratrol dimer), have anti-cancerous property and can reduce inflammation via inhibition of prostaglandin production and nuclear factor-κB activity, enzyme inhibition, along with enhancement of cytokine production (Hutchins-Wolfbrandt and Mistry, 2011, Costa *et al*. 2013 and Thakur *et al*. 2018).

Probiotics

Probiotics are the non-pathogenic group of microorganisms which provide beneficial effects on the host when administered in adequate number in an individual. The major organisms included in commercial probiotics include lactic acid bacteria (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Enterococcus faecium*) and *Bifidobacterium spp*. Probiotics helps in enhancement of the innate and adaptive immunity and modulate pathogen-induced inflammation, functions of dendritic cells, macrophages, and T and B lymphocytes (Vanderpool *et al.* 2008 and Yan and Polk, 2010). Matuzaki and Chin (2000) have reported that the intake of *Lactobacillus rhamnosus* (strain HN001) or *Bifidobacterium lactis* (strain HN019) can up-regulate the peripheral blood NK cell- mediated cytotoxicity against tumor cells. Clinical applications of the probiotic genes and probiotic-derived factors includes regulation of host immunity by enhanced phagocytosis by neutrophils and monocytes along with prevention and treatment of diseases including infectious diarrhea, antibiotic-associated diarrhea, atopic diseases, necrotizing entero-colitis, ulcerative colitis, irritable bowel syndrome, eczema, viral infection and extra-intestinal diseases, such as allergy (Yan and Polk, 2011).

HYPERSENSTIVITY

The defects or malfunctions in the innate or adaptive immune response are due to overactive immune response called as hypersensitivity which can lead to illness or disease (Marshall *et al.* 2018). On the basis of mechanism of action, Gell and Coombs classified hypersensitivity responses into 4 types. The immediate allergic reactions like anaphylaxis and cytotoxic or antibody-dependent hypersensitivity response are referred as Type I type II hypersensitivity responses, respectively. Type III hypersensitivity responses are mediated by antibody-antigen complex and Type IV hypersensitivity are cell mediated responses that incorporate with sensitized T helper cells (Marshall *et al.* 2018 and Basu and Banik, 2018). Recently, the stimulation of the endocrine system by immune responses in some autoimmune diseases has been categorized as fifth type of hypersensitivity responses (Basu and Banik, 2018).

CONCLUSION

Immunology refers to the study of the immune system and immune system includes various cells, tissues and their soluble products that defend the body from external and internal threats. The normal functioning of the immune system or ability of an individual to fight these threats is termed as immunity. The first line of defense against any microbial infection is called as innate immunity (within minutes) whereas later response is called as adaptive immunity (days after infection). To protect human body from the external and internal threats, both the defence system involving various blood borne factors (antibodies, complement, cytokines) and cells (leucocytes or white blood cells) are significant. 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. However, over activation of immune system can lead towards various hypersensitivity responses and can cause various auto-immune diseases and allergic reactions

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