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IMMUNO BOOSTER :A COMPREHENSIVE REVIEW

[1]Bhagyashri Natikar,[2]Diksha Gupta,[3]Dr. Rajesh Oswal

[1]Student,2Asst.Professor,[3]Principal

[1,2,3]Genba Sopanrao Moze College of Pharmacy,Waholi, Pune

ABSTRACT: - The immune system is one of nature's most fascinating inventions. It is an amazing protection mechanism designed to defend us against millions of bacteria, viruses, fungi, toxins and parasites. The immune system is very complex. It is made up of several types of cells and proteins that have different jobs to do in fighting against foreign invaders. If our immune system is working properly, we are protected from dangers caused by microbes. If not, we suffer sickness and disease. It is possible to intervene in this process and make our immune system stronger using immune boosters. Immune boosters work in many ways. Medicinal plants are not only popular for their ample store of active ingredients but also boast of several pharmacological properties including the modulation of components of the immune system. An adequate immune response is vital in counteracting the unwanted activities of pathogens such as bacteria, protozoa, and viruses. Some diseases caused by viral pathogens such as measles, chickenpox, Ebola, and human immunodeficiency virus may result in death or dire consequences in mammals with inadequate immunity.

Keywords: - Immune system, Immune boosters, Natural herbs, Medicinal Plant and Immunostimulatory.

INTRODUCTION

Immune system is the barricade made of a complex network of organs, cells, proteins, tissues, and chemicals that protect your body from different pathogens, viruses, and bacteria. The primary components of the immune system include antibodies, white blood cells, lymphatic system, gut, complement system, thymus, and the bone marrow. All of these together ensure you remain healthy and running at optimal functioning, as we all know that without good immunity, infectious germs will create havoc in your body, making you susceptible to falling sick all the time.This is where immunity boosters come into the picture. They help to strengthen yourbody's defences against harmful infections and ailments and keep you fit.

There are different types of immunity such as:

- **Innate immunity:** The body has its own immunity to fight against infection-causing pathogens. This innate immunity also involves the exterior barriers of the body, which act as the first line of defence such asskin.

- **Adaptive immunity:** If the pathogen manages to dodge the innate immune system, that's when the adaptive immunity gets activated. This form of immunity protects the body from pathogens as we progress through life. This means that as we fall sick and get exposed to diseases or get vaccinated, we automatically build up a reservoir of antibodies for different pathogens. This is also referred to as immunological memory asour immune system tends to remember our previous invading,pathogens.
- **Passive immunity:** Passive immunity is also referred to as "borrowed" immunity, given that it is obtained from another source and does not last forever. The best way to explain this is with an example. When a baby is born, it receives certain antibodies from the mother through the placenta and the breast milk. This form of immunity doesn't last indefinitely, but for the initial years of its life, it receives protection from various infections.

Immunization: Immunization is a process of protecting oneself against a disease or strengthening one's immunity by getting vaccinated. This term is often also known as vaccination or inoculation.

How do Immunity Boosters Work?

Immunity boosters work by strengthening your body's immune system against disease-causing pathogens. This they achieve by either providing your body with the nutrition that it may lack, or by helping it release certain chemicals and hormones that may reduce your stress levels and help you detoxify. A few examples of immunity boosters include exercising regularly, getting good quality sleep, consuming nutritive food and multivitamin supplements, and quitting bad habits like smoking and excessive drinking, among other things. The immune system works to detect an infection in your body.

Biomedicine & Pharmacotherapy

Immune boosting functional foods and their mechanisms: A critical evaluation of probiotics and prebiotics

Functional foods: - The definitions ascribed to functional foods are many, and include foods marketed with health claims; food sources with positive physiological properties beyond their nutritional uses of providing essential nutrients; and natural substances that can be consumed daily meant to regulate or affect a system of the body upon ingestion [1]. The European Consensus provided the commonest and most recent definition, which states that 'a food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either improved stage of health and well-being and/or reduction of risk of disease' [2]. A functional food can be natural, components-added, or components- eliminated foods via biotechnological processes [3]. The ingredients in functional foods based on technological factors can help in preventing some diseases or improve performance and well-being of consumers beyond its nutritional role, either whole or specific groups of the population defined by age or genetic differences [4,]. In fact, functional foods have been classified based on food type or active components added or naturally present in the foods i.e., fibre, flavonoids, vitamins, minerals, fatty acids, carotenoids, and so on [5]. Some functional foods are regarded as microbial medicines,

Prebiotics and Probiotics meant to target obesity and metabolic syndrome [6], as well as high blood pressure, oxidation, cellular damage and other diseases from sources/raw materials like vegetables, cereals, diary and meat products [7]. Host health benefits which include reduction of macular degeneration and prostate cancer risks were associated with certain lutein and lycopene, while flavones, catechins and anthocyanidins have been shown to possess antioxidative properties by chelating free radicals and reducing the incidence of certain chronic diseases [8]. Essential minerals and dietary elements were previously included in the production of functional foods such as calcium, iron, zinc and vitamins [9]; and now, among the most prominent and well researched functional foods are the probiotics and prebiotics, which have the capacity of boosting consumers immune status [10]. Each of them has its own immunomodulatory and immune boosting benefits and theycan beneficially interact in a "symbiotic" process to boost the immunity of the human host.

Probiotics: - The intention of consuming probiotics is to harness their benefits in a symbiotic or commensal relationship with the intestinal microbes. Initially, probiotics were defined as contributors to host's intestinal microbial balance [11]. The modern consensus definition of probiotics is that they are living microorganisms, which when administered in adequate amounts can confer health and well-being to the host [12]. Thus, probiotics benefits are beyond the mediation of gut microbiota based on associated mechanisms. A paramount criterion for obtaining effective probiotics is their ability to adhere to the gastrointestinal tract (intestinal mucosa and epithelial cells), in order to avoid being passed out via gut motility, and thus multiply, colonize and modulate the immune system of the whole body by competitively suppressing pathogens [13]. The commonest probiotics used in functional foods and other fermented products include Lactobacilli, Enterococci, Bifidobacterial and Leucon Stoc spp. Other than these lactic acid bacteria group, yeasts such as Saccharomyces spp. are also used as probiotics [14] In fact, the market for probiotics is ever increasing in size, and consumers' demands have risen spontaneously based on the immune-enhancing benefits of probiotics. They are already being sold as conventional foods, dietary supplements, medical foods, and drugs in the United States, and are often administrated in capsules, liquid or powder forms [15]. The immune boosting effects and mechanisms of some probiotics are listed in Table no. 1.

Immune boosting and mechanisms of action: - The action mechanisms of probiotics interfere with the gut epithelial and immune cells composition and functions. Several insights into the mechanisms of probiotics are deduced from in vitro, animal, cell culture or ex vivo human studies, and not all mechanisms have been confirmed in every probiotic strain or humans because a probiotic cell may exhibit several mechanisms simultaneously, further complexed by diverse factors [16]. There is a probiotic inherent immunomodulatory property which varies from strain to strain. For instance, a probiotic strain significantly reduced sepsis in a study, but upon reformulation allowed enterocolitis in infants [17].

There is a colonization resistance concept, which is possibly the sum outcome of the functioning of many of the different immune-boosting mechanisms of probiotics action in concert ;it is described as the occupation of host tissues by the native gut microbiota in order to exclude potential pathogenic infections[18]. The validated and proposed action mechanism of probiotics are represented in fig no.1. Probiotics are well known to boost the immunity of humans by protecting against gastrointestinal pathogens, thus the mechanisms of action by which they exert their beneficial effects on the host include secretion of antimicrobial substances, competitive exclusion for adhesion sites and nutritional sources, enhancement of intestinal barrier function, and immunomodulation [19].

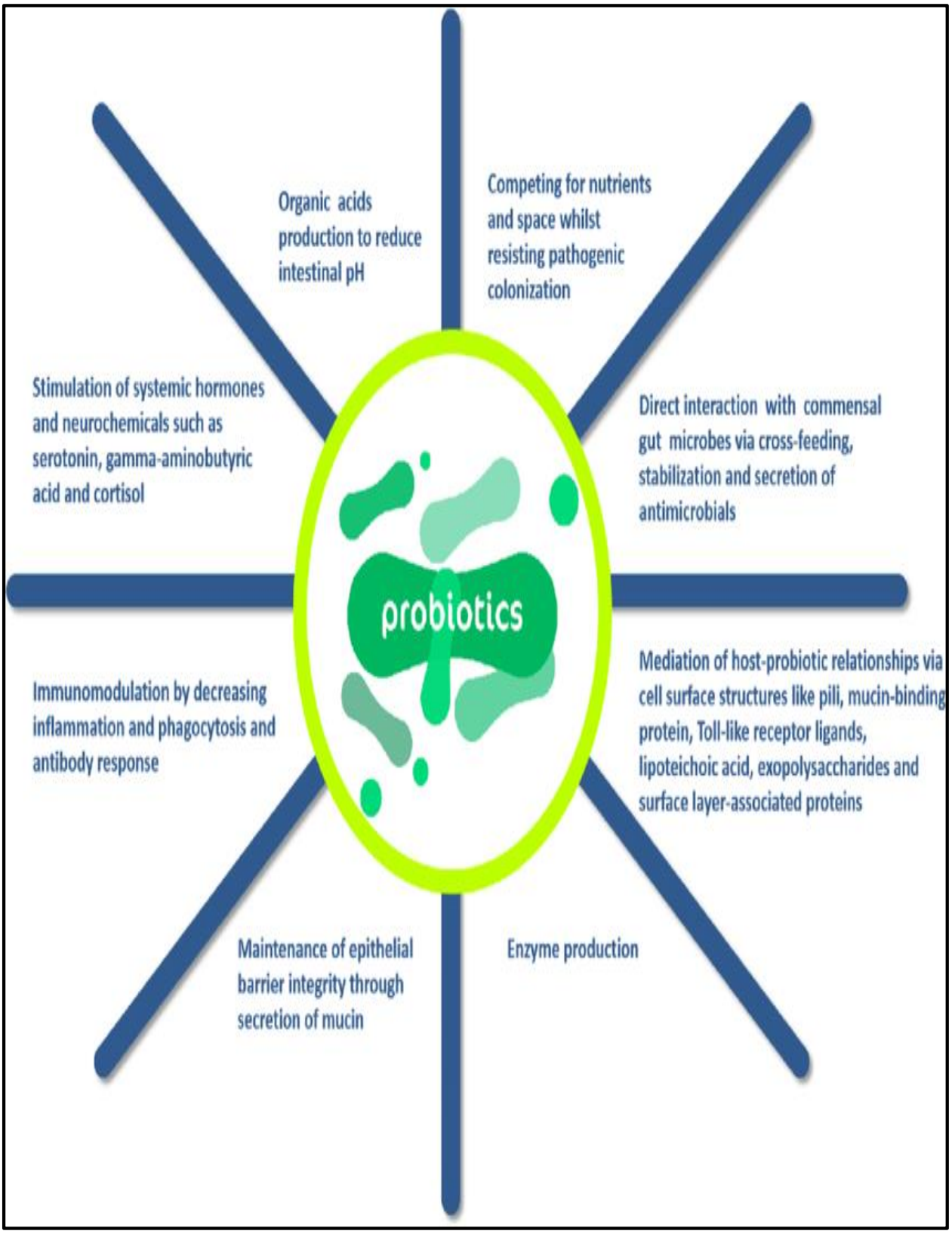

figure no: -1: probiotics

Table no.1: Probiotics Immune Boosting and Mechanism of Action

The immune boosting effects and mechanisms of selected probiotics			
Probiotic Organism	**Immune boosting functions**	**Mechanism**	**Citation**
Lactobacillus plantarum MONO3	Detoxify toxins	Binding via surface structures	Jebali et al. [11]
Lactobacillus kefiri KFLM3 Saccharomyces cerevisiae KFGY7	Detoxify toxins	Adsorption and biotransformation	Taheur et al. [12]
Acetobacter syzygii KFGM1	Detoxify toxins	Binding via surface structures	Ismail et al. [13]
Lactobacillus helveticus ATCC 12046	Detoxify toxins	Enzymic degradation	Rao et al. [14]
Bacillus licheniformis CFR1	Detoxify toxins	Binding via surface structures	Ismail et al[13]
Saccharomyces cerevisiae HR125a	Detoxify toxins	Binding via surface structures	Ismail et al[13]
Lactococus lactris JF 3102,	Protect-from enteropathogenic infection	Produce acetate and improveintestinal defence with epithelial	Fukuda et al.[15]
Lactobacillus plantarum NRRL B-4496	inhibit allergy	Suppress Th2 chemokines	Iwabuchi et al.[16]
Several other bifidobacterium Strains	Reduce inflammation	Inhibit IL-17	Miyauchi et al[17]

Prebiotics: -Prebiotics were referred to indigestible food ingradients capable of providing health benefits to the host through selective stimulation of the activity of colonic bacteria [20]. Subsequent comprehension of the gut microbiota and technological advancements such as metagenomics, nutrigenetics and meta transcriptomics have further elucidated on the intricacies and delicateness of this definition.[21] For instance, the International Scientific Association of Probiotics and Prebiotics (ISAPP) in London (United Kingdom), has defined a prebiotic as "a substrate that is selectively utilized by host microorganisms conferring a health benefit". This occurred in 2016, and is the most recent definition [22]. Therefore, prebiotics may not necessarily be carbohydrates, and may also be applied to other atypical "substrates"in the human body apart from the gut such as the skin or vaginal tract, capable of being colonized by the probiotics. This process have to follow stringent microbial selectivity. Other than the established prebiotics that are oligosaccharides [e.g. fructooligosaccharides (FOS), galact oligosaccharides (GOS), inulin and xylooligosaccharides (XOS)], which cannot be digested by enzymic

activities, rather used up by gut microbes like Saccharomyces, bifidobacteria, eubacteria and lactobacilli; certain compounds like proteins or peptides, unsaturated fatty acids, flavonoids, micronutrients and macronutrients also demonstrated prebiotic properties[23]. Critical observations show that prebiotics immune boosting effects are associated with probiotics stimulation and their metabolites produced such as short chain and branched chain fatty acids; and may also be derived from other uncommon microbial taxa such as faecalibacteria, eubacteria or roseburia [24]. Speculated ecosystemic metabolism of polysaccharides have been repeatedly presented but their modus operandi within the gastrointestinal tract is not clear yet [25]. Functional redundancy exists despite the presence of diverse taxa in gut microbiota. The ecological functions of bacteria are specific in different individuals [26], and less vivid comprehension of the functional ecology of the gut microbiota poses a challenge of describing prebiotics action mechanisms [27]. However, probable mechanisms of prebiotics leading to human health benefits can be postulated as shown in Fig. 2.

Immune boosting and mechanisms of action: - Dietary prebiotics are usually those indigestible fibrous compounds passed through the upper gut in order to stimulate probiotics growth. A Fig. 2. Action mechanisms of prebiotics. Caption: Upon selective utilization of prebiotics in the gut, the microbiota grows to exert various immune boosting functions at species and strain multi-levels. The bacterial cell wall and other biomass increase immunomodulation and fecal bulking for healthy bowel movement. Metabolites like organic acids reduce luminal pH, harmful to pathogens but aid solubility and absorbability of minerals such as calcium, as well as positively regulate hormones and epithelial integrity. GLP1: glucagon like peptide1; M cell: microfold cell; NK: natural killer; PYY: peptide YY; TGFβ: transforming growth factor-β; TH1, TH2: type 1 T helper, type 2 T helper; Treg: regulatory T; ZO1: zonula occludens 1. Adapted from Sanders et al. [28] simple case study is indigestible FOS, made of 1-kestose (GF2) and nystose (GF3), metabolized specifically by bifidobacteria and bacteroides amongst others, as energy sources for replication in the gastrointestinal tract[29]. This process alters the gut ecosystem based on series of the bacterial dynamics and movement of their metabolites, which then stimulate IgA secretion, an important intestinal immune system component [30]. In the same process, the larger GF3 molecule can increase intestinal bacteroides in order to stimulate IgA production [31]. Prebiotics may also interfere with type 2 T-helper reactions in order to alleviate allergy according to some studies in infants. Arslanoglu et al. [32] found out that feeding healthy term infants who are at atopy risk with prebiotic-supplemented hypoallergenic formula for 6 months could lead to a significant reduction in allergies prevalence even after 5 years of the feeding programme. In a similar study, there were reduced wheezing, atopic dermatitis and urticaria in infants fed with long-chain FOS and GOS formula, administered in a double-blind, randomized, placebo-controlled trial as compared to infants fed with non-prebiotic formula [33]. In these studies, the exact mechanisms remain unclear. SCFAs produced via prebiotic degradation by the intestinal microbiota also act in defense of the immune system. Tarantino & Finelli [34] reported that prebiotic treatment had some varied impacts among NAFLD and obese individuals who had undergone gastric bypass surgery with intriguing hypothesis based on molecular and biochemical mechanisms. Processes like minor conversion of indigestible carbohydrates into SCFAs or decreased local alcohol production may reduce the risk of worsening NAFLD by ameliorating insulin resistance. However, it is currently still unclear as to which bacterial groups play a role in the development of obesity in humans [35]. The production of acetic acids as bifidobacteria metabolites in the intestinal epithelial cells can prevent intestinal enterohemorrhagic Escherichia coli O157 infection [36]. There is a strong relationship between SCFAs and G-protein coupled receptors (GPRs) because SCFAs activate GPR41 and GPR43 on intestinal epithelial cells in order to stimulate immune responses via chemokines and cytokines swift secretion, reactions already confirmed to help in tissue inflammation andimmunity in mice studies [37]

Table No-2: Prebiotics Immune Boosting and Mechanism of Action

Prebiotics influences on immune boosting recently demonstrated in *in vitro*, animal and human studies					
Prebiotics Source	Experimental design	In vitro,animal or human studies	Analysed metabolites/bacteria	Resultant influences	Citation
Orange juice enriched with hesperidin and naringin	Ten healthy children and women in a controlled non-randomized clinical study for sixty days.	Human	Acetate, butyrate,lactobacilli and bifidobacteria	Up-regulation of insulin, glucose, triglycerides and total cholesterol.	Lima et al. [21]
Galactooligosaccharides (GOS) and sialyllactose	Caco-2, colon and gingival epithelial cells lines.	In vitro	Lactate, propionate, butyrate, bifidobacteria and Bacteroides.	Regulation and modulation of genes associated with cell cycle stages and cyclin-dependent kinases.	Perdijk[22]
Blackcurrant enriched with prebiotic polyphenols	Sixten Sprague-Dawley rats fed for 6 weeks,randomlydivided into8 groups.	Animals	Butyrate and Bacteroid- Prevotella-Prophyromonas group increased While bifidobacteria and C. perfringens decreased.Propionic acid.	Influences on food intake and body weight and disrupted large intestine biomarkers.	Paturi et al. [23]
Grapeseed flour enriched with prebiotic polyphenols and kefir- derived lactic acid bacteria	Ten Mice in random groups of six fed for 9 weeks.	Animals	Propionic acid.	Adipogenesis, permeable intestine, systemic inflammation, glucose and insulin resistance.	Cho et al. [24]
Inulin	Caco-2 cells plus fecal batch fermentations	*In vitro* .	Acetate,propionate, butyrate, bifidobacteria, actinobacteria and members of Bacteroides and Lentisphaerae	Improved and enhanced gut barrier and immune function(nuclear factor kappa b, transepithelial electrical Resistance, and	Van Den Abbeele et al [25]

				interleukins-10 and-6.	

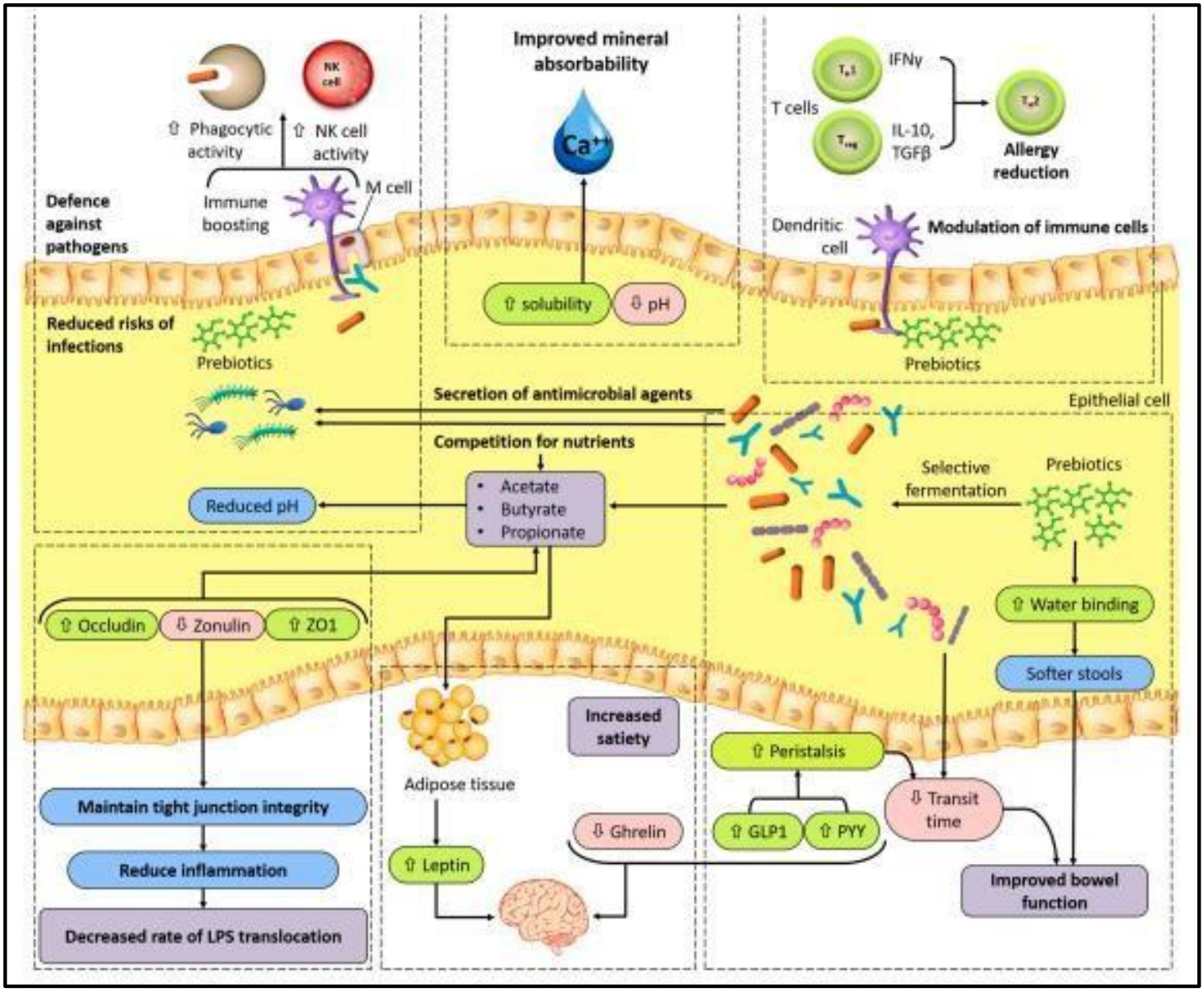

figure no.2: prebiotics

Immune Boosting foods: List of foods to Build Immunity

To have a disease-free healthy life, you need a strong immune system. There are some immune boosting foods [38]. The prime focus of these immune boosting foods is to amplify the fighter cells so that they can fight against cold, flu and other infections. Few changes in diet can largely help your immune system to geta boost and increase its ability to combat viruses and bacteria. Here is a list of 8 foods that build your immunity.[39]

Apples

There is old proverb saying that An Apple a Day Keeps Doctors Away" and this proverb is very true indeed. Apple tops the list of foods that builds immunity. Apple is a very healthy fruit rich in quercetin, which has wonderful properties todevelop immunity and maintain

blood sugar levels. Including an apple in your breakfast or eating it as day snacks can help you boost your immune system at large and prevent you from falling ill. Frapes, tea, red wine, onions and kale are some of the other foods rich in quercetin.[40,41]

Garlic

Garlic is not just limited for kitchen use; instead, it is one of the flavoursome foods that builds immunity. Garlic has sulphur-containing compound like sulphides and allicin which boost your immune system and increase its ability tocombat flu and colds making it one of the best immune boosting foods [42]. Italso acts as an antioxidant that decreases the accumulation of free radicals in bloodstream. Garlic also lowers the incidence of intestinal cancer and is helpful for your cardiovascular health.[43]

Spinach

Spinach is a wonder food, especially rich in iron and other nutrients. Iron deficiency may cause your immune system to function abnormally and this may increase the chance of infections. However, it is important that you know your daily iron requirement to avoid any excess. [44] Spinach, a green leafy vegetable when taken regularly can provide you with the required dose of iron and other nutrients making it an essential immune boosting food. The other good sources of iron are tofu, fortified cereals, red meat and lentils.[45]

Yogurt

Yogurt is really an immune boosting superfood. It is loaded with vitamin B5, riboflavin, phosphorous, potassium, iodine and zinc. Yogurt is a rich source of good bacteria called probiotics, which are the healthy bacteria helpful for healthy digestion. [46] Vitamin B12 in it helps maintain the red blood cells in body and even makes the nervous system function optimally. Most of the infections react to an abnormal gut, which leads to several problems. So, it is important to keep gut healthy to enjoy better overall health. [47] Yogurt shouldcertainly be included in your list of foods if you want to build immunity.

Mushrooms

Mushrooms are rich in selenium, which can mobilize the cancer fighting cells in body, while boosting the natural killer cells and immune system making it an essential immune boosting food [48] . The other selenium containing foods that boost immune system include cottage cheese, vegetables, whole grains, lobster,egg yolks, chicken, garlic, lamb chops, shrimp, brown rice, Brazil Nuts and RedSnapper.

Cashews

Cashews are not just a healthy snack but it can be healthy immune boosting food too. Cashews are a rich source of zinc and they help restore the level of zinc in your body.[49] Your body requires sufficient amount of zinc on daily basis to produce and activate T-cells, which boosts immune system. Hence, cashews too are very healthy and are one of the tastiest foods that boost your immune system. Other great sources of zinc are chicken, beef, crab, beans and fortifiedcereals.[50]

Black Tea

Hot tea is often served to people suffering from common cold because it helps in soothing the throat and also has other benefits which are beyond one's imagination. Black tea is considered as a healthy drink because it contains an amino acid called L-Theanine. This amino acid can build immunity, hence black tea is listed as one of the foods that builds immunity and helps combat against bacteria and viruses. These were the 8 immune boosting foods that should be included in

your daily diet regime to stay healthy. [51] You can consult your doctor or nutritionist, regarding the exact quantities to be taken and various ways in which they can be added to your diet.

KADHA

Immune Booster Herbal Kadha is pure herbal formulation. Sip on this Ayurvedic Kadha for your daily dose of Immunity, this is to ward off seasonal niggles like cold, cough and flu. The importance of working on your immunity is now on an all-time high. If you often fall ill, it means your body's immunity is low. You can strengthen it with the help of this herbal kadha which has a mix of several Ayurvedic herbs.[52] This pacifies tridosha (Vata, pitta and Kapha), stimulates digestion, strengthen your immunity, and also detox your body. This Kadha is helpful in flu and different allergicproblems. It consists of effective levels of antioxidants, Vitamin C and E which circulate in the body to protect it against the damage caused by free radicals. This Kadha has natural immune-modulator properties to prevent and ease coughing, sneezing, cold, itching, rashes, headache, shortness of breath and infections. [53] It provides relief from running nose, itching throat, body ache, and weakness

figure no.3 : kadha

BENEFITS OF IMMUNO BOOSTER KADHA

1. Helps to promote healthy immune resistance
2. Long term cell protection
3. Antioxidant in nature
4. Protect the body from various kinds of viruses and other lung infection
5. Coughing
6. Sneezing
7. Cold
8. Shortness of breath
9. Wheezing
10. Rashes
11. Sore throat
12. Lower blood sugar level
13. Provide relief from Headache
14. Insomnia
15. Helps in controlling high blood pressure

Vitamins & Minerals You Need for a Healthy Immune System

1. **Vitamin C: -** May help prevent infections or shorten their stay. Citrus fruits are a standout, but did you know there are other good sources:Spinach,Bell peppers. Brussels sprouts.Strawberries Papaya.

2. **Vitamin E: -** can be a powerful antioxidant that helps your body fight off infection. To get your vitamin E think high fat plant foods such as:Almonds Peanuts/peanut betterSunflower Seeds.
   Oils such as sunflower and soybean oil,Hazelnuts

3. **Vitamin A: -** Is an infection fighter and comes in two forms preformed such as in animal foods such as fist meat and dairy or from plant carotenoids. Such as:Carrots,Pumpkin, squashand Dark green leafy vegetables.

4. **Vitamin D: -** Vitamin D also known as sunshine vitamin it's one of the important and powerful nutrients for supporting the immune system. Food sources are limited but include Salomon.

5. **Iron: -** Iron, which helps your body carry oxygen to cells, plays a part in many of the immune system processes. It comes in different forms. Your body can more easily absorb hame iron which is abundant in Red meat (limit to smaller amounts and less often). Chicken.Turkey.Canned sardines.Oysters.Clams.Mussels.

If you're a vegetarian, have no fear. You can still find iron in: Beans.Broccoli.Kale.

❖ Cells of Immune system

Cells of Immune system: - Phagocytes are large white cells that can engulf and digest foreign invaders. They include monocytes, which circulate in the blood, and macrophages, which are found in tissues throughout the body, as well as neutrophils, that circulate in the blood but move into tissues where they are needed. Macrophages are versatile cells; that act as scavengers.[54] They secrete a wide variety of powerful chemicals, and they play an essential role in activating T cells.

Neutrophils are not only phagocytes but also granulocytes: they contain granules filled with potent chemicals. These chemicals, in addition to destroying microorganisms, play a key role in acute inflammatory reactions. Other types of granulocytes are eosinophils and basophils. Mast cells are granule-containing cells in tissue [55]

T Cells: - T cells contribute to the immune defences in two major ways. Some help regulate the complex workings of the immune system, while others are cytotoxic and directly contact infected cells and destroy them. Chief among the regulatory T cells are "helper/inducer" T cells.[55] They are needed to activate many immune cells, including B cells and other T cells. Another subset of regulatory T cells acts to turn off or suppress immune cells. Cytotoxic T cells help rid the body of cells that have been infected by viruses as well as cells that have been transformed by cancer. [56] They are also responsible for the rejection of tissue and organ grafts.

B Cells: - B cells are lymphocytes that play a major role in the humoral immune response. The principal functions of B cells is to produce antibodies against antigens, perform the role of antigen-

presenting cells (APCs) and eventually develop into memory B cells after activation by antigen interaction. B cells are an essential component of the adaptive immune system.

Natural Killer Cells: - At least two types of lymphocytes are killer cells - cytotoxic T cells and natural killer cells. To attack, "cytotoxic T cells" need to recognize a specific antigen, whereas natural killer or NK cells do not. Both types contain granules filled with potent chemicals, and both types kill on contact. The killer binds to its target, aims its weapons, and delivers a burst of lethal chemicals.[57]

CONCLUSION: - Functional foods such as probiotics and prebiotics are the future of health-promoting foods. The consumption of probiotics such as lactose bacilli and bid bacteria may proffer an option to antibiotics for prevention and treatment of microbial infections based on certain mechanisms including antimicrobial toxins production, maintenance of intestinal barrier integrity, competing for nutrients and adhesion, as well as modulation of the immune system. This is not dissimilar to effects and mechanisms of prebiotics, which are entangled in synergistic processes with the beneficial probiotic organisms. Thus, better comprehension of the mechanisms involved are required, as well as extensive human studies to validate excellent potent probiotic species/ strains and effective number of doses meant for particular diseases. Generally, the results of these interventions may be valuable for target populations. Researchers are bestowed with the responsibility of considering the importance of their findings to consumers, as well as their fundamentality to overall conclusions on products' efficacy. Moreover, more investigations and translational research on probiotics and prebiotics meant to help developing countries consumers are recommended.

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