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Review article

STRENGTHENING IMMUNITY WITH IMMUNOSTIMULANTS: A REVIEW

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Abstract

Background: *There have been various infectious pandemic or epidemic diseases that cause morbidity in living being. The disease causing microbes can spread from one person to another in a very short range of time, again change in environmental factors drive these pathogens to mutate and make it more vulnerable, so, the available drug become resistant to treat it. At the same time development of new drug or vaccine or treatment process requires more time. To resolve these problems strengthening the immune system is important.* ***Objective:*** *The objective of this review to provide a brief insight about the human immune system and various strategies to strengthen the immune system.* ***Methods:*** *Extensive literature survey was carried out and information from various databases viz. Pubmed, Medline, Google scholar etc., were retrieved for analysis.* ***Results and Discussion****: Several immunostimulants are found that modulate the immune system of host by inducing activation or increasing activity of its components and thereby increase resistance against various infections. Moreover, certain food and nutrients also give good options to build resilience against infection. The link between immune system with diet, exercise, sleep, stress, microbial exposure, alcohol, water, hygiene are found to influence the immune response to a greater extent.* ***Conclusion:*** *Immunostimulants and some immunity enhancing nutrients improves the functioning of the immune system. In addition, some preventive measures such as healthy diet or proper nutrition, moderate exercise, sound sleep, drinking adequate water, subclinical exposure to microbes and managing stress, good hygiene, are altogether capable of boosting the immune system.*

Keywords: Immunity; Lymph; COVID-19; Nutrients; Vaccine; Disease

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Introduction

Humans and other vertebrates reside in a world that is occupied by a huge range of pathogenic microbes and toxic substances that menace normal homeostasis; and immunity is a specialized form of host defence mechanism that works particularly in relation to the causes and prevention of diseases [1]. Manifestation of disease due to the pathogen depends on its virulence and capability of the immune system; and to achieve resistance against disease, the most important is strengthening the immune system [2]. If the immune system fails become under or over active, or hits the wrong target it can vent a variety of adverse consequences. Under-activity of the immune system lead to loss the defensive mechanism against infections; extreme immune failure results HIV disease, certain cancer, etc. whereas over-activity can lead to autoimmune diseases, including arthritis, inflammatory bowel disease, inflammatory lung disease, connective tissue disease, autoimmune endocrine diseases, multiple sclerosis, etc. So, proper understanding and strictly regulating the immune system has become mandatory. This review starts with a brief idea about the immune system followed by description of immunostimulants and how to boost the immune system by controlling diet, stress, sleep, lowering alcohol consumption, moderate exercise, good hygiene and hydration.

Immune System

The immune system consist of a complex network of specialized cells, tissues, molecules and biological processes within an organism that watches out the continually to protect it against attacks by "foreign" antigens or invaders (basically *microbes* - infection causing organisms such as *bacteria, viruses, parasites,* and *fungi* or any *injury*, and *disease*) [3]. The different organs of human immune system are shown in Fig. 1. Some of the potentially infectious agents includes: (a) Viruses, which are sub-microscopic non-living entities that replicates only inside the host cells (living organism) and often results in serious diseases. Examples include influenza virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV, which can cause cold sores or genital ulcers), a newly discovered virus named coronavirus (causes infection in the upper respiratory tract). (b) Bacteria are single-celled microbes capable of causing disease when get entry into the body through water, air, soil and also through physical contact. Examples include Staphylococcus and Streptococcus that cause acute infections such as abscesses and sore throats, Escherichia, Salmonella that cause food poisoning and Mycobacteria that cause chronic infections such as tuberculosis and leprosy. (c) Fungi, eukaryotic, non-phototrophic organisms with rigid cell walls, they can be unicellular or multicellular. Examples include Aspergillus that causes allergic disease, Candida that causes thrush, Cryptococcus that causes meningitis and meningo-encephalitis in patients with HIV infection and AIDS. (d) Parasites, which are eukaryotic

organisms that live off other organisms, or host, to survive. Some are them are single-celled protozoa that cause diseases for example, malaria; others are large, multicellular organisms (metazoa) example, worms that can be seen with the naked eye. In order to prevent disease, the immune system must able to scan, recognize and attack the foreign invaders by distinguishing self from non-self substances [2]. Self molecules are those components that belongs to an organism's body which the immune system can distinct from foreign substances. Autoimmunity is an immune response in opposed to its own healthy cells and tissues, which may lead to various diseases [4]. Non-self molecules are those recognized components that do not belong to an organism's body, they are foreign invaders. One example of non-self molecules is antigens that cause the immune system to promote the generation of antibodies against it and then combine specifically with them to induce an immune response [5].

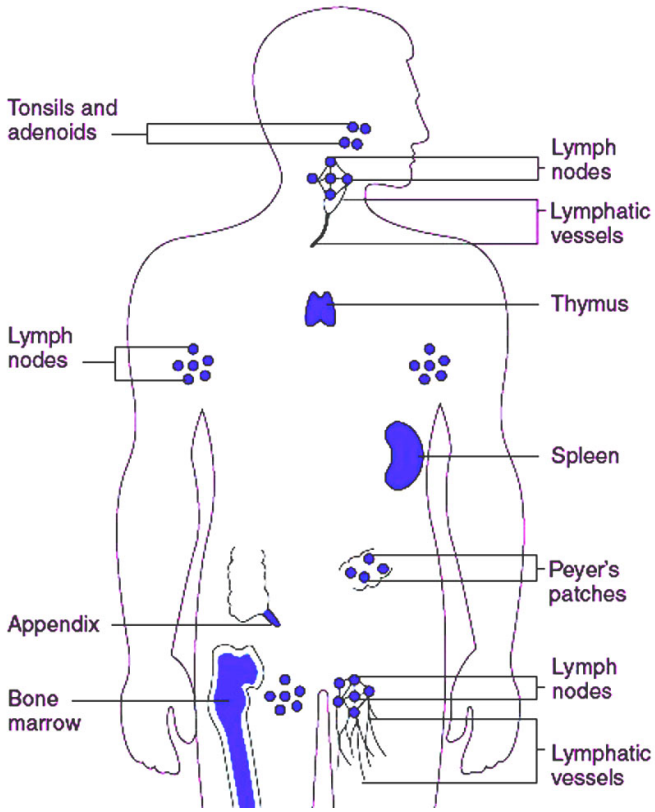

Fig 1: Organs of the human Immune System

Innate and adaptive immunity

Defence against infection is divided into two main forms namely innate immunity and adaptive immunity. Its components are shown in Fig 2. Some of the differences between innate and adaptive immunity are shown in Table 1.

Innate immunity

Innate immunity regarded as the first line of defense from both external and internal attack, also known as natural or native immunity. It is a nonspecific and antigen-independent defensive mechanism which responds immediately and within minutes or hours of meeting an antigen [6]. Its host defense mechanisms are encoded as their mature form by the germ-line gene of the host [1]. This type of immune response is lack in memory to recognize the pathogen, if the same pathogen invades for second time as they cannot generate that immunologic memory. Innate immunity consists of two major components: Humoral (include complement cells) and Cellular (includes neutrophils, macrophages, adnatural killer cells). The defensive barriers of innate immunity are of four types:

(a) Anatomical barriers e.g., skin and mucous membrane, the epithelial cell layers offers tight junction so there is tight cell to cell contact, the mucus layers over the respiratory, gastrointestinal and genitourinary tract, and when foreign particles are inhaled, the mucus layer get contaminated which are constantly discarded by the epithelial cilia.
(b) Physiological barriers e.g., temperature, low pH and chemical mediators
(c) Endocytic and phagocytic cells (neutrophils, macrophages), dendritic cells, natural killer (NK) cells and other innate lymphoid
(d) Inflammatory barriers e.g., a series of events occurs in inflammation process that plays an important role to destroy or inactivate microbes.

Adaptive immunity

Adaptive immunity is also known as specific or acquired immunity which means the resistance acquired by human during their lifetime. It is antigen-dependent and antigen-specific defensive mechanism and, thus delays the time of the antigen to get expose and to produce the maximal response. The advantage of adaptive immunity is their capacity to generate memory which permits the host to elicit a more rapid, stronger and efficient immune response against consecutive exposure to the antigen [7]. This type of immunity provides the basis for effectual immunization facing infectious diseases. The two major components of adaptive immunity are Humoral (comprises of antibodies formed by B lymphocytes) and Cellular (mediated by T

lymphocytes). B lymphocytes and T lymphocytes are two kind of lymphocytes found in this type of immunity that impart long lasting immunity against specific

Table 1: Differences between Innate and Adaptive Immunity

Feature	**Innate Immunity**	**Adaptive Immunity**
Cells involved	Dendritic leukocyte, Natural killer cells, Mast cell, Granulocytes/ Macrophages, Basophils, etc.	Killer CD8+ T-cells, Helper CD4+ T-cells, B-cells, Antigen presenting cells, etc.
Molecules involved	Cytokines, Complement cells, Interferon, Acute phase reactants/ proteins	Antibodies, Cytokines
Receptors	Germline encoded	Encoded in gene segments
	No somatic rearrangement	Somatic rearrangement necessary
	Non-clonal distribution	Clonal distribution
Action time	Immediate effector activation	Delayed effector activation
Response	Rapidly occurs (0-6 h ours)	Occurs over days to weeks
Order of defence	It is the first line of defense of immune system	Action against pathogens that are able to evade or overcome innate immune defense
Immunological memory	None	Confer Immunological memory
Types of Immune response	Inflammation, Complement mediated killing, Phagocytosis	Antibodies generation, microbial destruction by Helper T cells and Cytotoxic T cells
Subsequent exposure	Immune response does not get alter on repeated exposure	Immune response get improves with subsequent exposure
Reason behind immune evasion	Caused by pathogenic virulence	Caused by mutation of the recognized antigen
Allery or	None	Immediate and delay

hypersensitivity reaction		hypersentivity
Potency	Lower	Higher
Physio-anatomicalcal barriers	Skin, Mucous membranes, Temp, pH, chemicals, etc	Lymph nodes, spleen, mucosal associated lymphoid tissue
Functions	(a) Recruiting immune cells to site of infection; (b) Activation of complement cascade to identify antigens; (c) Identification & removal of foreign substances present in organs, tissues, blood and lymph; (d) Activation of adaptive immune system through antigen presentation; (e) Acting as physical & chemical barrier to infectious agents.	(a) Recognition of specific "non-self" antigens during the process of antigen presentation; (b) Generation of responses that are tailored to maximally eliminate specific pathogens or infected cells; (c) Development of immunological memory, through memory B cells and memory T cells.

antigens by proliferating into 'memory cells'. Lymphocytes are generated from the bone marrow and the type that mature in bone marrow turns into B lymphocytes whereas the type that leave the bone marrow and migrate to thymus gland get mature into T lymphocytes and based on 'cluster of differentiation' (CD) molecules on their surface they acquire certain genetic and immune surface characteristics which determines their different functions [8]. B lymphocytes are responsible for formation of specific antibodies by differentiating into plasma cells while T lymphocytes get activated in presence of appropriate antigens presented by macrophages like APC and Histocompatibility Complex (MHC). The function of B lymphocytes are like military intelligence system, they find out the target and organise defensive action, while T lymphocyte perform like soldiers, they destroy the invading substance identified by the intelligence system i.e. B lymphocytes [9]. Antigen specific receptors are encoded by genes that are assembled by somatic rearrangement of germ-line gene to form intact T cell receptor (TCR) and immunoglobulin (B cell antigen receptor; Ig) genes. Millions of different antigen receptors are formed from the collection of a few hundred germ-line-encoded gene elements assembly of antigen receptors, each of which are potentially unique and

antigen specific [1]. The advantage of this diverseness of receptors helps adaptive immunity to identify any kind of pathogen [10]. They are of two types i.e., naturally acquired adaptive immunity and artificially acquired adaptive immunity.

Naturally acquired adaptive immunity: In naturally acquired active adaptive immunity, antigens enter the body naturally then the body develop antibodies and specialized lymphocytes whereas in naturally acquired passive adaptive immunity, antibodies passes from mother to foetus/infant through placenta/mother's milk. Naturally acquired active adaptive immunity lives longer than naturally acquired passive adaptive immunity.

Artificially acquired adaptive immunity: In artificially acquired active adaptive immunity, antigens are introduced into the body through the use of vaccines then the body generate antibodies and specialized lymphocytes against it whereas in artificially acquired passive adaptive immunity, preformed antibodies in immune serum are introduced into the body by injection. Artificially acquired active adaptive immunity lives longer than artificially acquired passive adaptive immunity but, when there is very less time to develop active immunity then passive type is more effective as it can prevent the infection in any stage and its process is rapid.

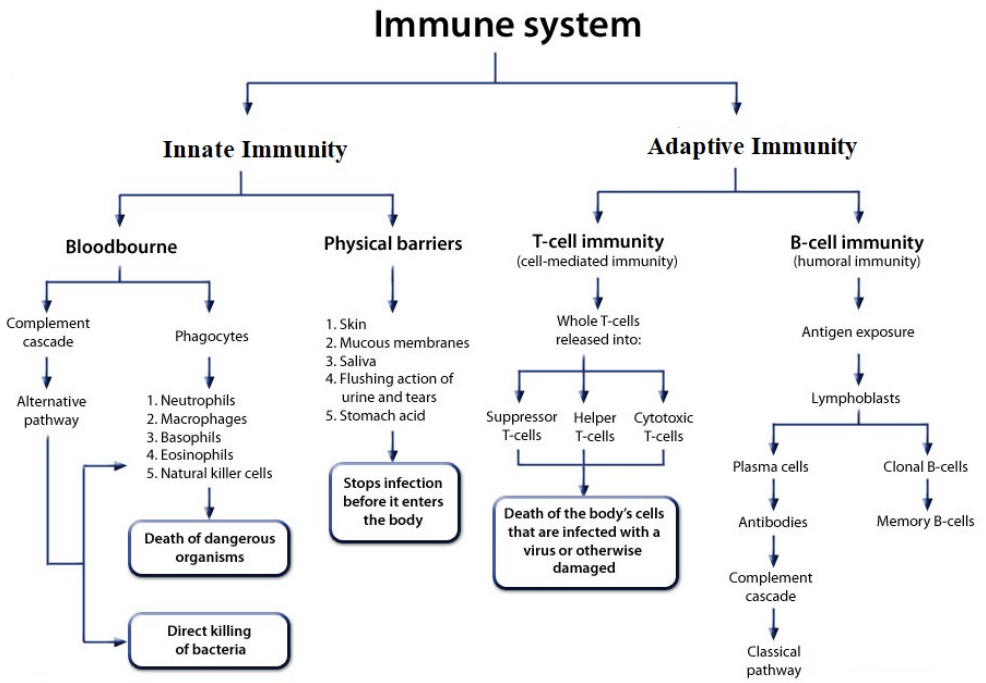

Fig 2: Flowchart of basic components of human Immune system

Functioning of immune system

The immune system comprised of cells and proteins that uphold the body from the foreign invaders[11]. These cells emanate from the pluripotent stem cells of bone marrow. Of the two pathways - (I) the myeloid pathway, in presence of IL-3, becomes excited giving rise to the production of platelets, erythrocytes, monocytes and granulocytes. (II) the lymphoid pathway, in presence of IL-7, becomes excited giving rise to the production of innate and adaptive lymph cells (Lymphocytes). The pathways distinction relies on the chemical signals in the surrounding area [12-13].

When pathogens invade the host body, innate immunity provides the first line of defense. Leukocytes like dendritic cells, monocytes, neutrophils, macrophages, eosinophils, mast cells, are allowed by the pattern recognition receptor (PRRs) to detect and react rapidly towards a large population pathogen which is structurally similar, known as pathogen associated molecular patterns (PAMPs). An example of these are the components of bacterial cell wall like lipopolysaccharides (LPS) and double-stranded ribonucleic acid [14]. The binding of PRPs with PAMPs triggers the release of cellular messenger called cytokines (e.g. interleukin) and causes inflammatory reaction. Inflammation leads to vasodilation, increased vascular permeability and cellular infiltration due to which the microbial cells get destroyed. Other cells, like “natural killers” are the critical members of innate immunity as they able to pursue and kill a vast number of pathogens along with malignant cells. All the cells of immune system are capable to suppress or induce inflammation by communicating one another over direct cell contact or through generation of cytokines. Again a complex systems of proteins known as the ‘complement system’ also induces inflammatory response that aid to fight infection. This type of immunity also aid to remove dead cells or foreign substances from different organs, blood and lymph [10]. The adaptive response takes over when the innate immune response becomes ineffective to eliminate pathogen.

In adaptive immunity at first antigen presenting cell (APC) like macrophages and dendritic cells recognizes, engulfs and process the antigen; and displays the specific part of antigen on its surface then present it to T- cells. T-cells receptors are there that bind with the specific antigenic sites and triggers proliferation and differentiation processes in lymphoid tissues [2]. There are two classes of T-cells namely, helper T-cells and Cytotoxic T-cells which can be discriminate by their presence of some molecules on their surface like CD4+ and CD8+ respectively. T-helper cells aid the immune response in recognition of antigen and then activate other T and B-cells by secreting cytokines whereas Cytotoxic T-cells aid the immune response by killing pathogen infected cells or tumor cells. One other class of T-cells, known as suppressive T-cells are able to secret suppressive cytokines that can inhibit the actions of other T-cells. Antigen binding and helper T-cell can

trigger the differentiation process of B-cells into plasma cells and secret antibodies which circulate in the blood and causes destruction or inactivation of the antigen [15].

Factors affecting immune system

Age

Elderly and early age are more susceptible to infectious diseases, inadequate response to vaccination and several variations in the immune systems intervenes the regulation of various components of immune process thereby leading to devastation of body cells. In case of infant, hepatitis B virus infection shows no sign of a disease due to inadequate immune mechanism [16-17].

Alcohol

Research workers have reported that excessive consumption of alcohol may be exaggerated which may result in various health problems subverting the normal host defenses thereby impairing the function of T and B lymphocytes including cell mediated and humoral response **[**18][19].

Hormones

Some hormones (lymphokines) suppress the immune system. Enhanced levels of stress hormone (cortisol) liberated by the adrenal glands complicate the normal functioning of the immune system. Immunologic endocrine disorders particularly diabetes mellitus, hypothyroidism and adrenal dysfunctions enhanced susceptibility to infection that increase morbidity and mortality [20].

Nutrition

The immune system itself is dependent on the presence of micronutrients viz., vitamin (A, C, E and B - 3, 5, 6, 7), zinc, selenium, iron, protein etc. Insignificant of these nutrients can alter the immune response to the body. Poor nutrition or malnutrition is also associated with impaired phagocyte function, IgA secretion, cell mediated immunity and cytokine production, however, over nutrition also lessen immunity [21-22].

Toxicity

Exposure to chemical warfare agents or toxic agent can lead to autoimmune disease, whereupon, the immune system fails to recognised self-antigens from foreign antigens allowing the immune system destroys the healthy tissue. Such example is that, pesticide induces immune dysregulation and response against the red blood cells leads to haemolytic anaemia [23].

Smoking

Tobacco smoking have a greater impact affecting the immune system making the host body more susceptible to infections of immune and autoimmune disorders like influenza, pneumonia and descended the levels of protective antioxidants in the blood. Further evidence implies smoking leads to rheumatoid arthritis (an autoimmune disorder) [24].

Immunostimulants

Immunostimulants (or immune stimulants) are biologically active substances obtained from natural or synthetic sources with different chemical characteristics and mechanism of action that modulate the immune system of host to increase resistance against various infections [25]. They interact with specific receptors and cellular components of innate and adaptive response to modulate the immune response. They used during suppressed immunity condition like cancer disease, AIDS, SARS etc. to improve the host's resistance [25]. Immunostimulants are classified into two categories: specific and non-specific immunostimulants. Specific immunostimulants stimulate an immune response to specific antigenic type (e.g., vaccines) whereas non-specific immunostimulants do not have antigenic specificity and are extensively used in chronic infections, malignant disease, immunodeficiency and autoimmune disease. The human body can produce chemical substances which can function as immunostimulants such as cytokines, beta-glucans, several probiotics, antioxidants, minerals, vitamins, female sex hormones, growth hormones, etc. Immunostimulants function by the recognition of toll-like receptors which is a pathogen associated molecular model, in the innate immune cells thereby initiating an immune response, also, ingestion of cytokines can trigger the response of the immune cells. Other means of regulating the immune system is by means of altering the activity of TLR signalling passage. Components of the bacterial cell wall, modified viruses, DNA sequences that imitate the bacterial DNA and cytokines are considered as prospective immunostimulators.

Immunity enhancing Drugs or Preparations

Different preparation of immunostimulants generally found are bacterial vaccine, colony stimulating factors, interferons, interleukins, therapeutic vaccines, combinational vaccine and viral vaccines [26].

Bacterial Vaccines: Bacterial vaccines are composed of killed or live-attenuated bacteria that ultimately activate the immune system to built antibodies against the particular bacteria, which prevents re-occurrence of bacterial infection [27]. Examples include tuberculosis vaccine, cholera vaccine, typhoid vaccine, etc. The

mechanism of this immunostimulant on bacteria is the responses produced by innate immunity or adaptative immunity where activation of dendritic cells occurs first, of which the pivotal role in T-cell differentiation is already well known. Example of such of bacterial immunostimulants used for anti-infective therapy is Ribomunyl® [28].

Colony stimulating Factors: Colony stimulating factors (CSFs) are a diverse group of glycoprotiens that bind to surface protein of hemopoietic stem cells and promote production of white blood cells in response to infection [29]. Some types of CSFs are: multiple-colony-stimulating factor or interleukin 3, macrophage-colony-stimulating factor, granulocyte-macrophage-colony-stimulating factor, granulocyte-colony-stimulating factor [30]. CSFs can improve the granulocyte count in neutropenic patients receiving cancer treatment [31-32].

Interferons: Interferons (IFNs) are a group of soluble glycoproteins produced by host cells in response to viral and bacterial infections (or other stimuli) [33]. These are mainly of two classes: type I (IFN- α, IFN- ß, etc) and type II (IFN- ɣ) [34]. Along with antiviral effects they also have immunomodulating and antiproliferative properties. They can also be used in chronic hepatitis B and C, leukemia, Kaposi's sarcoma in AIDS patients. In racehorse, oral admistration of IFN-α shows reduction in inflammatory airway disease [35]. Some Pharmaceutical preparations of IFNs are Multiferon, Roferon A, Intron A, Avonex, Actimmune, Pegasys, Besremi, Pegetron, etc.

Interleukins: Interleukins (ILs) are a group of cytokines which direct other immune cells to divide and differentiate, as well as in their proliferation, maturation, migration and adhesion [36]. Most of them are synthesized by lymphocytes, monocytes, macrophages, and certain other cells [37] and plays essential part in both innate and adaptive immunity [38]. They comprise of a large group of proteins and have redundant functions. Classification of IL includes, IL-1 family (IL-1α, IL-1β, IL-18, IL-33), IL-2 family (IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, Il-21), IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, Il-28, IL-29), IL-12 family (IL-12, IL-23, IL-27), IL-17 family (IL-17A-F, IL-25) and family of "like' cytokines (IL-3, IL-5, IL-6 and IL-11). Some functions of IL includes, IL-4, IL-5, and IL-13 stimulate differentiation of B-cell and are growth factors of B-cell. IL-1 promotes the release of IL-2 by activating lymphocyte. The expression of cytokines receptors get increased by pathogenic stimulation of B-cells [39].

Therapeutic vaccines: Therapeutic vaccines are vaccines that are intended to be use after the occurrence of the disease. They stimulate/boost the immune system of the

patient to target the infection or cure a disorder or diseased cells such as a cancer cell [40]. They can also be used to prevent tuberculosis. They can improve the condition of patient so have the capability to become the latest in personalized medicine [41].

Combination vaccines: Combination vaccines merge antigens that offer protection against multiple disease/strains in one shot. This reduces the number of injections required to prevent some diseases [42]. Some examples of common combination vaccines for children are: Comvax (Hib and Hep B), Twinrix (Hep A and Hep B), Pediarix (DTaP, Hep B, and IPV), ProQuad (MMR and varicella), Kinrix (DTaP and IPV) and Pentacel (DTaP, IPV and Hib) [43].

Viral Vaccines: Viral vaccines are suspension of inactivated/killed virus or attenuated viruses used in the prevention or treatment of viral disease. Inactivated or killed viral vaccines are prepared by inactivating viruses with heat, phenol, formalin which make them inactive to replicate but they promote response as they contains more antigen than live vaccines [44]. Attenuated or live vaccines contain the live from of the virus which are attenuated or weakened. These viruses become harmless but are able to stimulate an immune response, for e.g., live BCG vaccine which is used as non-specific immunostimulant agents [45]. Their mechanism of action is activation of macrophage in presence of pathogen and then subsequent release of IL-1, tumor necrosis factor and CSF [46]. Some pharmaceutical preparations of viral vaccines are Afluria (Pro) Engerix-B, FluMist (Pro), Fluzone, Ixiaro (Pro), Mupsvax, RabAvert (Pro), RotaTeq (Pro), Varivax (Pro), YF-Vax (Pro), etc [47].

Immunomodulators: Immunomodulators Thalidomide (lowers the supply of blood to cancerous cells and thereby helps the immune system to attack those cells). Other example of stronger form of thalidomide is Lenalidomide. Pomalidomide is FDA approved newest drug of this type for multiple myeloma [48].

Immunity enhancing Foods

Balance diet plays a vital role in the body and all of its organs system to function properly. The immune system can be strengthened by incorporating immunity enhancing foods in the diet plan. In Table 2, the list of food items that boost immunity are mentioned.

Table 2: List of immunity enhancing food items

Nutrients enhancing immunity	**Description**	**Examples**	**Ref.**
Important vegetables	Fresh vegetables and salads are preferable per meal to strengthen the immune system competency, also, crucial for patient with digestive system disorder.	Carrot, parsley, broccoli, pumpkin, egg plant, beetroot, cabbage, potatoes, beans, cabbage etc.	[49-50]
Important fruits	Its constituents like antioxidants, fibers, oils, phytonutrients and acids are liability for immune modulating and restorative properties. The body utilize these bioactive compounds to tackle against infections and inflammation, and also uphold detoxification and immune cell function via manifold mechanisms.	Banana, grapefruit, melons, berries, apples, cherries, cantaloupe, kiwi, pineapple etc.	[51]
Dairy products	They enhanced the immunity by fermenting the indigested plant fibers, turning them into chemicals and allowing them to permeate into the bloodstream.	Turkey cheese, fermented milk, yogurt and skimmed yogurt	[52-53]
Cereals and legumes	Well-known for their nutritive properties like protein, phosphorous, carbohydrates, iron, trace elements, minerals, vitamins etc. that helps in balancing blood sugar level in blood, crucial for cardiac disorder and strengthen the immune system.	Chickpeas, soybeans, lentils, barley, corn, wheat etc.	[54]
Germinated food	Serve as a natural anti-oxidant and improve immunity. They are also used for blood sugar level management and in the treatment of diabetes (type 1 and 2).	Fenugreek and Al-Shamchick peas	[55-56]
Functional foods	Make contribution to enhancing immunocompetence, prevention and subsidence of causative factors for various disorders.	Turmeric, black tea, mushroom, fibers, tuna salmon (omega-3), fish oils, vitamins E, D, C, A, Folic acid, B12 and B6 etc.	[57]
Probiotics	Probiotics or friendly microbiota generate myriad of vitamins vital for the body. Probiotic refine the cellular immunity in the GI that helps in combating the pathogenic microbes, hence, further avoid intestinal carcinoma.	*Bifidobacterium lactis* HN019	[58]

Strengthening immune system

The strategies to boost immunity are described below and mentioned in Fig 3**.**

Fig 3: Strategies to boost immunity

Diet and Immune system

"Excellent nutrition is the backbone of maintaining good health and a strong immune response throughout the year" says Demeter [59]. Adequate and appropriate nutrition has a profound impact on immunity and healthiness. Deficiencies of nutrition decline the function of immune system which results in rise of disease and morbidity [60]. Prolonged undernutrition and micronutrient deficiency affect cytokine response and immune cell trading. The combination of chronic infection and malnutrition impairs the immune reaction, causes distorted immune cell amount, increases inflammatory intermediaries, reduces leukotrienes, weakens bacterial ingestion and killing. The general influences might include changed microbial colonization of mucosal surfaces and weakened host reaction to new pathogens [61-62]. Certain food like almonds, garlic, ginger, yogurt, sunflower seeds, turmeric, papaya, kiwi, shellfish, poultry, mushrooms, citrus fruits (oranges, grapefruit, clementines, tangerines, lemons, and limes), green tea, spinach,

cayenne pepper, gives the body good options to build resilience against infection [63].

Protein calorie deficiency can affect the innate immune system whereas micronutrient deficiency impact both innate and adaptive immunity [64]. T-cell memorial reaction against antigens and thymus function get impaired due to low consumption of protein calorie [65].

Salt intake should be moderate, increase in its amount result inflammation and can impair the autoimmune mechanism as the IL-7 get increase [66].

Consumption of plant based and low-fat diet gives promotion to the immune system which is dependent on the white blood cells (WBC) that develops the antibodies and tackle the invaders, bacteria and viruses. Several studies have shown that vegetarians have greater efficient WBC over non-vegetarians owing to higher vitamins and low-fat intake[67]. It is reported that high-fat intake can hamper the WBC function and alter the gut microbiota. Therefore, balancing the dietary fat intake will assists in strengthening the immune defense [68].

Saturated fatty acids can destructively influence on immune system by enhancing the prostaglandin system that convert to the arachidonic and prostaglandin E2 (PGE2). PGE2 is pro-inflammatory, increases IL-17 amount, and activates macrophage by other pathways. Also, dietary fats by changing the lipids of the membranes of immune cells, can disturb the immune functions [69].

Omega-3 fatty acid can convert to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are precursor of anti-inflammatory mediators such as resolvins and protectins. These mediators decrease inflammation, stimulated neutrophil infiltration, boost the sifting of inflammatory chemokines, and improve macrophage phagocytosis to disappear apoptotic cells [70]. Some studies indicate that vitamins can considerably change macrophage phagocytosis and several of its component phases. Also can improve the production of cytokines such as tumor necrosis factor (TNF-a), interleukin (IL-1 and -6), inflammatory mediators such as prostaglandin E2 (PGE2), and interferon (IFN).

Vitamin C: These are present in broccoli, brussels sprouts and fruits Vitamins C and E supplementation increase neutrophil adherence, natural killer cell activities, phagocytic capacity, lymphocyte proliferation, and chemotaxis and decrease superoxide and oxygen free radicals production by neutrophils [71].

Vitamin A: These are present in carrots, kale, oranges and also in eggs, milk, fish, meat and other dairy products**.** Vitamin A and its metabolites [particularly retinoic acid (RA)] play a great role in the control of both innate and adaptive immune responses. Vitamin A by impact on the integrity of mucosal epithelia, the diversity, quantities, and cytokine secretion profiles of macrophages, monocytes, neutrophils,

and natural killer cells improve innate immune responses. Also by developing, maturing the thymocytes, increasing the quantity of T-cells, specifically the CD4+ subpopulation has effect on adaptive immune responses [72-73].

Vitamin D: These are present in cod liver oil, egg yolk, severbcal sources of omega-3 fatty acidsand fortified milk and dairy products. Moderate exposure to sunlight helps in generation of small proportion of Vitamin D. Hence, the statement tells us the fact whypeople tends to become sick more frequently in wintertime (least daylight and people are unlikely to be outdoor) than in summer.

Zinc: Several disease progressions lead to zinc deficiency and low plasma amounts of zinc cause weakened immune function. Supplementation with zinc stimulated cytokine production, mainly IL-1, IL-6, and TNF-α [74].

Iron: The ability of neutrophils to kill bacteria decreases in iron deficiency [75].

Proper diet delivers energy and nutrients to the body and boost the immune system keeping the host stay healthy thereby combating the foreign invaders and viruses. Intake of cold and uncooked foods must be diminished amidst cold and flu, however, at such time, intake of hot meals like soup and teas must be scaled up. On the other hand, improper diet subverts the immunity making the host more susceptible to infections like respiratory illness, influenza, COVID-19 and pneumonia are major cause of mortality globally. Obesity has associated to greater risk of illness like pneumonia and influenza. Therefore, keeping hold of healthy weight favours the immune system [76]. Plant-based diets which are rich in fiber are useful for minimising inflammatory biomarkers, lowering BMI and mass loss or weight loss without additional calories, hence, subjected to improvement of the immune system [77-78].

Exercise and Immune system

A person exercising hard in weekend and inactive in weekdays makes the immune system more prone to respiratory illness. Exercitation aids in smooth functioning of the body, staves off stress, in lowering inflammation, combat infections and maintains the regular flow of the energy and blood. To remain active, it is not always necessary to work out in the gym, other activities like jogging, yoga, walking, cycling etc. are recommended for one to stay sharp and safe from risks[79]. However, extended periods of intense workout or training is capable of suppressing proper functioning of the immune system may led to the adoption of infection [80]. It appears that innate immune system reacts to overexertion or excessive exercise thereby expands NK cell activity jam-up neutrophil function. The effects of exercise over the innate immune system is influenced by multiple factors viz. (i) intensity and period of exercise; (ii) measurement timing in connection with exercise session; (iii) types of immune modulating agents and its dose which aimed at stimulating the cell *in vitro* or *in vivo*; (iv) location of cellular

formation [8]. The antipathogen activity of macrophages takes place in correspondent with an increased recirculation of neutrophils, NK cells, anti-inflammatory cytokines, immunoglobulins, cytotoxic T cells and immature B cells during moderate moderate and vigorous intensity activity of less than 60 min thereby promoting immune defense activity [81-85]. Regular exercise is eligible in governing the immune system and retarding the onset of immunosenescence (immune dysregulation with aging) and have been associated in the following ways-[16, 86-87]

- T cells proliferation and vaccination response is enhanced
- Neutrophil phagocytic and NK cell cytotoxic activity is increased
- Inflammatory cytokines and senescent T cells are reduced
- Leukocyte telomere length is expanded

Evading impairment of protein and micronutrients like Vitamins (A, D, E, B6, B12), iron and zinc, also, acquiring recovery and sleep are important aspects in order to maintain stronger immunity [88].

Sleep and Immune system

Sleep plays an important role for the body to develop the capacity to respond to disease and to get effectively recover from it [89]. There is a bidirectional link between sleep and immune response. A study showed that 70 % of immune cells can get reduced due to a single night improper sleep. Lack of sleep creates both mental and physical health issues, including the impairment of immune system. Several studies show that lack of sleep results decrease in activation of integrin by the specialized immune cells called T-cells and also decrease a protein that target inflammation or infection called cytokines [90]. Normally T-cell works by attaching themselves to infected cell with the help of a sticky class of adhesion molecules, integrins. In sleeping condition the activation of integrin by T-cell is more compared to awaken condition. This integrin can be inhibited by stress hormones adrenaline and nor-adrenaline and pro-inflammatory molecules prostaglandins and lead to poor immune response. During sleep these hormones and chemicals get reduce so the function of integrins get stronger which promote the contact time of T-cells and target cells thereby improve the T-cell functioning [91]. Prolonged sleep loss along with the higher risk of causing a cold or flu, can disable the body to responds to flu vaccine, thus make it ineffective [92]. Seven to eight hours of sleep a night keep the immunity function intact and can aid in prevention of other disease like heart disease, diabetes, and obesity. If the optimal sleep duration, i.e. 7-8 hours, get deprived then a person should take two naps for duration of 30 minutes each in morning and afternoon to make up the lost [89].

Stress and Immune system

The central nervous system (CNS) and the immune system delicately balance the communication between them which can be easily disrupted by any type of physical or psychological stress [93]. Stress can prompt dysregulation of both innate and adaptive immune response. The immune response is modulated by a complex bidirectional signals between the CNS, endocrine and immune system. Moreover, their interactions trigger generation of stress hormones cortisol and catecholamines (adrenaline and nor-adrenaline) by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (Sam) axis. Such hormones changes the immune response through two mechanism: one is by directly binding with the receptor on the surface of a target cell and other indirectly by inducing the generation of cytokines like IL-1, IL-2, IL-6, interferon-γ (IFN-γ), and TNF [94][95]. Psychological stress generally takes place when one's fail to cope up with the events occur in their life and this lead to generation of stress hormone in higher amount [96]. In a person experiencing stress, the level of stress hormones get elevated in blood which diminishes the number of white blood cell and activity of NK cell and with time it become more vulnerable. Even the production of antibodies against foreign particles gets affected with stress for which person becomes more susceptible to infection [97]. Moreover, they can reduce the capability of immune response to vaccines, toxoid and healing wound. Stress causes various adverse effects in human but sometime short-term release of these stressors may be beneficial as cortisol can relief inflammation and thereby boost immunity. Minor stress can also increase the function of NK cells and leukocytes production [98-99]. Management of the stress level is critical for smooth running of the immune system. For that people should not become panic over some misinformation and should always try to be relaxed or calm, engulf in activity that makes them happy.

Microbial exposure and Immune system

Living in microorganism free environment will make the immune system inactive. In such condition the body will recognise substance which aren't pathogens (like allergies) and subject the body to allergic illness or asthma. Infectious or non-invasive microbial exposure in early life can make the both innate and adaptive immune system alert towards such allergy, asthma, inflammatory bowel disease (IBD) and can reduce its development risk [100]. In IBD and asthma pathogenesis, the major role is played by the invariant NKT cells [101-102]. They secret proinflammatory cytokines like IL-4, IL-13 on recognition of endogenous and exogenous lipid antigens presented by MHC class I-like protein CD1 [103-104]. Moreover, microbial exposure can also improve resistance against pathogenic

disease, respond to vaccination and can alters the immune response for future infectious challenges [105].

Moderate life and Immune system

Anything in excess amount is unhealthy like consuming alcohol or sweets in excess amount affect the immunity function and make the body more susceptible to diseases. High dose of alcohol causes dehydration in the body that lead to impairment or disruption of immune system [106]. It can affect the migration capacity of WBC to the sites of infection or injury, impair T and B lymphocytes, NK cells, macrophages cytokines, and can reduce both cell-mediated and humoral immunity [107]. Moreover, alcohol can alter the microbial flora of gut that support immune system. They can damage the cell line of intestine that provide defensive mechanism against pathogen by preventing its entry and can cause diseases like Pneumonia, Tuberculosis, Septicemia, Cancer, Leaky gut syndrome, Hepatitis B and C, HIV [108]. Chronic consumption of alcohol can lead to autoimmune disease by increasing the levels of immunoglobulins in the blood. Conversely, alcohol consumption in moderate level can boost the immune system. A standard unit one 12-oz beer or 5-oz glass of wine per day is found to be safe for women and its double amount is found safe for men [109].

Hydration and Immune system

For supporting a healthy immune system, hydration is a key component as human body is composed of 60-70% of water. Dehydration can bring about headaches, muscle tension, low serotonin production, problems in transporting nutrient to cells and digestive issues [110]. Skin and mucus membranes are the first line of defense to hinder entry of pathogens inside the body. So, it is essential to keep them hydrated regularly by drinking sufficient Volume of water. Skin and mucus membranes can flush out toxins, unwanted substances and infectious agent naturally thereby fights off cold flu or other infectious diseases [111]. Drinking plenty of water helps to oxygenate the blood and make them healthy. Furthermore, water can increase the production of lymph, which is a clear, colourless fluid and the word “lymph” derived from the latin word “lympha” meaning “connected to water” [112], they transports WBC to destroy the invading pathogen hence boost immune system [113]. A person should consume water at least half of their body weight in ounces and more during exercise.

Hygiene and Immune system

Personal hygiene is the best way to protect the body. Proper and frequent washing of hands before any type of work can remove potential contagions and prevent

transmission of communicable diseases. Sneezing or coughing with a tissue covering the nose and mouth or coughing on the elbow rather than on hand contributes to good hygiene. Therefore, the easiest way fight against spreading contagious diseases is to maintain a good hygiene. A hand sanitizer can be use if frequent washing is not possible [114-115].

Conclusions

The climate change, pollution etc., has caused the microbes to undergo frequent mutation. Irrational use of antibiotics also has resulted development of resistant strains. There are also possibilities of creating havoc by genetically modified microbial strains. History reveals that human civilization has experienced naturally occurring pandemic or epidemic diseases killing millions of people within a short period of time. For control or treatment of such diseases it required a significant time, as drug or vaccine development process is always time consuming. Considering all these aspects, it is therefore very important to improve the strength of inherent immune system, and at the same time, it is also important to understand our immune system and the ways of strengthening the body immunity with the aid of immunity boosting agents. Hence, immunostimulants, healthy diet, exercise, sleep, drinking adequate water, subclinical exposure to microbes and managing stress, hygiene etc., are important approaches to create a protective shield against these pathogens.

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