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Role of Nutraceutical in Immunity Booster

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Abstract: New dietary habits, current trends in production and consumption have significant health, environmental, and social implications. The European Union is addressing diseases typical of the modern era, including obesity, osteoporosis, cancer, diabetes, allergies, and dental issues. Developed nations are also confronting challenges associated with aging populations, high-calorie foods, and unbalanced diets. This paper discusses the potential of nutraceuticals, functional foods, and food supplements in alleviating health issues, particularly in the gastrointestinal (GI) tract. Specific members of gut microflora (e.g., probiotic/protective strains) contribute to the health of the host through their roles in nutritional, immunological, and physiological functions. The potential mechanisms by which nutraceuticals, functional foods, and food supplements may influence a host's health are also emphasized in this document. The development of innovative functional cell models of the GI tract and analytical tools that facilitate testing in controlled experiments are greatly needed for gut research.

Key Words: nutraceutical; functional food; food supplement; intestinal health; probiotic; intestinal cell models; gut research

I. Introduction

Nutraceuticals are food-derived products that provide health benefits, including the enhancement of the immune system. These substances, which include vitamins, minerals, amino acids, probiotics, and plant-based compounds, play a significant role in boosting immune function[1].Several nutraceuticals, suchas vitamin C, vitamin D, zinc, and probiotics, have been shown to support immune responses by enhancing the activity of immune cells like T-cells, macrophages, and natural killer cells. Additionally, certain herbal products like echinacea, garlic, and turmeric possess anti-inflammatory and immune-stimulating properties, which can help defend against infections and diseases[2].Recent studies have demonstrated that the incorporation of nutraceuticals into one's diet can improve immune resilience, reduce the duration and severity of illness, and help in disease prevention. However, it is important to understand that while nutraceuticals can support immune health, they should be used as a complementary approach rather than a replacement for medical treatment[3].The body's immune system is among its most intricate biological systems. It is a complex and diverse network of specialised cells, organs, proteins, and chemicals., and is crucial in providing defence against cancer cells as well as a variety of pathogens, including bacteria, viruses, and fungus. Innate (non-specific) and adaptive (specific) immunity are recognised to make up host immunity [4].

Therefore, research into safer, more natural, and more potent adjuvants that can improve immune system performance by triggering immune cells and immune molecule modulation is required[4]. Plant-based functional foods are made from natural or processed plant foods that contain bioactive ingredients, either recognised or undiscovered. Due to their high levels of bioactive components and health advantages, they have been widely consumed in recent years (Mohamad et al., 2020). Of particular note is the mounting evidence from preclinical studies showing plant-based functional diets can lower the risk of a number of conditions, including diabetes, cancer, heart disease, hyperlipidaemia, and hyperuricemia[4].

Studies on immune boosters based on plant-based functional foods have drawn a lot of attention due to growing awareness of the potential of these foods to combat diseases, and more people are choosing plant-based functional foods to enhance immune system functions[4].

Long-term clinical investigations have demonstrated the nontoxicity of astragalus polysaccharide. More significantly, APS has a broad range of pharmacological effects linked to immune system regulation, including raising the immune organ index, encouraging immune cell proliferation, inducing cytokine release, and influencing immunoglobulin secretion and immune signal transmission[4].

The biological elements of immune-boosting plant-based functional meals are highlighted in this review, as is their potential for immune-boosting uses, such as the creation of novel disease treatment approaches[4].

In order to prevent an undesirable reaction to either harmless alien chemicals or healthy tissues of the body, the immune system also develops the proper tolerance.

The strength of an individual's immune system varies greatly from person to person, mostly due to genetics, environment, lifestyle, nutrition, and the ways in which these factors interact . A high rate of morbidity and mortality from infectious diseases is mostly caused by nutritional inadequacies, which are still common in less developed areas. Specific vitamin deficits, less-than-ideal food composition, and excessive calorie consumption are all difficult realities in nutrition, even in affluent nations where broad nutritional deficiencies are uncommon . Although many other members of the aforementioned categories are also known to impact immune function, we have only included a small number as representatives in the current review. This is primarily because they have been studied more thoroughly and their immunomodulating qualities are generally accepted, despite the fact that it is widely

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acknowledged that there is still much disagreement regarding the nature and extent of their actions, as well as the effectiveness and potential application's translational value[5].

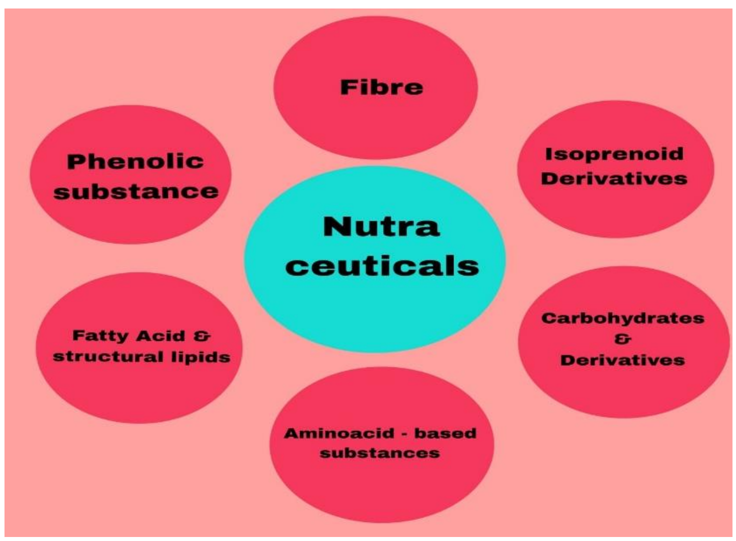
Derived from the words "nutrition" and "pharmaceutical," the phrase "nutritraceutical" describes any product that is separated from herbs, nutrients, certain diets, processed meals, and beverages and utilised for both medicinal and nutritional objectives. Prebiotics, probiotics, fatty acids, amino acids, phytochemicals, antioxidants, and other bioactive derivatives from edible sources are all included in nutraceuticals. Numerous of them have medicinal qualities that can influence the immune system. According to their origin, kind, and use,to provide a thorough analysis of nutraceuticals in this Special Issue[6].

Eating patterns and the production and use of food have an impact on society, the environment, and human health. Gut health is impacted by diet. Intestinal microbial flora overgrowth and imbalance cause gut problems such ulcerative colitis, Crohn's disease, irritable bowel syndrome, and gluten therapy-resistant coeliac disease, which are linked to dietary factors. Food is broken down into nutrients in the human gut, nutrients are then more easily absorbed into the bloodstream through the intestinal walls, and harmful and foreign substances are kept out of the bloodstream . The apparent disparities in the health of the continent's populace are largely caused by variations in diet and consumption throughout Europe. The European Union (EU) population continues to struggle with modern-day diseases like obesity, osteoporosis, cancer, diabetes, allergies, stress, and dental issues, despite the fact that consumers today are more concerned with food safety, quality, and health-related issues[7].

Interestingly, the diet in the United States offers the most calories at the lowest cost in the world. Additionally, the USA has the greatest supply of refined and processed food items as well as large-scale agricultural commodities[7].

What is Nutraceuticals?

Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ, initially used the terms "nutrition" and "pharmaceutical" to create the phrase "nutraceutical" in 1989[7].



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While many of these "natural" substances have been found to have high therapeutic potential, future research should include well-designed clinical trials evaluating combinations of these compounds to realise possible synergies they bring to human health. A number of naturally derived food substances have been studied in cancer therapies. Examples of nutraceuticals widely studied in human health include vitamin E, selenium, vitamin D, green tea, soy, and lycopene.In addition, phytochemicals and polyunsaturated fatty acids (PUFAs), which comprise omega-3 and omega-6 fatty acids, are key dietary bioactive substances. Numerous facets of immunity and metabolism are influenced by a diet rich in polyunsaturated fats . The potential benefits of phytochemicals (bioactive non-nutrient plant compounds) as antioxidants, antiestrogenics, anti-inflammatory, immunomodulatory, and anticarcinogenics have sparked interest in human nutrition. For instance, the gut bacteria can change and impact polyphenols' absorption and effects. Human health is impacted by interactions between functional food ingredients such gut microbiota, phytochemicals, probiotics, and prebiotics [7].

Role of Nutrition in Immune Function:

All cells, including those in the immune system, need proper and sufficient nutrients to operate at their best. The need for energy is further increased during infection by a "activated" immune system; for instance, fever results in a higher basal energy consumption. It is well known that undernutrition weakens the immune system, whether it be from famines or food shortages in developing nations or from malnutrition brought on by hospital stays in rich nations .Additionally, a single nutrient can have a variety of

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immunological effects. For example, vitamin E functions as an antioxidant, inhibits the activity of protein kinase C, and may interact with transport proteins and enzymes[8].

In areas where malaria is endemic, iron supplementation may raise morbidity and fatality rates. In addition to nutrition's ability to successfully address immune deficiencies brought on by inadequate intake, there is a lot of interest in determining whether certain nutrient interventions can also improve immune function in subclinical settings, thereby delaying the onset of infections or chronic inflammatory diseases. The human immune system, which is impervious to disease, is made up of tissues, immune cells, and organs that work together to shield the body from external substances called antigens . If immunity is less, compounds that infect humans can become more prevalent and spread to other individuals, leading to disease, serious infection, and even death [8].

The antibodies involved in this sort of immunity include neutrophils, basophils, eosinophils, dendritic cells, macrophages, and mast cells. This innate immunity is the main one that starts to work as soon as the virus touches the host, which can happen minutes to hours later. Immune system specialised inflammatory cells are called neutrophils. Antigen-presenting dendritic cells are phagocytic and activate acquired immunity . Additionally, monocytes are blood-circulating phagocytes. monocytes transform into macrophages as they travel into tissues . Adaptive immunity is triggered when there are many pathogens present, which can lessen the impact of innate immunity. Adaptive immunity is such as an additional benefit and a more advanced defence mechanism made up of T cells and B cells . Because the human body takes time to produce antibodies through vaccination and only invades a specific antigen, adaptive immunity is antigen specific. The system's lymphocytes and adaptive immune mechanism are activated in response to the pathogen's detection.Vaccination is based on adaptive immunity, which has the ability to identify and eliminate particular things, such as pathogens (immunologic memory is present—meaning antibodies are produced by injection). The second line of defence is adaptive immunity, which is triggered for the secondary exclusion of infectious organisms .The purpose of the killer cell, a kind of T cell, is to eliminate any cells that seem aberrant or that are contaminated with the antigen. It is a protein that eliminates antigens in the bloodstream, and B cells are in charge of activating the antibodies [8].

Immunological Response System:

Leukocytes, or white blood cells, are a group of cells, cytokines, and antibodies that make up the two functional divisions of the immune system . Leukocytes include phagocytes, monocytes, and lymphocytes . Beginning in the bone marrow, all of the immune system's cells circulate in the circulation, are arranged into lymphoid organs such as the spleen, thymus, lymphoid tissue, and lymph nodes, or are dispersed throughout the body in various locations [8].

A cytokine may have multiple effects on different cells. These chemical messengers work by attaching themselves to certain cell surface receptors and then causing modifications in the target cell's growth, progress, or behaviour, innate immunity first reacts swiftly to immunological stimuli and acts immediately to eliminate infections. This response will be regulated by the removal of germs through the production of cytokines (interleukin-1, interleukin-6, and tumour necrosis factor-α) by cells linked to the innate reaction, especially macrophages and monocytes. Furthermore, cytokines promote lipolysis and proteolysis in skeletal muscle and adipose tissue, respectively, and they profoundly influence the liver to promote intense stage protein synthesis .An immune system that can defend itself against antigens and is resistant to disease is a sign of a healthy body. Usually, the human body produces white platelets, which play a crucial part in the production of secure cells. Proteins and synthetic substances (chemicals) that can attack and eliminate the antigens are also delivered by it. Before the antigens have a chance to proliferate and spread, the human defence system locates them and eliminates them [8].

The Next Step in Nutritional Wellness:

Vitamins

Vitamin A : (Retinol)

Intestinal innate immunity and the homeostatic maintenance of the gut barrier are two unusual functions of vitamin A (also known as retinoic acid). The three primary forms of this vitamin are retinal, retinoic acid, and retinol. The retinoid The primary active metabolite, acid, is partially produced by intestinal dendritic cells [9].

Vitamin A deficiency can affect T cell immunocompetence at different levels, including lymphopoiesis, distribution, expression of surface molecules, and cytokine production [9].

Vitamin A deficiency may increase proinflammatory responses and impair normal antibody activity Given that its deficiency is linked to more persistent infections optimal vitamin A levels are necessary against enteric pathogens and colonic inflammation. Numerous studies have demonstrated that inflammatory conditions increase retinoic acid synthesis and signal transmission[9].

According to available data, blood vitamin A levels in healthy individuals are noticeably higher than those in TB patients. Vitamin A insufficiency is, in fact, dose-dependently associated with the development of tuberculosis, and supplementing with it reduced the incidence of tuberculosis in HIV-positive individuals, according to a longitudinal cohort research[9].

Vitamin C: (Ascorbic Acid) An important micronutrient with antioxidant and anti-inflammatory properties is vitamin C. By encouraging T and B cell differentiation and proliferation as well as antibody production, it significantly enhances adaptive immunity and stimulates the fibroblast migration, proliferation, and collagen synthesis required to stabilise epithelial barriers[9].

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Vitamin D : (Calciferol)

A steroid hormone, vitamin D affects immunological responses at the cellular level by promoting macrophage activity and decreasing the expression of inflammatory cytokines.Consequently, vitamin D prevents T cell proliferation, which makes it easier to induce Tregs, and inhibits B-cell proliferation, differentiation, and Ig production. Research indicates that vitamin D may lessen the synthesis of IFN-α, IL-2, and IL-12, hence preventing the adaptive immune system's suppressive effects on Th1 cell development[9].

Anti-inflammatory cytokines, such IL-10, are eventually encouraged to rise while inflammatory cytokines, especially IL-17 and IL-21, are gradually reduced by the modulatory actions. Monocytes and dendritic cells are similarly affected by vitamin D, which stops them from producing inflammatory cytokines like TNF-α, IL-1, IL-6, IL-8, and IL-12. Additionally, vitamin D prevents dendritic cells from differentiating and maturing, maintaining an immature phenotype Additionally, vitamin D stimulates the production of antimicrobial peptides (AMPs), primarily cathelicidin and defensin, which are found in neutrophils, monocytes, NK cells, and epithelial cells lining the respiratory tract and which shield the lungs from serious infections like tuberculosis[9].

Vitamin E: (Tocoferol)

Vitamin E affects innate immunity in several ways and is necessary for immune cells to operate normally. It lowers monocytes' adherence to the endothelium and their generation of reactive oxygen species (ROS), for example. Several animal studies have demonstrated that vitamin E supplementation contributes to increased resistance against a number of pathogens, and dietary interventions involving vitamin E have been shown to improve cell-mediated and humoral immune responses in a variety of animal species. Notably, vitamin E supplementation increased lymphocyte proliferation, Ig and IL levels, and NK cell activity[9].

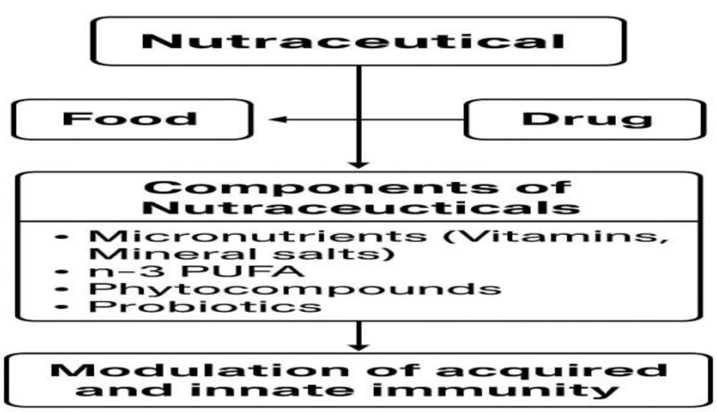
Vitamin B Complex:

The control of the immune system is another function of B vitamins. For example, vitamin B1 reduces NF-κB-induced oxidative stress, has anti-inflammatory qualities, and affects mitochondrial membrane potential, apoptotic proteins, and protein kinases [p38 mitogen-activated protein kinases (p38-MAPK)]. T cell infiltration, chemokine (C-C motif) ligand 2 activation, and the upregulation of proinflammatory molecules including IL-1, TNF, IL-6, and derivatives of arachidonic acid can all result from a vitamin B1 shortage . Riboflavin, often known as vitamin B2, has anti-inflammatory and antioxidant properties. vitamin B2 supplementation in mice really improved the phagocytic activity of macrophages infected with Staphylococcus aureus while lowering the levels of IFN-, IL-6, and IL-1.[9].

Cobalamin, another name for vitamin B12, is a water-soluble vitamin that is essential for DNA synthesis as well as the metabolism of amino and fatty acids. By lowering proinflammatory cytokines and maintaining lymphocyte Treg numbers within the normal range, this vitamin is believed to control the immune system. Lately,Research has verified its role in boosting NK and CD8+ cell activity. A lack of vitamin B12 has been connected to decreased NK cell function and circulating lymphocyte counts. By boosting CD8 T cell and NK cell activity, vitamin supplementation can change these immune responses.Furthermore, vitamin B12 is a useful regulator of the immunological and inflammatory states of HIV patients[9].

Foods that increase immunity and their health benefits:

Natural sources of immune-boosting foods, such as fruits and vegetables, have demonstrated anti-inflammatory, anti-cancer, anti-viral, antioxidant, and immunomodulatory effects. The Every immune-boosting diet contains many elements, including vitamins, minerals, and lipids, all of which are necessary for optimal health.The following describes some of the immune-boosting foods that have been extensively researched over the past 20 years, including almonds, rambutan, durian, avocado, passion fruit, ginger, broccoli, citrus fruits, pomegranate, elderberry, garlic, kiwi, red bell pepper, spinach, yoghurt, meat, and egg products[10].



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Almonds

Almonds are a type of organic, dry fruit that is widely eaten to help prevent and treat colds brought on by viral illnesses. Almonds are tiny and packed with nutrients that are good for the body.Almonds are a wonderful source of vitamins C and E, which strengthen the immune system. Its abundance of antioxidants helps control free radicals, prevent infections, have anti-inflammatory effects, strengthen the immune system, and avoid hepatotoxicity . It has been suggested that almonds speed up the passage of food through the colon, avoiding colon cancer . For food to pass easily through the colon, the fatty acid composition of almonds—which is high in unsaturated oleic acid—is crucial. Almond oil also plays a significant role in signalling molecules that have an impact on the growth of colon cancer cells and the viability of tumour metastases . Almonds' vitamin E also lowers the risk of heart disease, and when paired with magnesium, it can prevent coronary heart attacks[10].

Almond oil is useful for massaging, enhancing skin appearance, and reversing the signs of ageing. Almonds can be consumed in a variety of ways, such as making almond milk a nutritious beverage that is superior to milk and used as a top-up in yoghurt or muesli. Vitamins, minerals, and phosphorus have been linked to bone development and strengthening[10].

RAMBUTAN:

Rambut is a brilliant crimson to maroon fruit with the Malay-Indonesian term meaning "hairy". Vitamins and other nutrients are added to rambutan.

B, natural carbohydrates, calcium, potassium, and magnesium fibre. Antibacterial, antihyperlipidemic, antioxidant, hepatoprotective, biosorbent, antidiabetic, antimalarial, antiadipogenesis, and antiproliferative qualities are among its immune-boosting qualities . Rambutan's health benefits include healing viral infections, diarrhoea, lowering body fat, enhancing skin, preventing cancer, enhancing sperm quality, and protecting hair. Rambutan can be used by humans as canned fruit jam, fresh fruit, juice, and jellies[10].

Durian (Durio zibethinus) :

The nutrient-dense reddish-orange durian fruit contains copper, magnesium, calcium, phosphorus, potassium, favonoids, tannins, and vitamins A, B, C, and E. It also enhances the production of white blood cells. Many health benefits are still present in durian fruit, including antioxidant, antiproliferative, antipyretic, cholesterol, blood pressure, diarrhoea, protection of the eyes, proper digestion, insulin induction for menstrual issues, inhibition of metabolic syndrome, and increased fertility in polycystic ovaries. Candy, jams, ice creams, toffes, milkshakes, and cakes may all be made with durian fruit [10].

Avocado (Persea Americana):

Carotenoids, phytosterols, folate, lutein, flavonoids, potassium, calcium, iron, magnesium, omega3-fatty acids, epicatechin, lipids, peptides, sodium, vitamins B, E, C, and K, and potassium are among the nutrients that contribute to immunity .Numerous therapeutic benefits, including antioxidant, antibacterial, antidiabetic, anticancer, antifungal, cardiovascular, healthy ageing, and weight management, are abundant in the complete avocado (pulp, peel, and seed) . Dried avocado, honey, oil, packed slices, salads, bread toasts, sandwich fillings, guacamole or avocado puree, ice creams, and milkshakes can all be made naturally from avocado pulp [10].

Passion fruit (Passifora incarnate):

It is enhanced with dietary fibre, antioxidants, vitamins, and minerals such as vitamin B, ribofavin, niacin, magnesium, iron, phosphorus, vitamin C, favonoids, beta-carotene, and folate . Good bone structure, muscle, cartilage, anticancer, anti-stress, antidiabetic, anti-obesity, and anticarcinogenic properties are all benefits of passion fruit for the human body. It increases both blood vessel and brain activity. It has been demonstrated to have hepatoprotective, anticholesterolemic, and hyperlipidemia-preventive properties. Passion fruits can be eaten raw or processed to make juices, pies, cakes, jams, ice cream, fruit salads, cool drinks, sherbets, and squash[10].

Immuno-Stimulating Molecules

Natural components included in oral supplements, such as probiotics, multi-element boosters, and complex multivitamins, have demonstrated a potent potential to strengthen cancer patients' immune responses(11).

Furthermore, vitamin D was able to modify the immune system of patients with multiple sclerosis by lowering the severity and recurrence of a relapse[12].

In fact, the GIT is home to a wide variety of microorganisms that perform vital tasks for their host species. Although microflora components are present in the intestine from birth or hatching, little is known about how they affect normal growth and function. The GIT has a higher density of microorganisms than any other organ[13].

The gut microbiota can be affected by a variety of variables, including pathogenic infections, nutrition, and antibiotics. Given clinical presentation and organ damage, the ideal antibiotic substitute should be able to stop infections from different bacteria or

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lessen their effects. The ideal substitute would ideally use the same immunomodulatory and microbiota-modulatory mechanism as antibiotic growth promoters[14].

Aquatic Salmonella In contrast to serovar Typhimurium, which affects pigs, cattle, and poultry, serovar Enteritidis is typically linked to poultry and its derivatives[15].

This bacterium is found all over the world and significantly reduces chicken industry profits. Only young chicks that exhibit depression, drooping wings, ruffled feathers, anorexia, emaciation, and watery diarrhoea often exhibit the clinical symptoms of a Salmonella infection. Weight loss or growth retardation are typically seen during the first two to three weeks of life, when morbidity and death are at their highest. In older birds, clinical symptoms are uncommon[16].

Commercially available probiotic supplements, such as EarlyBird® (Pacific Vet Group USA Inc., Fayetteville, AR, USA) and FloraMax-B11® (Pacific Vet Group USA Inc., Fayetteville, AR, USA), were tested for their ability to prevent intestinal colonisation by Salmonella Enteritidis, either alone or in combination with glycerol[17].

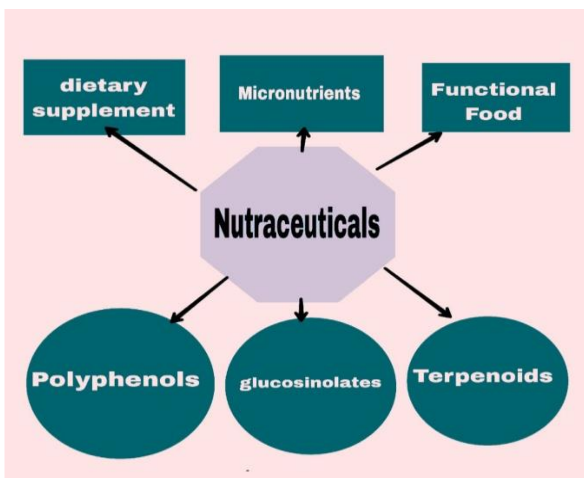
Prebiotic research mostly focusses on the utilisation of oligosaccharides such inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and mannanoligosaccharides (MOS). When MOS is used, Salmonella spp. activity can be inhibited, decreasing the adherence to intestinal epithelium because of the lumen's mannose content[18].

Acid in organic form:

As a potential antibiotic substitute, organic acids have drawn interest. Numerous impacts on the GI tract were demonstrated by earlier research, including enhanced nutrition utilisation, decreased Salmonella spp., increased growth performances, and anti-inflammatory actions[19].
With regard to propionic and fumaric acids, the gizzard and crop are where the highest concentration is achieved following oral delivery. Even though the crop is the first place where an infection settles, the ceca is where Salmonella spp. colonise most frequently, thus it's critical that organic acids can reach the low intestinal tracts to improve animal health. Since uncoated butyrate absorbs more quickly, it cannot get to this location[20].

Additionally, it has been demonstrated that adding formic acid to grill feed seems to stop Salmonella spp. from moving from challenged to non-challenge sheds, albeit this does not necessarily result in a decrease in Salmonella spp. Counts[21].

Additional Immunomodulatory Nutraceuticals



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The functions of coenzyme Q, magnesium, and selenium among the other nutraceuticals with immunomodulatory activity are particularly noteworthy in relation to viral infections.

With a function in T cell growth, antibody synthesis, cytokine release, and signalling, magnesium is a necessary component for several processes linked to the immune system and response to viral infection[22].

Magnesium functions at the molecular level by affecting the activation of intracellular signalling pathways, including PIK3-dependent processes, enzymes, and cationic channels, particularly cation channel subfamily M member 7 (TRPM7). It also directly regulates transcription[23].

Yahfoufi et al. examine the evidence supporting the significance of dietary polyphenols in lowering the risk of cancer, certain neurological disorders, and cardiovascular disease. They also describe the processes by which polyphenols can have immunomodulatory and anti-inflammatory effects[24].

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Acute inflammation can be a fast, intense, and debilitating process in clinical settings. This severe systemic inflammation causes sepsis, which leads to multiple organ failure and death if left unchecked. According to estimates, sepsis accounts for 30% of neonatal fatalities and kills around 6 million people annually, making it a leading cause of death worldwide[25].

There may be chances for focused therapies to restore immune function because certain micronutrient deficiencies have been linked to such deteriorating immunity[26].

It has been suggested that a variety of bioactive substances present in fruits and vegetables provide one explanation for the protective effect of diets high in fruits and vegetables (such as the Mediterranean diet) on the lower risk of non-communicable diseases linked to chronic inflammation (such as cardiovascular disease). Dietary polyphenols are one class of chemicals that are known to play a part in controlling inflammation[27].

A number of chronic non-communicable illness conditions, including autoimmune diseases like rheumatoid arthritis and cardiovascular disease and stroke, have persistent systemic inflammation as a major underlying characteristic. The ageing process and other co-morbidities, such as obesity, cardiovascular disease, and insulin resistance, are positively connected with this chronic inflammation. Remarkably, a study conducted on healthy persons revealed that growing older was a risk factor for chronic systemic inflammation, independent of blood pressure, body mass index, and blood lipid profiles[28].

The Mediterranean diet is higher in fruits, vegetables, nuts, legumes, fish, and "healthy" dietary fats than the Western diet. A lower risk of chronic illnesses like cancer, heart disease, and, more recently, Alzheimer's disease is linked to a Mediterranean diet[29].

There are still several limitations with the present antiviral treatments, including efficacy, safety, and high prices, despite the recent development of several novel antiviral medicines[30].

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