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Immunomodulators in Day to Day Life: A Review

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Abstract: There are ongoing trends of immunomodulation to combat a vast range of human and animal diseases including the incurable diseases like viral diseases, cancers, autoimmune diseases and inflammatory conditions. Animate as well as non-animate factors, surrounding us are interacting with our immune system. A balanced diet should contain all essential components from energy to vitamin and trace minerals. Each of these constituent has a very special effect on the immune system starting from their development to active role in immunity therefore, the outcome of their deficiency often ends in disease. Edible items which we consume like various vegetables, spices, herbs, fruits etc., are also equally responsible in manipulation of our system either in positive or negative way. Water has biggest share in our body and acts as the main medium to support the activities of the different system of body without exception of immune system. Proper environmental temperature is essential to maintain body's functions and experiments carried out regarding the effect of temperature suggest that extremes of the temperature are often cause immunosuppression directly by acting on the cells of immunity or indirectly through inducing stress and thereby increasing production of catecholamine which are potent anti-immune molecules. Various pathogenic as well as non-pathogenic bacteria cause immune suppression and immune potentiation, respectively. Proper exercise hold a prime position in the healthy life as it supports immunity and keeps disease away. The present review deals with all these immunomodulators having both positive and negative impact on the health status of an individual.

Key words: Immunity, immunomomodulation, food, vitamins, minerals, protein, fat, microbes, probiotics, environment, water

INTRODUCTION

Since a long time, the pathogens of humans and animals are coexisting but the development in economies and changing global scenario are creating the risk of new diseases and enhancing the old known diseases. Due to change in the structure of human and animal population, the prevalence of zoonotic diseases like salmonellosis (Verma *et al*., 2007, 2011a, b), brucellosis (Kumar *et al*., 2009), campylobacter (Kumar *et al*., 2012a,b), *Arcobacter* infection (Patyal *et al*., 2011), swine flu (Pawaiya *et al*., 2009; Dhama *et al*., 2012), leptospirosis (Verma *et al*., 2012a,b) etc. are increasing day by day. Apart from zoonotic diseases certain animal diseases causes direct and/or indirect economic losses to livestock industry for examples such as foot-and-mouth disease (Verma *et al*., 2008a, b), calf diarrhea (Dhama *et al*., 2009, 2011; Malik *et al*., 2012; Hansa *et al*., 2012), mycoplasma infection (Kumar *et al*., 2011, 2012; Jain *et al*., 2012) and canine parvovirus (Singh *et al*., 2013). In poultry too some of the diseases like chicken infectious anemia (Dhama *et al*., 2002; Bhatt *et al*., 2011), avian tuberculosis

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(Dhama *et al*., 2011a, b), avian influenza (Dhama *et al*., 2005), fowl adenoviral infection (Gowthaman *et al*., 2012), marek's disease (Singh *et al*., 2012) poses a major threat to poultry industry (Dhama *et al*., 2008). In modern days, there are ongoing trends of immunomodulation to combat with a vast range of human and animal diseases including the incurable diseases like viral diseases, cancers, autoimmune diseases and inflammatory conditions (Pirofski and Casadevall 2006; Actis *et al*., 2008; Hart *et al*., 2012; Mahima *et al*., 2012a-c; Yao *et al*., 2013). Immune system acts as a protecting shield, which protect the body from various pathogenic microbes like bacteria, virus, fungi and some free radicals. So in a healthy body, the immunity has to be in perfect condition. There are variety of the factors around us those are constantly manipulating our immune system at large or silently. These factors surround us all the time or encounter occasionally but definitely leave a mark on our health in the form of either suppression or stimulation of our defense system. This may either plunge us to disease or save from the same. From the wake at morning to sleep at night and from birth till end of life, we are constantly being bombarded with these animate as well as inanimate objects. No living being can escape their beneficial or the ill effect. Perhaps the health is an example of the perfect balance between these two forces acting in opposite direction on the animals, an imbalance in this generally leads to the condition we know it by the name disease (Fig. 1).

As mentioned, both living as well as non living objects can act as an immunomodulators. The inanimate objects include food derived microparticles like aluminium silicate and titanium dioxide (Becker *et al*., 2012; Wischke *et al*., 2012) our very next environmental factors such as air, radiation, temperature, pressure, water, food, toxins and the most important the stress generated in the body of an individual by complex interaction of these factors which again manipulate our immune system (Bengmark, 2012). The living objects includes various infectious agents namely, bacteria, viruses, parasites, fungi, protozoa, different plants.

Factors encountering with animals in daily life such as:

- Food
- Water
- Temperature, pressure, humidity and pollution, constituting environment
- Stress

Food: It is well said that 'we are what we eat'. The food, we eat consists mainly of carbohydrates, proteins, fats, vitamins and mineral (Mahima *et al*., 2012a). A proper combination of these substances is very essential to maintain the health of the individual and to prevent the illness. Too much is always bad as too little, same is applicable for the consumption of these food ingredients.

Fat and immunity: The amount of fat deposited in body tissues is a mirror of calorie intake of the individual in the form of carbohydrates or fats. It has the potential for manipulation of the immune response as fatty acids may be metabolized as a powerful biological mediators those play an important role as immunomodulator (Calder and Field, 2002). Foods containing essential fatty acids may foster a healthy immune system (Pond, 2005). Two major classes of the PUFA are found in the diet namely n-6 and n-3. Linoleic acid is precursor of the n-6 and found in the oils of plant origin, corn and soybean. Inside body linoleic acid is converted to arachidonic acid in plasma membrane of immune cells therefore their amount in the plasma membrane is important as they are precursors of the prostaglandins and leukotrines which plays an important role during inflammation by enhancing it. On contrary long-chain n-3 PUFAs diverts immune system toward non inflammation by decreasing production of n-6 products either directly competing for enzyme or indirectly acting at the gene expression level to downregulate the expression of inflammation favoring gene (Calder, 2001). Thus, n-6 PUFA are inflammatory in action opposite to their n-3 counterpart. It suggests that diet rich in n-3 PUFA decreases the inflammation by increasing the membrane levels of the eicosapentanoic acid and docosahexanoic acid at expense of arachidonic acid (Mantzioris *et al*., 2000). The enzyme is common for the both these fatty acids. So it has been advised that one should eat more n-3 PUFA during inflammation associated with the autoimmunity and neoplastic conditions. But excessive intake of the n-3 PUFA may also lead to the immune-suppression therefore proper balance is equally important (Benzoni *et al*., 2012; Pae *et al*., 2012).

Proteins: Amino acids are the building blocks of the body. They are engaged in variety of the body functions, of those one important is the immune function. Antibodies are primarily protein in nature therefore proper functioning of this machinery balanced intake is very important. Among various amino acids, arginine is important for the oxygen dependant killing in the phagocytic cells (Duff and Daly, 2002). Arginine is direct precursor of the nitric oxide, a potent killer chemical in phagosomes. Glutamine is essential for the activation of the immune system and proper functioning of the macrophages and lymphocytes during the inflammation as

it has been observed that the consumption of the glutamine is higher during the inflammation in these cells. It is also required for the cell division, secretion of antibodies and cytokines (Calder and Field, 2002). Both low and high protein:carbohydrate ratios in the diet of pregnant animal leads to significant impact on the offspring defense system (Tuchscherer *et al*., 2012).

Vitamins-the vital part of life: Casimir Funk discovered these vital molecules. Vitamins are essential for the normal functioning of the body's defense system by taking part in various immune functions. The common vitamin taking part in host's defence mechanism are as follows:

Vitamin A: Vitamin-A, known as anti-infective vitamin, is a very important vitamin required for normal functioning of both innate and adaptive wings of immune system. Retinol, its active form is essential for the maintenance of the epithelial barrier which is an important hurdle for the infectious agent during entry to produce disease. Deficiency of vitamin A leads to degenerative changes in these epithelial cells, squamous cell metaplasia and decrease in number of goblet cells and mucous secreting cells in the gut epithelium (Quadro *et al*., 2000). It is required for proliferation of T cells via action of IL2 and boosts cytotoxicity of T cells towards infected and transformed cells in body (Dennert and Lotan, 1978; Ertesvag *et al*., 2002). Vitamin A metabolises to other substances and interact with their specific receptors located on the B cells to delay its apoptosis thereby maintaining the proper antibody titre during the infection (Lomo *et al*., 1998). Deficiency also causes inhibition of activity of the natural killer cells, phagocytosis and effective oxidative bursts. It causes the increased production of the IL-12 and TNF-alpha which subsequently activate the macrophages which may promote the inflammation process (Semba *et al*., 1998). Vitamin A is important to maintain the normal Ab mediated response. A study in retinol deficient rats has shown that vitamin A is essential to maintain the normal antibody production to take care of bacterial invaders (Pasatiempo *et al*., 1990). Molecular studies regarding the cytokine production have shown that the vitamin A up-regulates the expression of IL-10 while inhibits the pro-inflammatory cytokines such as IL-12 and TNF alpha suggesting the role directing the inflammation in body (Wang *et al*., 2007). Its deficiency results in the abnormal production of these cytokines and subsequent suppression of the Th-2 response which make animal vulnerable for the attack of extracellular pathogens (Kim, 2011; DePaolo *et al*., 2011).

Vitamin B complex: A study has been carried out on the pregnant rats by inducing vitamin B deficiency resulted with the abnormality in the development of lymphoid organs such as spleen and thymus in their offspring, indicating role in development of these vital organs as well as reduction in circulating lymphocyte (Dhur *et al*., 1991). The deficiency also causes decreased number of plasma cell, lymphocyte proliferation, CT cell activity etc., resulting in lowered DTH response (Fawzi *et al*., 1999).

Vitamin C: It is found in high concentration in the activated neutrophils (Washko *et al*., 1993) and promotes their function (Guerra *et al*., 2012). It protects the body against various infectious pathogens by acting as a potent antioxidant and improving the functioning of immune system (Puertollano *et al*., 2011). It is essential during the respiratory burst in phagocytes to protect the host cell from generated free radicals. Diet lacking sufficient quantity causes impaired phagocytosis as well as free radical injury to host cells. The condition changes after the administration of the ascorbic acid as increased sensitivity of B cells towards the mitogen, proper DTH and inhibition of T cell apoptosis (Hartel *et al*., 2007). Dietary supplementation of vitamin C improves the immune function of juvenile cobia, Rachycentron canadum (Zhou *et al*., 2012).

Vitamin D: Many immune cells have been identified with presence of the specific receptors for the vitamin D suggesting a strong evidence of its role in immune action (Yu *et al*., 1991). It has a potent action as an immunosuppressant when mice are challenged with autoimmune encephalomyelitis (Deluca and Cantorna, 2001). Inhibition of T and B lymphocyte proliferation, reducing toxic potency of natural killer cells, down regulation of IL2, IL12 and TNF gamma are some of known actions of the vitamin D and it inhances IL4, IL5 and IgA response (Akbar and Zacharek, 2011). It also plays important role in activating the peripheral blood monocytes after BCG vaccination in bovines (Dhama *et al*., 1999).

Vitamin E: This anti ageing vitamin protects against free radical attack on the cell membrane having lipid bilayer. Food supplemented with adequate vitamin E increases the Th cell activity and DTH response of skin (Meydani *et al*., 1990; Pekmezci, 2011). It is responsible for the stimulation of NK cells towards infections and shows addictive effect on supplementing with ascorbic acid especially in phagocytosis (De la Fuente *et al*., 1998; Hughes, 2002). It is one of the important antioxidant, which protects the body from various microbes including bacteria, viruses or parasites (Puertollano *et al*., 2011).

Minerals: Minerals as like vitamins play a key role in immune modulation. Their actions in the body are somewhat complex in nature. Important minerals manipulating the immune systems are:

Copper: Neutropenia is a usual outcome in copper deficiency in infants while in case of adults it causes thymic hypoplasia, splenomegaly along with anaemia. In adult humans failure of the MNC proliferation in peripheral blood is seen. Copper is essential for the secretion of IL 2 which is important for the proliferation of the T cells therefore deficiency results in the lymphopenia (Percival, 1998), making it valuable for healthy immune system (White *et al*., 2009). In cattle, deficiency causes disturbed plasma cells causing drop in antibody production and decreased interferon and TNF-alpha production by MNC (Spears, 2000). Excessive copper administration is found to be linked with reduced proliferative response to the concanavalin A in mice. Increase in copper levels in the serum are associated with lymphocyte inhibition to mitogens suppression leading to suppressed immunity, as is revealed by *ex vivo* study (Pocino *et al*., 1991).

Iodine: *In vitro,* it works with the myeloperoxidase in the phagocytic cells to kill the bacteria and it stimulates IgG synthesis by the humans B lymphocytes. Its deficiency is generally reported with the increased risk for immunodeficiency and cancers by antioxidant mechanism (Venturi *et al*., 2000). Excessive intake of iodine is associated with the hypo or hyperthyroidism which is characterizes by impaired natural killer cell activity (Wenzel *et al*., 1998). The antigen presentation activity of macrophages is increased with increase in iodine concentration in rats (Zhao *et al*., 2008), thus making iodine inducing factor in thyroid autoimmunity.

Iron: Reduced serum iron level is an important phase during the acute phase reaction to slow down the growth of the iron loving bacteria this is a protective mechanism of body but only for certain period abnormally prolonged lowered state of serum leads to multiple negative effects such as reduced mitogen stimulation, abnormal DTH, less cytokine production as well as degeneration in many lymphoid organs (Food and Nutrition Board Institute of Medicin, 2001; Cherayil, 2011). It will cause alteration in the DTH, cytotoxic activity of neutrophils and macrophages. The effects of iron deficiency on immune system reflect the multiple roles of iron in the mitochondria during the energy generation and the respiratory burst and its functions as a component of numerous enzymes such as NO synthatase, COX, lipoxynase and catalase (Weiss, 2004).

Magnesium: Magnesium is as essential element having potent role in variety of metabolic reactions in cell. Chronic deficiency in lab animals is found to be responsible for thymic atrophy, reduced overall immune response as well as induction of malignancy and increased risk for anaphylactic shock. Its relation with shock is supported by activity of calcium and magnesium. These two minerals cause degranulation of mast cells releasing histamine, thereby causing shock (Ashkenazy *et al*., 1990; Malpuech-Brugere *et al*., 1999; Sampson, 1999).

Selenium: Selenium is one of the most important trace elements having potent antioxidant activity and improves the immune defence of body to fight against various microbes (Chaudhary *et al*., 2010; Puertollano *et al*., 2011; Mahima *et al*., 2012a). Selenium being important part of glutathione peroxidase one of the free radical scavenger of cell functions to protect cells from these unwanted highly reactive by-products of cellular oxidation (Huang *et al*., 2012). Diet deficient in selenium causes reduced response of lymphocytes towards mitogen, impaired chemotaxis of macrophages, abnormal redox status of the cell and poor antigen recognition and presentation by the macrophages leading to autoimmune thyroid diseases (Prabhu *et al*., 2002; Zhao *et al*., 2008; Ren *et al*., 2012).

Zinc: Zinc is probably only one mineral taking part in number of metabolic reactions in body including immune function. It is evident that less amount of zinc is the root cause of increased susceptibility to a variety of pathogens (Fraker *et al*., 2000; Prasad, 2012).

Immunomodulators around us: Apart from these basic food constituents the various other materials added in our food commonly or occasionally during cooking or processing including fruits and vegetables also affect the immune system in either positive or negative way. Such food items include the plants, fruits, vegetables and spices (Table 1, 2).

Water: Water is otherwise called as life. It flushes toxins from the body and allows all the defence systems viz., skin, blood, mucous and saliva to function smoothly, discouraging flu and other infections from entering the body. It takes active participation in the immune functions too. Studies have shown properly hydrated individuals

Table 1: Commonly used food ingredients

Turmeric	Potent anti-inflammatory effect, bactericidal property and anti-tumour activity.	Al-Snhaimi *et al.* (2011) and Chang *et al.* (2012a, b)
Peepli	Good analgesic and CNS depressant activity.	Al-Mamun *et al.* (2011)
Sitaphal	Has anti-inflammatory properties and promote the tissue healing process by rich vitamin contents as well as hepatoprotective role. It is also having anticancer property.	Saleem *et al.* (2008) and Sun *et al.* (2012)
Aloe vera	It has many medicinal properties such as antimicrobial, analgesic, anti-inflammatory, powerful immune stimulator, anti tumor agent, antioxidant acting on both humoral and cell mediated immunity.	Chandua *et al.* (2011) and Halder *et al.* (2012)
Onions	Its phytochemicals has got antimicrobial and immunoboosting property.	Hannan *et al.* (2010) and Mirabeau and Samson (2012)
Tomato	Tomato reduce risk of cancer (colon and prostrate). Lycopene in tomato modulates antioxidant status and immune function. Help in fighting against Herpes virus	Gill *et al.* (2004)
Apple	Contains flavanoids which helps to lower mortality. Reduce chances of liver and colon cancer.	Wolfe *et al.* (2003) and Boyer and Liu (2004)
Garlic	Increase potency of T lymphocytes and macrophages. Active ingredient of garlic is allicin, which inhibit the secretion of IL 8, INF-γ-inducible protein of 10 kD. Local application of allicin has powerful immune mediating property in inflammatory bowel diseases. It also prevent the plasmodium infection by enhancing host immune response.	Langa *et al.* (2004) and Feng *et al.* (2012)
Turmeric	Fight against cold and microorganisms. Having antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal and anticancer activities Beneficial in treatment of anorexia, cough, wounds, hepatic disorders, rheumatism, sinusitis, diabetes, allergies, arthritis, Alzheimer's disease and other chronic diseases	Prasad and Aggarwal (2011) and Gupta *et al.* (2012)
Kiwi fruits	Influence various biomarkers of oxidative stress and beneficial immune responses. Reduce the incidence and severity of symptoms of upper respiratory tract infections	Skinner *et al.* (2013)
Carrot	It augment lymphocyte activation and secrete multipotent cytokine IFN-γ	Cherng *et al.* (2008)
Soya bean	Active ingredients include saponins and flavonoids which possess anti-inflammatory, anti-oxidative, anti-mutagenic and anticarcinogenic effects.	Cos *et al.* (1998), Sangwan *et al.* (1998), Dixon and Ferreira (2002) and Yamaki *et al.* (2002)
Rice and wheat	LPS like component leads to IL 10 production.	Yamazaki *et al.* (2008)
Mushroom	Mushroom proteins mimic mitogen and also act as an immunomodulator, which stimulate macrophages, splenocyte and thymocytes.	Ye *et al.* (2005) and Bhanja *et al.* (2012)
Honey	Its active ingredient is the royal jelly (RJ) which suppresses allergic reaction.	Okamoto *et al.* (2003) and Kohno *et al.* (2004)
Green Tea	Contains the antioxidant, which reduces the risk of cancer. Inhibits the growth of harmful bacteria in gut. Potent antiviral activity	Lee *et al.* (2012)
Chilly	Rich in beta-carotene, which turns into vitamin A in the blood and fights microbes	Ahamad *et al.* (2007)
Egg plant	Rich source of iron, calcium, potassium, phosphorus, vitamin B complex	Diab *et al.* (2011)
Potato	Rich in glycoalkaloids, alpha-chaconine and alpha-solanine	Vlachojaunis *et al.* (2010)

Table 2: Indigenous herbs with immunomodulatory effects

Plants	Active ingredient	Property	Reference
Allium sativum	Allicin	Activate NK cell and stimulate T lymphocytes. Increases the CD4 and total WBC counts.	Bongioruo *et al.* (2008) and Mirabeau and Samson (2012)
Zingiber officinale	Terpenes and oleoresin, gingerols, shogaol	Antioxidant, antibacterial properties, Combats travel sickness helpful in cough and cold	Park *et al.* (2012)
Aloe vera	Carboxypeptidase and salicylate.	Anti inflammatory effect Improves wound healing	Davis *et al.* (1994) Chithra *et al.* (1998)
	Acemaunan	Enhance production of IL 1 and TNF α from macrophages; Beneficial effect in antiretroviral therapy.	Saeed *et al.* (2004) and Awodele *et al.* (2012)
Andrographis paniculata	Ethanol extract and diterpene andrographolides	Stimulate antibody and DTH Inhibit induction of NO synthase	Puri *et al.* (1993) Chiou *et al.* (1998)
Asparagus racemosus	Steroidal saponins	Anticancer activity	Negi *et al.* (2010)
Azadirachta indica	Terpenoids	Stimulates production of IL 1, IFN gamma and TNFα; Lysis of tumor cells	Mahapatra *et al.* (2011) and Mallick *et al.* (2013)
Curcuma longa	Curcumin	Anti inflammatory effect Chemopreventive effect against cancer	Sharma *et al.* (2006) Sharma *et al.* (2006)
Nyctanthes arbortristis	Lipids	Hepatoprotective, antileishmanial, antiviral and antifungal	Puri *et al.* (1993)
Ocimum sanctum	-	Anticancer activity Leads to increase in IFN-Y, IL-4, T helper cells, NK cells	Khan *et al.* (2010) and Mondal *et al.* (2011)
Panax ginseng	Saponins and glycosides	Macrophage migration, antibody plaque forming cells; stimulate lymphocytes and cytokines.	Lee *et al.* (2007)
Phyllanthns emblica	Phyllemblin	Source of vitamin C Enhance NK cell activity	Singh *et al.* (2011) Suresh and Vasudevan (1994)
Picrorhiza kurroa	Glucoside	Enhance DTH response	Sinha *et al.* (2011)
Tinospora cordifolia	Tinosporone	Anticancer activity Enhanced humoral response. Induce cytokine production	Praveen *et al.* (2011) Praveen *et al.* (2011) Aranha *et al.* (2012)
Withania somnifera	Alkaloids, steroidal lactones, saponins	Production of IL 1 and TNFα from macrophages	Schumacher *et al.* (2011)
Allium cepa	Quercetin, volatile supfur compounds	Helpful in anaemia, skin disorders, stomach cancer, bacterial infection, eye infection, reducing low density lipoprotein, suppress plate; Commonly used to treat cold, cough, bronchitis and influenza; Prevent asthma attack	Lanzotti *et al.* (2012)

show less fluctuation in immune cell number when exposed to the environmental stressors and harsh physical activity compared to their dehydrated counterpart (Mitchell *et al*., 2002; Penkman *et al*., 2008). Adequate nutrition is required to boost the immune system and in this regard, water is indispensable because of the reason that it helps to digest the food (www.fitday.com). Drinking adequate water oxygenates the blood and thereby cells, allows kidneys to function properly to remove toxins from the body. Urinary tract infections are generally associated with the dehydrated individuals as oligouric state is mainly responsible for pathogens to establish in urinary tract due to impaired flushing action of urine (Beetz, 2003). The retained waste products in our body show detrimental effect on the immunity by plunging body to the stress. As water is the basic fluid component of the blood and lymph. These two body fluids are very much essential for the circulation of the immune cells as well as for providing nutrients and removing waste from the cell.

Temperature: The extreme temperature inhibits formation of T and B cells and suppresses phagocytic action of leukocyte (Kadymov and Aleskerov, 1988). Increase in the level of serum corticosteroid due to rise in temperature may suppress the cell proliferation factor or interleukin (Santin *et al*., 2003). Temperature stress also causes decrease in the production of the antibodies. The reason has been mentioned that increased secretion of the inflammatory cytokines causes hypothalamus to secrete the stress hormone releasing factors which in turn stimulates adrenals to secrete the corticosteroids which inhibit the B cells to synthesize and secrete antibody production and secretion. Also many biological agents contaminate our surrounding areas which include gamut of creatures from size of nanometers to several meters. The common bacterial agents manipulating our immunity are various Gram negative/positive as well as acid fast bacteria. Of this type mainly two different streams arise as pathogenic bacteria and non pathogenic bacteria.

MICROBES

Pathogenic bacteria: These include: *Bacillus*, *Erysepalothrix*, *Staphylococci*, *Streptococci*, *Brucella*, *E. coli*, *Hemolphilus*, *Pasterurella* and *Mycobacteria* spp. etc., of these agents few are causing minor manipulation while others show major effects on the components of the immune system. The mechanisms by which they act are summarized (Table 3).

Viruses: Similar to the bacteria a group of viruses also manipulate precisely suppress the immune response through various ways. Oncogenic viruses need a special mention, classical example being human papilloma virus (Boon and van der Bruggen, 1996). Few important viruses are shown in Table 4.

The fungal agents and toxins liberated by them are responsible for the development of granulomatous lesion by stimulating the immune cells and mycotoxins secreted

Table 3: Bacteria that manipulate the immune response

Bacterium	Mechanism(s) of action
Bacillus spp.	Its lethal factor stimulates the macrophages to produce ROS and cytokines such as interleukin-1-beta and TNF-alpha
Erysepalothrix spp.	In chronic infection it causes formation of the immune complexes which leads to the accumulation in various sites thereby causing inflammation and tissue damage by the action of own defense machinery.
Staphylococcus sp.	Its protein A binds with the Fc portion of the Ig molecule thereby blocking the attachment with the phagocytic cells
Streptococcus sp.	The peptidase destroys the 'C5a' potent chemotactic peptide M protein binds fibrinogen masking C3b binding sites
Brucella spp.	Prevents intra macrophage killing, activates IFN gamma and IL-2
E. coli	LPS provokes the secretion of IL-1 and TNF which have major destructive role in its pathogenesis.
Hemophilus spp.	It has a protease which selectively destroys IgA molecule.
Pateruella spp.	Produces the leukotoxin which kills neutrophils and macrophages
Mycobacteria spp.	Cord factor causes granuloma, LAM causes inhibition of macrophage activation by IFN gamma, induce macrophages to secrete TNF alpha and IL-10

Table 4: Viruses that manipulate the immune response

Virus	Mechanism of action
Pestivirus	Causes leucopenia and thrombocytopenia
Paramyxoviruses	A autoimmune attack on the neurons causing de-myelination and a condition 'old dog encephalitis'. In riderpest it causes the marked leukopenia
Lentivirus	In visna, it provokes the host immune system to attack the virus infected cells
Lentivirus (FIV)	Selectively attacks the T lymphocytes, macrophages and astrocytes
Biruavirus	B lymphocyte and their precursor are the main target cells, causes destruction of lymphoid cells within the bursa, spleen and caecal tonsils.
Parvovirus (Feline panleukopenia)	Causes severe leucopenia hampering the immune system of the animal
Herpes virus (MD)	Primarily affects the B cell population
LL virus	It attacks on the lymphoblast cells converting them to malignant form and thereby forming the nodular structures
Papilloma virus	Possess oncogenes and regulates the expression of high level of tyrosinase enzyme that help in transforming melanocytes to melanoma.

by the A*spergillus favus* causes immune-suppression by causing atrophy of the bursa, spleen and thymus making animals vulnerable for the attack of various pathogens.

Besides these immunosuppressive activities of the microbes several agents have been reported to be beneficial as they stimulated immune system thereby prevent diseases and maintains health.

Various studies have been carried out to find a better alternative for the present adjuvant substances such as Freund's complete adjuvant which is being used for the enhancement of the potency of poor immunogenic substance. The substances known as MPL (Monophorphoryl lipid A) which is found in the cell wall of the Gram-ve bacteria is being tested as a safe and effective alternative. The non-toxic MPL have capacity to eliminate the expression of T cell activity without interfering its normal function. This shows a great hope in future for the cancer research area.

Lactic acid bacteria are well known for their capacity to ferment the carbohydrates and production of lactic acid. Extensive research is being carried out to use this bacterium as a host system for the production of the various immunomodulant molecules such as specific antigens and antibodies and cytokines for manipulating the immune response in positive way.

Non-pathogenic/beneficial bacteria, fungi and yeasts: There is a vast group of commensals inside the gut of a living individual. They are present in the large intestine doing their protective function and getting the food and shelter from the host. These bacteria are very essential for the protection against the pathogenic forms which are successfully eliminated by the commensals in healthy individual (Dhama *et al*., 2011a, b; Kapka-Skrzypczak *et al*., 2012; Bengmark, 2013). Non pathogenic/useful/helpful bacteria whatever we call are group bacteria which help in prevention and treatment of many gastro intestinal diseases. These bacteria are referred to as probiotic bacteria (Klaenhammer *et al*., 2012). During last decades, probiotics have used extensively for improving gut health but they can also improve the health other than the gut for example skin health along with skin innate immunity (Lew and Liong, 2013). Cell wall, certain metabolites and dead bacteria can evoke immune response on skin and improve its anatomical barrier function of innate immunity. They restore the normal microflora of intestine and prevent the inflammation of gut and related disease conditions (Hemarajata and Versalovic, 2012).

Different strains of probiotic bacteria viz., *Lactobacillus delbrueckii* subsp. *Bulgaricus* along with *Lactobacillus casei*, *Lactobacillus acidophilus* and *Bifidobacterium animales* vary in their mechanism of action for immunomodulation viz., increasing the production of immunoglobulins; stimulation of cell mediated immunity; increasing the phagocytic activity; and increase in cytokine production etc. (Table 5) (Kosaka *et al*., 2012; Lamprecht *et al*., 2012; Mokrozub *et al*., 2012; Tsai *et al*., 2012; Deng *et al*., 2013; Dongarra *et al*., 2013). Usually *Streptococcus* and *Leukonostoc* strains are the strong inducers of Th1 cytokine. Sticking to *Bifidobacterium* and *Propionibacterium* genera promised to have the best anti-inflammatory potential by inducing IL-10 production.

The probiotic bacteria act at the local as well as systemic level. At local level these bacteria are presented to the M cells or epithelial cells or interdigitating dendritic cells in the intestinal wall. Epithelial cell of intestine

Table 5: Probiotic bacteria and their mechanism of action

Bacteria	Activity (*in vitro* models)	Reference
Lactobacillus	Regulate the metabolism of commensal organisms. Alter the cytokine production in tumour bearing mice into a Th1 protective pattern Enhance activity of macrophages.	Kuisma *et al*. (2003), Siigur *et al*. (1996), Maroof *et al*. (2012) and Marranzino *et al*. (2012)
Lactobacillus, *Bifi dobacterium* and *Propionibacterium* strains	Inhibition of pathogen adhesion. Increase in endogenous interferon production.	Collado *et al*. (2006, 2007) Mokrozub *et al*. (2012), Hemarajata and Versalovic (2012) and Howarth and Wang (2013)
Lactobacillus, *Bifi dobacterium* and *Streptococcus* strains	Induction of mucin production	Caballero-Franco *et al*. (2007), Mack *et al*. (1999, 2003)
E. coli and *L. rhamnosus*	Powers mucosal barrier in mice	Madsen *et al*. (2001), Ukena *et al*. (2007) and Johnson-Henry *et al*. (2008)
L. rhamnosus	Enhancing the power of tight junction	Zyrek *et al*. (2007)
L. rhamnosus	Regulate cytokine expression of macrophages and dendritic cells	Miettinen *et al*. (2000), Veckman *et al*. (2003) and Veckman *et al*. (2004)
Lactobacillus and *Bifidobacterium*	Increase phagocytosis	Arunachalam *et al*. (2000), Olivares *et al*. (2006) and Roessler *et al*. (2008)
B. animalis ssp. *lactis*	IgA secretion increased in infants	Rautava *et al*. (2006)
L. helveticus	Hike mast cell and goblet cell which helps in mucosal patrolling at the infection site	Vinderola *et al*. (2007)

secretes the IL-6, while the macrophages and DC produce TNF alpha and interferon gamma these causes the proper communication between the cells of immune system. Of these, IL-6 is important as it is responsible for the clonal expansion of the IgA B cell so that their population will increase and produce the sufficient Ig-A molecules which is the primarily responsible for the mucosal immunity.

In systematic fashion the various cytokines are produced which are responsible for the T independent switch of IgM to IgA B cells. These IgA producing B cells then migrate to various organs the intestine via lymphatic route and secure other mucosal sites.

Allergens: Our immune system protects us but certain substances prove themselves as notorious by switching immune system to go evil. Not all but many individuals are prone to different types of allergies. These allergens constantly show their presence stimulating immune system in exaggerated fashion. There are countless substances present in our environment those target many of us. Many people are sensitive to certain foods associated with intestinal distress, fatigue and even weight gain. Among all, food allergies or food intolerance is important one. Food items such as dairy, egg, milk, gluten (protein in wheat), soy, corn, royal jelly, honey, peanut and food additives etc., are common part of our diet. But in 90% of individuals, they cause variety of symptoms pushing them towards restlessness, milk allergy being the most common in children (Soheilia *et al*., 2006; Harada *et al*., 2011; Yadzir *et al*., 2011; Lee *et al*., 2013; Munasir and Muktiarti, 2013). These substances play with our immune system by stimulating the IgE production which takes charge for further consequences (Taylor and Hefle, 2001; Lee, 2013). Assessment and diagnosis of the incidence of food allergens are problematic. It is difficult to track the changes over a particular period of time and to trace the underlying causes of food allergy without the availability of proper data (Hadley, 2006).

Stress: The word 'stress' is derivative of the Latin *Stringere*, means "to draw tight". All those things which are responsible for causing stress are considered as stressors. A wide list of the stressors includes environmental as well as psychological which are all around us. And their effect on the individuals depends mainly on their intrinsic factors such as age, sex, target cells etc., Psychological and environmental stress like heat, cold, altitude, climate, pollution; physical stress like over-exertion, sleep deprivation etc., leads to the impairment of functions of the immune cells those regulates inflammatory and cytotoxic responses and result into occurrence of diseases (Korzeniewski *et al*., 2013). As an average, a person needs between 6 and 10 h of sleep at night. Too little or too much sleep disturbs the hormonal balance and result into the diseases.

Several models regarding effect of stressors on the body has been developed. Studies indicate that short term stress is an essential phase of proper stimulation of immune system like a danger alarm to make immune system component active to face the coming danger. This is beneficial for the short period but in case of chronic cases it leads to exhaustion of the immune cells to perform their defense function. This is important regarding the redistribution of T cells which orchestrate the proper immune function. Chronic stress was found to be associated with the impaired distribution of these important cells (Dhabhar and McEwen, 1997, 2002). In a study conducted by Xie *et al*. (2013), beak trimming stress suppressed the immune response of chicks. Stress down regulates the functioning of suppressor T cells and natural killer cells, thereby decreasing the production of IFN-γ (Kiecolt-Glaser and Glaser, 2002). The catecholamines suppress the immune function, including natural killer cell activity (Savard *et al*., 2003).

Increase in catacholemines may also rapidly alter cell numbers via redistribution of immune cells. Indeed, increase in epinephrine levels are thought to reflect lymphocyte migration as it alters the interaction of the lymphocyte-endothelial cells (Carlson *et al*., 1996). Various studies have shown that stress is responsible for the asthmatic attacks (Isenberg *et al*., 1992). Psychological stress causes acid secretion leading to peptic ulcer (Levenstein *et al*., 1999) and may have deleterious effects on the early gene expression level of the innate as well as adaptive immune cells. Stress and immune interactions have significant physiological consequences even before the behavioral or gross pathological changes are observed. Moreover, mind-body interaction is an important determinant of stress proving that psychological stress has got a negative impact on immune regulation (Kiecolt-Glaser *et al*., 2002). Stress hormones released during the stress affects at gene level. It down regulates the expression of the multiple cytokines and MHC molecules on APCs. It alters the apoptotic genes of the most immune cells. The mind can also influence the body, so laugh, meditate, play music and stay happy to increase the immunity.

Age and immunity: Age is one of the biggest factors which affect the immunity of the person. Person's immunity changes as the age goes up. New born child's immune system will be developing and it will be naïve so that its adaptive immunity will be under developed. Slowly

the intestinal microbes take upper hand and it flourishes helping in the development of intestinal immune system (Rautava and Walker, 2007). Nutrition and nature of the food taken also plays a major role in sustaining the bacterial load in the gut and also helping the improvement of immune system (Calder *et al*., 2006). As age goes on there will lot of changes in the immune system. One or two immune functions may go down which is immediately combated by other. Th1 responses, lymphocyte proliferation and antibody levels goes down as the age goes up and Th2 responses and prostaglandin E2 levels have a direct relation with increasing age, resulting in decreased infection.

Alcohol: Excess consumption of alcohol is dangerous to our body because it depresses the nervous system, inhibits the bone marrow's ability to regenerate blood cells, hepatotoxic, depletes B-vitamins and dehydrates the body, thereby suppressing the immunity. This in turn increases the susceptibility to diseases like tuberculosis, HIV, Hepatitis C and D etc. (Corrao *et al*., 1999; Hendriks, 2002).

Exercise and immunity: Relaxation skills like pranayama or yoga and exercise increase immunity and breathing capacity thereby decreasing stress hormone production. Exercise increases the sweating, which is helpful in removing the toxin from the body also improves the general metabolism. Physical exercise may also improve the health condition of body by changing the functioning of the immune system. Breathing rate often increases during physical activity thereby decreases chance of the airborne diseases by the rapid flushing action and keeping lungs their optimum capacity. Also increases the output of the waste products through the sweat and urine to minimize the stress. It increases the rate of blood circulation so that it causes the rapid movement of the immune cells through the body. It also increases the body's temperature slightly which has detrimental effect on the bacteria. Little but regular exercise boosts immunity but over exercise does the opposite effect on the body (Gleeson, 2007; Davison, 2012). Exercise of moderate intensity shift the immune response towards Th1 pattern thereby reduces the chances of getting diseases. Generally, the markers of immune function in athletes in

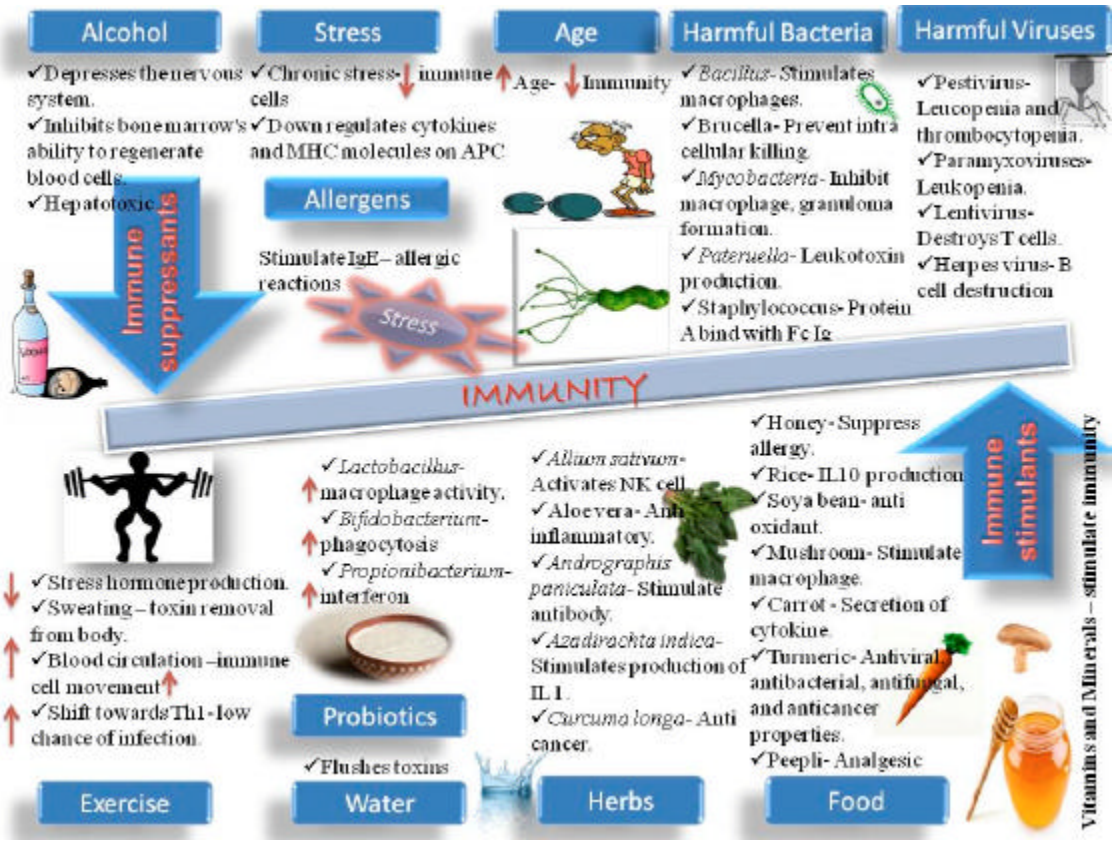

Fig. 1: Factors playing important role in immunomodulation

the true resting state are more or less similar to their sedentary counterparts. But when they are engaged in periods of intensified training, immune function may be chronically depressed (Gleeson, 2005). Increase in training load in well-trained athletes inhibits Type 1 T cells function, thereby decreasing cytokine production along with fall in stimulated B cell immunoglobulin synthesis and SIgA (Bishop and Gleeson, 2009; Walsh *et al*., 2011). Tai Chi and qigong exercise improved the humoral and cellular immunity by increasing the antibody production and activity of macrophages, NK cells etc. (Wang *et al*., 2012; Ho *et al*., 2013).

CONCLUSION AND FUTURE PERSPECTIVES

Immunity is considered as the defense system of the body. It depends on the optimum function of its different components but there are many factors we are encountering with, in day to day life that have potential to manipulate the function of the immune cells. No one can escape their good or bad effects. Allergens, physical and psychological stress, advanced age, alcohol and excessive exercise are the main factors causing immune suppression directly or indirectly to cause the ill health. Therefore keeping the stressors away from our life may bring a good health. Supplemental intake of one or mixed nutrients especially the vitamins and minerals will enhance the immune status of the individual. Understanding the immunomodulatory substances present in the food items will definitely help the individuals to have a better life style. By understanding the usefulness of probiotics and prebiotics it can help to prevent some disorders like allergy, asthma. Proper calculation of the dose and regimens will make it much effective so that it can even replace the medicines. If these vitamins, minerals and food items are taken in right amount one can lead a disease free life. By this way we can really experience the meaning of the worthy quote, “Let food be thy medicine and medicine be thy food” by great Hippocrates.

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