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Bioactive Components in Functional Foods, Mechanism of Action and Impacts on Health with a Focus on COVID-19 – A Review

REVATHI CHANDRAN[1], SENTHILKUMAR OBULIRAJ[2]*, SOUNDESWARAN SUNDARARAJAN[3], SRIDEVI BASKARAN[4], and MURALISANKAR MARGABANDHU[2,5]

[1]Department of Chemistry, Chellammal Women's College, Chennai, Tamil Nadu, India.
[2]Department of Chemistry, Ramco Institute of Technology, Rajapalayam, Tamil Nadu, India.
[3]Department of Chemistry, Dr. Ambedkar Institute of Technology, Bengaluru, Karnataka, India.
[4]Department of Chemistry, Presidency College, Chennai, Tamil Nadu, India.
[5]Department of Chemistry, Velammal College of Engineering and Technology, Madurai, Tamil Nadu, India.

Abstract

Functional food plays a critical role on enhancing an individual's health, in the current scenario. The health benefits of functional foods are elaborated through a review of bioactive components present in these foods. The importance of the components such as minerals, polyols, prebiotics, probiotics, carotenoids, flavonoids, proteins, dietary fibres, vitamins, and fatty acids such as Omega n-3 fatty acids which are present in our daily diet and their role in promoting human health is reviewed in this article. The mechanism of action of these components in the gut and their biochemical responses are discussed. This study also emphasizes the use of controlled delivery of the components by nanotechnological research, typically conducted "*in-vitro*." A detailed note is included to describe how these bioactive ingredients work to treat and prevent COVID-19 infection. The functional components present in foods such as garlic, green tea, curcumin and so forth, can impede the spike glycoproteins of the COVID 19 virus and the ACE2 (Angiotensin Converting Enzyme) receptors present in the human body. These components act by modulating the host immune response against the SARS CoV2 virus in addition to their own inherent antiviral action. Since COVID infection has become an endemic, the daily dietary supplementation of functional components is a novel idea of battling the same. A few of the adverse effects of the bioactive components are also outlined.

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CONTACT Senthilkumar Obuliraj senthilkumar@ritrjpm.ac.in Department of Chemistry, Ramco Institute of Technology, Rajapalayam, Tamil Nadu, India.

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Introduction

In its report, the World Health Organization (WHO) confirmed that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused over 760 million illnesses and over 6.9 million deaths worldwide since December 2019. People already suffered with other potential sickness were found to be vulnerable to covid-19 sickness.[1] A significant number of patients were above 60 years old, majority of them were men.[2] This shows that these individuals are not immune competent. Furthermore, it was noted that the majority of SARS-CoV-2 fatal patients already had many underlying medical conditions.[3] It makes it abundantly evident that maintaining overall health and a robust immune system are essential for reducing the risk factors related to COVID-19 and raising the likelihood of survival and recovery. In addition to that a robust immune system helps to control a number of harmful illnesses. People around the world rely more on complementary and alternative medicine, including traditional medicines made from plants, along with commonly used contemporary drugs. For ages, nearly all civilizations across the globe have utilized plants such as Curcuma longa, Echinacea, Curcuma xanthorrhiza and Cinchona as traditional remedies to treat a wide range of chronic illnesses, including viral disorders. The bioactive components present in the plants such as Quercetin, Glycyrrhizin, Alkaloids, polyphenols etc., provide healing capabilities.[4-6] Additionally, the health-improving potential of functional and nutraceutical supplements have been the subject of scientific validation efforts in recent decades. Phytochemicals found in various plant chunks give plants their therapeutic abilities; these chemicals function similar to those found in traditional pharmaceuticals. Studies have revealed that various classes of compounds, such as polysaccharides,[7] terpenoids,[8] alkaloids,[9] and flavonoids,[10] have immunomodulatory qualities and cause fewer side effects than allopathic medications.[11] For example, herbal remedies for diabetes that have been used traditionally may yield important insights for the creation of new medications and treatment approaches. Nigella Sativa (NS) is a black cumin, which helps to regenerate β-cells in pancreas and hence induces the metabolism of carbohydrates. Berberine (BER), an alkaloid was found to induce secretion of insulin, glycolysis and glucose uptake.[12] A herb, French lilac was used to produce biguanide Metformin which was the first approved herbal based treatment for diabetes.[13] The most common medications at present cannot control every pathophysiological mechanisms of diabetes such as Insulin resistance and β-cell dysfunction.[14] They are expensive and not readily available to many rural populations, especially in developing countries.[15] It is evident that alternatives are required. As a result, the study of bioactive components present in food and their biological influence on the human body has become vital in preventing and treating a number of disorders including covid-19.[16] For example, garlic is effective against a number of gram-negative, gram-positive, and acid-fast bacteria, including Escherichia Coli, Staphylococcus, Salmonella, Vibrio, Mycobacteria, and Proteus species.[17] The goal of the current review is to incorporate readily available functional foods and bioactive substances that are biologically active and have immune-modulating qualities against a range of diseases caused by respiratory tract infections and other possible disorders.[18] It is a recognized fact that in pandemic scenarios like the one caused by COVID-19, functional foods and their bioactive components could boost immunity and help people recover from disease.[16] This review compiles the characteristics of the common bioactive ingredients found in foods and their mechanism of biochemical action in the gut.

Materials and Methods

The following databases were used to find the relevant research articles; PubMed, Google Scholar, Bio Med Central, and Scopus. Additional sources were searched using Google Media. A few of the data were collected from the website of World Health Organization (WHO). The search keywords used were “Functional food”, “Bioactive components of food”, “Probiotic”, “Minerals absorption”, “Probiotic”, “Carotenoids”, “Flavonoids”, “Covid-19”, “Polyols”, “Dietary Fibers”, “Mechanism of action in Gut”, “Mechanism of SARS-CoV-2” , “Medicinal Herbs”, “Functional Food for Covid-19” etc. The year of publication was carefully chosen to be after 2020. However, in case of unavailability of sufficient documents, the search was made from 1995. The search was carried out using English as a default language. The abstract, introduction, full text and conclusions were reviewed by the authors and reported their contributions. A general consensus

was obtained by the corresponding author with the proper consent from the contributing authors. The reviewer suggestions were included in appropriate sections of the articles.

Table 1: Approved FOSHU Products[19]

Health Benefits	Major Ingredients	Bioactive component	Reference
Control of blood cholesterol	Soybean protein, chitosan, degraded sodium alginate	Amino acids and isoflavones	20
Maintenance of blood sugar levels	Dextrin, guava tea & wheat albumin	Polyphenols	21
Balance of blood pressure	Sardine peptide, Lactotripeptide, tochu leaf glycoside, casein peptides.	Peptides	22
Improvement in gastroin -testinal conditions	Oligosaccharides, dextrin, guar gum, polydextrol, lactose, bifidobacteria, lactic acid bacteria, dietary fiber etc.	Polyols, fibres, pre/probiotics	23
Mineral absorption	Hem iron, calcium citrated malate, fracto-oligosaccharides & casein phosphopeptides	Perbiotics and minerals	24
Osteogenesis	Milk basic proteins, Rhizoma drynariae	Flavonoids	25
Dental hygiene	Maltotriose, palatinose, erythrytol	Polyols	26

Bioactive Components of Functional Food

In Japan, the concept of functional food emerged in the 1980s through a regulatory body called FOSHU (Food for Specified Health Uses).[19] A list of FOSHU approved products is given in the table 1.

Japan introduced a food labeling system 'Foods with Functional Claims' (FFC) to promote informed consumers.[19] Other countries have developed their own concepts of functional food regulation systems. Functional food is known to possess physiological advantages compared to regular food. Global surveys show that consumers are more conscious of the ingredients and are increasingly careful of what they eat or drink. This has led to the creation of a new market segment in food that is growing approximately 10% per year and it is estimated to be worth $192 billion US dollars.[27] Indian nutraceutical market involves 68% of food and beverages and 32% of dietary supplements. The market estimate in India is believed to be USD 2.2 billion in 2023. This is due to the increase in health consciousness and consumerism of the people.[28] There are various definitions in use. A most widely used definition for functional food is 'beyond basic nutrition' as suggested by The Food and Agriculture Organization (FAO) of the United Nations. A new definition was proposed by,[29]

"Functional foods are novel foods that have been formulated so that they contain substances or live microorganisms that have a possible health-enhancing or disease-preventing value, and at a concentration that is both safe and sufficiently high to achieve the intended benefit. The added ingredients may include nutrients, dietary fiber, phytochemicals, other substances, or probiotics"

In general, functional foods mostly include whole grains, eggs, milk, fish, nuts and fruits. They may consist of phytochemicals such as polyphenols, phytosterols, polysaccharides, micronutrients such as zinc, iodine, selenium etc., and macronutrients such as sodium, calcium, potassium etc.[30] Even a single food item may contain one or more of these components. The nutrients are available in the form of minerals, polyols, pre-biotics, pro-biotics, carotenoids, vitamins, etc. The following sections describe the characteristics of these nutrients and the mechanism of their action in the human body.

Minerals

Mineral nutrients include metals, inorganic compounds, and their constituent elements that function as cofactors for enzymes. They are important to many biological processes like teeth and bone development, transmission of nerve impulses, functioning of cells, regulation of glucose levels etc.[31] Plant based food is generally recommended for increasing micronutrient intake.[32] Food supplements with functional claims that include minerals and vitamins. More commonly added minerals are zinc, iron, calcium, magnesium and copper. Some of the claims related to health benefits include loss of mineral in bone after menopause that is compensated with calcium supplement. Anemia is cured with iron. On the other hand, functional food with low sodium was recommended for high blood pressure. Magnesium is generally considered as an essential mineral for the activation of enzymes and the membrane function. It is naturally bound with biological components such as proteins and nucleic acids. The deficiency in magnesium causes over-functioning of innate immunity. Both innate and adaptive immunity are enhanced by the intake zinc. Zinc deficiency affects the maturity of B cells and hence the production of antibodies. Immune competence is provided by copper and its deficiency reduces cellular immunity and humoral function.[33] Minimum requirement of many of the macro minerals is more than 100 mg per day whereas few milligrams are sufficient in the case of micro minerals. For example, recommended daily intake of sodium is around 3000-7000 mg/day and zinc is only around 12 mg/day.[28]

In a reported study, out of 221 health related claims, 83 were related to calcium, 42 for zinc, 22 for iron, 24 for magnesium, 13 for selenium and rest was contributed by iodine, phosphorous, sodium, potassium and chromium.[23] Another study in which 198 women aged around 18 to 53 years, presenting with complaints of unreasonable fatigue, were administered with iron supplements, following which, more than 60% were relieved from fatigue.[34] However, consumption of Ayurvedic or Chinese herbs rich in minerals was found to be unsuitable as reported. They may contain excess of copper and a few of the toxic elements such as mercury, arsenic, cadmium lead in general. 35 Hence, Food and Drug Administration (FDA), USA issued guidelines on the preparation and composition of the supplement products.[36] Mineral intake only happens through food source. But all the minerals are not consumed and absorbed by the body. It depends on chemical environment and combination of other components. The bioavailability of zinc and iron is typically low because of the interaction with enhancers or inhibitors. Ascorbic acid was found to be a good enhancer whereas phytate was an inhibitor.[37] The absorption of minerals is recently enhanced by nanoencapsulation by which bioactive compounds are encapsulated using nanostructures having size less than 1000 nm. This method might provide better ways to distribute minerals and other functional elements that are more physicochemically stable, water-soluble, bioaccessible, and bioavailable.[31] In a study conducted in Poland, the consumption of Voluntarily Fortified Food (VFF) and Vitamin-Mineral Supplement (VMS) by the adolescents in the age group of 13-19 was investigated. The study confirmed that over-consumption of these supplements especially VMS in excess of Dietary Reference Intake has to be monitored to prevent unwanted health complications.[38] Another study confirmed that the consumption of mineral supplements favored by larger population for the intended benefits, however there are no sufficient evidences to correlate their efficacy in the prevention of cardiovascular diseases.[32]

Mechanism of Mineral Absorption

Generally, divalent ion-based minerals produce potent compounds with anti-nutrients such as phytate, fibre, tannin, and lectin. Phytates induce the release of minerals such as calcium, iron and magnesium. Then, they can be absorbed across the gastrointestinal mucosa and reach the circulation.[31] The microbiome present in the gut generally increases the absorption rate of the minerals and also influences the release of minerals from dietary components through the synthesis of enzymes. Dietary calcium absorption rate is directly correlated with the production of short chain fatty acids (SCFA) producing members. They lower the pH and increase the solubility of calcium.[39] Amelioration of phosphorous content in the bone was observed by the intake of Enterococcus faecium, a probiotic given to broilers.[40] On the other hand, intake of iron containing powders by the infants caused the risk of diarrhea and infection in respiratory tracts. Iron content negatively affects the microbiome composition.[41] Generally, there are three distinct

pathways available for the assimilation of the majority of minerals. When consumed at elevated concentrations, numerous minerals are capable of utilizing paracellular absorption, which involves the minerals passing through the tight junctions or being transported along with the bulk flow of water within the intestinal epithelial cells in order to gain entry into the bloodstream. Paracellular movement involves the ionized element and not any neutral ligand. Paracellular absorption depends on the quantity of minerals solubilized in the lumen.[42] When dietary calcium was present as gluconate, the absorption was found to be efficient compared to the carbonates and phosphates of calcium as they precipitate at the alkaline pH. At reduced dietary concentrations, the human body resorts to transcellular absorption, as a means to satisfactorily fulfill its mineral requirements. Transcellular absorption necessitates the use of specialized transporters that facilitate the movement of minerals from the chyme through the apical membrane of the enterocyte, a mechanism for translocating minerals across the cell, and an additional transporter that facilitates the translocation of minerals across the basolateral membrane of the enterocyte. One of the main challenges that hinder the absorption of minerals is the capacity of the diet to deliver an adequate amount of ionized minerals to the apical membrane of enterocytes, which is essential for their transcellular absorption. Typically, the process of transcellular absorption plays a pivotal role in enabling an animal to fulfill its mineral requirements in scenarios where the concentration of minerals in the diet is suboptimal. Calcium entry by transcellular pathway is regulated by calcitriol that function through the channels of transient receptor potential-vanilloid subfamily (TRPV6) and (TRPV5), calbindins, Ca^{2+} pump (PMCA1b) and the $Na+/Ca^{2+}$ exchanger. Dietary calcium absorption is generally promoted through lactation, growth and pregnancy. However, aging results in poor absorption of calcium.[43]

Solvent drag helps in solubilizing small-sized ligands in water (i.e., amino acids, peptides, & volatile fatty acids) and passes through cellular tight junction there by facilitating the complex to be soluble in water. Osmotic and hydrostatic pressures in the interstitial space control how much water moves across tight junctions. Minerals may become insoluble and nonionizable in the rumen, and to a lesser extent in the intestine, thereby rendering them functionally inert for the animal.[44] The gut microbes (GMs) make enzymes that can breakdown minerals and increase their absorption. Absorption of minerals is generally hindered by phytic acid which is present various plant based foods. The gut microbes like lactobacillus family produce phytase which help to breakdown phytic acid which in turn release the minerals. GMs can also produce short chain fatty acids from the fermentation process of dietary fibers that help the mineral absorption. They can also modify the expression of genes thereby supporting the absorption of minerals.[45]

Polyols

Polyols are low-calorie, slowly digested, and low-glycaemic carbohydrates. They resemble sugars structurally, but instead of an aldehyde or ketone group, they have a hydroxyl group. Polyols are often called sugar alcohols, even though they are neither sugars nor alcohols.[46] Sugar alcohols are derived from saccharides by reducing the aldehyde or ketone group to an alcohol group chemically or biochemically. Most polyols are natural. Erythritol, sorbitol, xylitol, and mannitol are plant-sourced. Lactitol, isomalt, and HSH are synthetic and not found in nature. The sweetening potential of sugar alcohols depends on their physical and chemical properties, processing, and sensory characteristics. The sweetness of the sugar alcohols is compared to sucrose and it ranges from half to equal that of sucrose. Polyols can replace bulk sugars in many of the products such as chocolates. The shelf life of chocolates can be improved by the type of polyols added and optimization of the process parameters such as refining, conching and tempering.[47] They have an advantage over intense sweeteners because they do not require bulking agents as tabletop sugar replacements. They have high heat of solution and mouth cooling effects. So they find application in pharmaceutical products like breath mints and cough syrups. Erythritol and isomalt are generally used to achieve the strongest and mildest cooling effects respectively. Generally, a decrease in molecular weight increases osmolality, decreases freezing point, decreases viscosity and increases boiling point. These parameters directly influence cookie spread, ice cream texture, cake volume, mouth-feel, and shelf life of many of the sugar based products. Polyols are generally highly soluble at higher temperature like xylitol. Others like mannitol have minor limitations, but are still used in

food applications. Solubility affects crystallization of substances. Crystal formation tendency reduces with increasing solubility. Controlled heating and cooling can prevent crystal formation as observed in other sugars. On the other hand, uncontrolled temperature conditions create supersaturated solutions so that confectionery will crystallize quickly. Adding certain polyols can prevent crystal formation, creating a smoother food product. For example, Sorbitol or polyglycitols can alter the crystallization process in confections by affecting the crystallization rate, size, and balance. Sorbitol is frequently found in syrups and jam because it prevents the formation of crystals in liquid sugar systems. On the other hand, use of low hygroscopic polyols instead of sugars improves crispness in baked goods. The advantage of this property is that the product is having a longer shelf life by preventing moisture absorption. In addition, the consumption of polyols supplemented with xylitol and magnolia bark extract are highly useful in the prevention of caries. 48 The usual limit of polyols intake is restricted below 10-15 mg/day looking at the digestive problems at higher concentrations. 28 Continuous consumption of polyols over several days in each meal produced discomfort in digestion process as confirmed by a study.[49]

Mechanism of Action of Polyols in Digestion

Polyols are converted into monosaccharides after ingestion. The small intestine captures the majority of monosaccharides inertly. The percentage of other polyols that are partially absorbed by the small intestine ranges from 0% to 80%, the remaining 20% of polyols are fermented by bacteria in the colon, where they stimulate the growth of specific bacteria that are good for human health. If a polyol stimulates the formation of Bifidobacteria, then it can be called a pre-biotic (e.g., maltitol, lactitol and xylitol). Short chain fatty acids (SCFA) are also produced as a result of erythritol and are then absorbed by the body to provide energy. Xylitol along with lactobacilli was found to be useful in the reduction of pathogenic bacteria such as Clostridium.[50] On the contrary, polyols are incompletely metabolised in humans, as evidenced by their recovery in urine and so provide less energy than sucrose due to their partial absorption and incomplete metabolism.[51] They act as substrates of fermentation leading to gas, bloating, and diarrhea. However, it has been observed that moderate doses of polyols may induce the microbiome leading to the production of bifidobacteria in healthy individuals. But, motility of small intestine was found to be altered in patients diagnosed with irritable bowel syndrome (IBS).[52] Generally foods with fermentable oligo-, di- and monosaccharide, and polyol (FODMAP) removed with certain polyols are recommended for IBS patients. Because these kind of food additives may cause microbial changes in the gut and result in IBS symptoms.[53]

Probiotics

According to World Health Organization (WHO) probiotics are,

"Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host in sufficient quantities, produce beneficial effects on the host beyond those of basic nutrition".

An ideal probiotic should be the type of bacteria that come from plants or animals and is safe for humans. They should be able to survive extreme conditions of pH like stomach acid and bile, able to stick to the lining in our gut without leaving our intestines, prevent the growth of harmful microbiota in the Gastrointestinal Tract and confer intestinal immunity. Probiotics refer to harmless microorganisms that, when administered in appropriate doses and during suitable periods, provide advantageous effects to the host.[54] Moreover, probiotics have been found to enhance intestinal cell adhesion and stimulate mucin production, while also regulating the functioning of gut-associated lymphoid tissue and the immune system. Likewise, the metabolites produced by probiotics have the capacity to engage the brain-gut axis and exert an influence on behavior.[55] Approximately 108 to 109 microorganisms present in the probiotics should be consumed by a normal human being for a beneficial effect. Lactic acid bacteria (LAB) present in the fermented food such as kefir or yogurt or pickle produce exopolysaccharides (EPS) which is essential for gut and mental health. The gut barrier activity is improved by regulating the levels of immunoglobulins and inflammatory cytokines.[56]

Mechanism of Probiotic Action in Gastro Intestinal Tract

Many different mechanisms have been put forth to define the action of probiotics. The ability of

bacterial strains to produce probiotic effects is commonly acknowledged to be elicited through the process of colonization. Moreover, the potential of probiotics to suppress the growth of various pathogens is attributed to the synthesis of diverse inhibitory compounds including organic acids, carbon dioxide, hydrogen peroxide, acetaldehyde, short-chain fatty acids, acetoin, bacteriocins, and bacteriocin-like inhibitory substances. Out of which, bacteriocins are peptide or protein antimicrobial agents that undergo ribosomal synthesis in various bacterial strains. They display a broad spectrum of antimicrobial action against a variety of Bacillus, Listeria, Staphylococcus, Clostridium and other harmful microorganism strains.[55] Probiotic bacteria create bacteriocins, which have gained importance primarily due to their safe use in a number of products, including food, pharmaceuticals, veterinary and human treatments. However, absorption of probiotics in the gut is poor because of the different conditions. Encapsulation of probiotc components in a protective matrix results in survival rate, bioavailability and controlled delivery in the gut.[57]

Prebiotics

"The International Scientific Association of Probiotics and Prebiotics" defined "dietary prebiotics" as

"a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health".

The identification of a prebiotic compound relies upon various established discriminating factors, including: (i) its capacity to withstand the acidic pH and resist hydrolysis by mammalian enzymes while staying insoluble in the digestive system; (ii) its capacity to be fermented by the bowel microbiota and (iii) the compound's capacity to specifically promote the growth and/or activity of gut bacteria, enhancing overall human health. Prebiotics have the unique property of not being absorbed or digested in the upper GI tract but instead moving to the larger intestine. They do not undergo acid hydrolysis in the stomach and moved to the large intestine. They enhance the growth of Bifidobacterium and Lactobacillus and help to prevent the GI tract diseases such as Clostridium perfringens by restricting the growth of pathogens. This process helps to improve the absorption of elements such as Ca, Mg,and Fe.[58] Prebiotics are categorized into the following groups: (i) Fructans: This group consists of oligofructose, fructo-oligosaccharides, and inulin. A linear fructose chain with β (2→1) linkage makes up their structure. (ii) Galacto-Oligosaccharides: They are split into two categories: (a) GOS formed from lactose through enzymatic trans-glycosylation, and (b) GOS containing additional galactose at C3, C4, or C6. (iii) Starch and Glucose-Derived Oligosaccharides: Resistant starch (RS), a form of starch which is difficult to be digestive by the upper digestive tract. (iv) Other Oligosaccharides: Pectin, a polysaccharide, is the source of several oligosaccharides. Pectic oligosaccharide (POS) is the name given to this oligosaccharide. (v) Non-Carbohydrate Oligosaccharides: Although carbohydrates are more likely to meet the criteria for prebiotics, other substances, like flavanols derived from cocoa, which are not classified as carbohydrates, are suggested to be classified as prebiotics. A daily dose of 2.5-10g of prebiotic is required for the beneficial functions as reported.[59]

Mechanism of Prebiotic Action in Gut

Due to the lack of specific enzymes that may hydrolyze their polymeric bonds, prebiotic chemicals in the human intestine demonstrate a significant ability to tolerate digestion and persist in the gastrointestinal tract. Prebiotics are efficiently transported by the body to the large intestine where they are degraded by the action of intestinal flora and selectively fermented to produce particular secondary metabolites. Following absorption by the intestinal epithelium, these metabolites are either excreted by the liver or transported through the portal vein, both of which have beneficial effects on various physiological processes in the host, including, but not limited to, immune regulation, pathogen resistance, augmentation of intestinal barrier function, and stimulation of production. Generally, Short Chain Fatty Acids (SCFAs), which predominate in the colonic environment, are well acknowledged for their capacity to promote intestinal as well as systemic health. These beneficial bacteria species break down SCFAs into acetate, butyrate, and propionate. Moreover, the facilitation of the proliferation of specific microorganisms is a notable benefit of prebiotic consumption. After the consumption of targeted prebiotics such as inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS), there is potential to stimulate the growth and proliferation

of advantageous microorganisms. This phenomenon can promote positive competition against other microbial species through the encouragement and protection of the fermentation products.[60] In a recent study, alginate nanoencapsulation was carried over a prebiotic component of pomegranate peel phytogenics which also consisting of multi-component probiotic species for animal feeds. This particular compound was investigated to produce an alternative to antibiotics which was used as a bioactive feed for animals to improve their health sustainably and prevent anti-microbial resistance.[61]

Carotenoids (Antioxidant Immunomodulators)

Foods can occasionally create free radicals after digestion, which can cause oxidative stress or cell damage. Antioxidants are chemicals that prevent, slow down, or scavenge the oxidation of bioactive materials. These anti-oxidants can be found in food in the form of minerals (selenium), vitamins (Vitamins A, C, and E), carotenoids (Beta carotene & lycopene), and polyphenols. Out of these components, organic pigments called carotenoids play a significant role in preventing neurodegenerative diseases (ND). They are produced by fungi, bacteria and the plastids of plants and algae. In nature, more than 600 carotenoids (CTs) have been found. Water-soluble CTs must be ingested every day from external sources because they cannot be synthesized by the body. Some carotenoids are lipid-soluble plant pigments with around 40 carbons and a large conjugated double bond system, which can include both oxygenated and non-oxygenated hydrocarbons. The presence of anti-oxidants may be identified by their unique colors. For instance, tomatoes, and cherries are identified by red, mango, saffron, and corn are typically recognized by their deep yellow coloring, carrots by its orange, while grapes and blueberries are recognized by their purple color. Red grapefruit, papaya, dried apricot, tomato, and watermelon are all rich sources of the pigment lycopene. Essentially, the carotenoids can be divided into polar (lutein) and non-polar (beta-, alpha-, and lycopene) carotenoids. Dark green leafy vegetables like kale, mustard greens, spinach, green beans, sweet potatoes, squash and carrots are high in lutein. However, quantity and availability of carotenoids are influenced by the age of vegetable sources and storage conditions. CTs have a variety of bioactive properties due to their distinctive structure, including anti-inflammatory and antioxidant actions. Research on carotenoids revealed that they can stop the onset of various chronic illnesses in people, such as cancer and heart disease. In addition to biological activities, the effects of stimulants on gap junction communication, the immune system, control of cell proliferation, and cell differentiation were studied.[62] In order to improve bioavailability and absorption in the gastro-intestinal (GI) tract, β-carotene based nano-emulsions were prepared. Small-sized droplets of nano-emulsions were found to distribute the encapsulated bioactive components inside the GI.[63] The recommended intake of β-carotene is around 4 mg/day, lutein is more than 3.3 mg/day and α-carotene is more than 0.6 mg/day. The optimum intake of these antioxidants reduced the risk of lung cancer as reported in.[64]

Mechanism of Action as Anti-Oxidants

Carotenoids act as excellent antioxidants and act upon a range of oxidizing radicals by electron transfer process. A series of reactions such as oxidation, reduction, abstraction of hydrogen atom or addition through which carotenoids act upon reactive oxygen species. Its structure encourages integration into hydrophobic membranes, and its polar ends anchor to the polar groups on the membranes' surface to prevent oxygen from penetrating the membranes. Carotenoids act along with other components such as tocopherol, beta carotene, or ascorbic acid and enhance anti-oxidant property by preventing pro-oxidant reactions. As an example, capsanthin present in the chilli pepper fruits along with ascorbic acid and capsaicin exhibit anti-oxidant properties. They prevent the occurrence of oxidative damage, cancer, cardiovascular disease, strokes, etc.[65]

Flavonoids (Phenylchromones)

Flavonoids are secondary metabolites, and sources from plants have produced almost 6000 different types of flavonoids. Numerous physiological and biological processes are influenced by their structural variation. Three hydroxyl groups are present in flavonoids, two of which are found on ring 1 at locations 5 and 7 and one of which is found on ring 2 at position 3. Based on the degree of unsaturation and oxidation of the middle ring (i.e., ring 3), they can be separated into subgroups.[66] Isoflavones are flavonoids with a connected ring 2 at the third position of the C ring. These are the several subclasses of flavonoids: flavones, flavanones,

flavonols, catechins and anthocyanins. Additionally, some authors have differentiated the subclasses of flavanonols, chalcones, and neoflavonoids.[67] Some of the flavonoids and their plant sources are listed in table 2.

Table 2: List of flavonoids, examples and their food sources

S.No.	Flavonoids Subclass	Examples of compounds	Food sources available	reference
1	Anthocyanins	Pelargonidin, peonidin, cyanidin, petunidin, malvidin and delphinidin,	Blueberries Cranberries, strawberries, black berries & raspberries, red cabbage, black beans, plums, grapes, cherries, purple corn & red turnip	[68]
2	Flavanols	Gallocatechin, Epicatechin, epicatechin gallate (ECG), epigallocatechin gallate (EGCG), epigallocatechin (EGC), & catechin	Apple, cranberries, grapes, red pepper, peaches, potatoes, lettuce, kale, tomatoes, onions, broccoli & nuts.	[69]
3	Flavanones	Eriodicytol, naringenin, hesperetin & naringin,	Lemon, orange, lime, mandarin & grapes,	[70]
4	Flavones	Tangeretin, sinensetin, luteolin, isosinensetin, chrysin, galangin, apigenin & nobiletin	Citrus fruits, red pepper, broccoli, lettuce, thyme, rosemary, peppermint, oregano, olive oil & green tea.	[71-73]
5	Flavonols	Quercetin, kaempferol, myricetin & Isorhamnetin	Blackberry, Chinese cabbage, Ginger, onion, Cranberries, Fennel leaves.	[74]
6	Isoflavones	Daidzein, & genistein	Beans and legumes	[75]

According to recent studies, flavones and catechins are the most effective at defending the body against reactive oxygen species.[76] Flavonoids are found to possess anti-oxidant, anti-inflammatory, anti-tumor, anti-viral, hepatoprotective, metabolism regulation etc., The anti-viral properties are utilized to work against Covid-19. However the poor bioavailability of these bioactive components obtained from fruits and plants is a hindrance. Nanoencapsulation of flavonoids by liposomes, emulsions and biopolymers such as chitosan was reported to be effective in enhancing availability and absorption.[77] In another report, polyphenols encapsulated with nanocarriers were found to improve anti-diabetic characteristics compared to those not having encapsulation.[78] The recommended dietary intake of flavonoids is in the range of 50-400 mg/day. In a report, higher intake of dietary isoflavone in Asian countries compared to that of western countries confirmed the reduction in breast cancer up to 60%.[79]

Mechanism of Action of Flavonoids as Antioxidants

The hydroxyl groups on flavonoids are responsible for their physiological and biological functions. These groups mediate these capabilities via scavenging free radicals and/or chelating metal ions. The suppression of reactive oxygen species (ROS) creation, either by inhibiting enzymes or by chelating trace elements involved in free radical synthesis,

scavenging ROS, and upregulation or protection of antioxidant defenses are some of the mechanisms underlying such effects. They are very active compared to vitamin C and E. The physicochemical characteristics of the released dietary flavonoids, such as their molecular size, structure, lipophilicity, solubility, and pKa determine how well they are absorbed. The flavonoid can enter the colon before absorption or can enter from the small intestine. The majority of plant flavonoids, with the exception of the subclass catechins, are attached to sugars as b-glycosides. The small intestine can readily absorb aglycans, whereas flavonoid glycosides must first be converted to aglycan form.[72] By creating pattern recognition receptors (PRRs), flavonoids have been discovered to improve the innate immune system. They are capable of identifying pathogen-associated molecular patterns (PAMPs) that are present on pathogen surfaces. It has been discovered that the primary innate immune response effectors, NK cells, attack infections by producing perforin and granzyme. Flavonoids induce various other functionalities such as dendritic cells which recognize tumors, macrophages for eliminating foreign antigens, neutrophils which provide first defense line against pathogens, production of T and B cells and hence actively fighting against auto immune diseases and tumors.[80]

Proteins

In addition to carbohydrates and lipids, proteins serve a crucial structural and functional role in the macronutrient groups. Proteins are bio polymers with nearly 20 amino acids linked through amide (peptide) bonds. The structural and functional characteristics of proteins are determined by the length of the polymer chain and the order of the connected amino acids. Proteins are part of hormones, antibodies, hemoglobin and several other compounds of biological systems. The four major structural levels of protein are: primary, secondary, tertiary and quaternary proteins.[81]

The amino acids which are acquired from diet are said to be essential amino acids and those which are synthesized by the species itself are classified as nonessential amino acids. The necessary amino acids for humans include lysine, histidine, phenylalanine, isoleucine, leucine, tryptophan, threonine, methionine, and valine. In addition, developmental stage, health or pathological status, gut microbiota, and environmental factors all affect the quantity and specific amino acid requirements. Some of the aminoacids are classified as conditional amino acids since their need depends on specific circumstances like pregnancy, lactation, environmental stress or variety of diseases and/or conditions. In the case of healthy individuals, for the stimulation of muscle protein synthesis (MPS), the consumption of proteins around 25-30 g was required per each meal as reported in.[82] Typically, proteins from animal sources are referred to as "complete protein" and contain all of the essential amino acids that are required, but proteins from plant sources (seeds, pulses, and other vegetables like beans, peas, etc.) either lack or contain only a portion of the essential amino acids. Lysine is often lacking in cereal proteins, while methionine, tryptophan and cystine are lacking in pulse proteins. 83 This can be balanced by consuming pulses with cereals. The nutritional value of the proteins and the corresponding amino acid requirements are determined by how easily they can be digested.[84] Additionally, the difference between plant and animal proteins is clinically important, with plant proteins being less accessible or less easily digested than animal proteins.[85] The various functionalities, nutritional values and other characteristics of the proteins are determined by the surface charge, hydrophobicity, topology, isoelectric point, molecular weight, secondary structures, and tertiary structures of that particular biopolymer in that particular state.[86] Due to the good effects of plant protein on health and the negative effects of animal protein (such as increased saturated fat), plant proteins are frequently used in the food business. A more recent meta-analysis investigated the benefits of plant protein over animal protein in terms of lowering cardiac metabolic risk and hypercholesterolemia.[87] For instance, some vegetable proteins have been utilized in place of animal proteins in the production of vegan cheese, soy milk, almond milk, meat analogues and egg substitutes such as mung bean protein isolates.[88] The solubility and viscosity of plant-based proteins are crucial for specific functions during the production of food products.[89] Various functions include gelling, thickening, emulsifying, and foaming are used typically in the food industry. Some of the attractive properties of proteins are being utilized in nano encapsulation for protecting as well as controlled delivery of various bioactive components in the body.[90]

Mechanism of Action of Proteins and Peptides
Antihypertensive Activity
The primary factor causing the increase in blood pressure is angiotensin converting enzyme (ACE). In the clinical treatment, inhibition of ACE is one of the main targets. Plant derived ACE inhibitory peptides are being used instead of chemical drugs.

Hypocholesterolemic Activity
By interacting with bile acids or cholesterol in the gut, plant-derived peptides have hypocholesterolemic effects. Tyrosine and leucine, two hydrophobic amino acids, attach the peptides to the cholesterol in the body.

Immunomodulatory Activity
The defense response of the host is induced by promoting immune modulators such as antibodies, chemokines and cytokines. The proteins and peptides increase the NK cells, induce phagocytosis, promote lymphocytes and immune cells etc.

Antioxidant Activity
The mechanism of activity of antioxidant peptides are listed as (i) scavenging of free radicals (ii) inhibit the peroxidation reactions of lipid (iii) chelating with metal ions (iv) induce antioxidant defense system. In addition to these activities, antimicrobial and cognitive improvement activities were also reported.[91]

Dietary Fibers
Dietary fibers are basically complex carbohydrates. Dietary fibres are of two varieties: soluble fibres and insoluble fibres. Generally soluble fibers impede the hydrolysis of digestion and absorption in the small intestine. These fibers are not fermented or broken down by human endogenous enzymes. Instead, they are passed on to lower gut where they act as substrates in the large intestine. Then, the colonic bacteria become active and supported the fermentation of bacterial enzymes.[92] They produce short-chain fatty acids (SCFA) that is important for the activities of the gut microbiota. When the fibers are hydrophilics such as cellulose, starch, they attract water in the intestine and regulate peristalsis process. Such components are present in cereals, potatoes, cabbage, carrots, broccoli, apples, bananas, etc. Insoluble fibers are made up of structural materials present in the cell walls of the plants. Table 3 lists some of the important fibers, their source and functionalities.[30]

Table 3: Fibers, source and functionalities

Type of Fiber	Food items	Effects	Reference
Soluble fiber	Apples, carrots, citrus fruits, barley, beans, oats, peas, psyllium seed husk	May slow down the level of total blood cholesterol	30
Insoluble fiber	Whole wheat flour, bran (wheat & corn), skins of fruits, vegetable (Potatoes, cauliflower, green beans) & nuts,	May promote the mainten -ance of a healthy digestive system, may reduce risk of colon or breast cancer	
Whole grains	Whole wheat bread, bulgur, buckwheat, grains, cereal, brown rice, rye, oatmeal, sorghum & millet	May reduce the risk of gas -trointestinal malignancies, coronary heart disease, and a number of hormone-dependent cancers. May lower the chance of developing diabetes and keep blood sugar levels at a healthy level may help a person achieve and maintain a healthy weight.	

β (Beta) glucan	Oat products such as bran, barley & rye,	May reduce triglycerides and cholesterol & the risk of developing type 2 diabetes. May enhances the immune system

Daily consumption of dietary fibers is recommended at a level of 18-38 g of fiber/day. World Health Organization recommends a minimum value of 25 g per day. The advantage of taking higher natural dietary fiber (NDF) leads to lesser possibility of metabolic diseases such as obesity or diabetics or cardiovascular diseases. These fibers support the intestinal environment, influence the gut microbiome, and improve the gastro-intestinal immunity, nitrogen cycle, endocrine responses and metabolism.[93] It has been suggested that investigations into the influence of single, isolated fibers may not give a clear picture of their effect on gut microbiota, because the fibers are consumed as part of whole foods, which may contain numerous other molecules such as glucose, mannose, xylose, galactose etc. They are interlinked by several glycosidic bonds which create complex digestive activities in the gut and important for the human health.[94] As a specific example, wheat dextrin present in the bread stimulated the decrease in cholesterol, insulin, etc.[95] Fruits and vegetable contain NDF called oligo-fructose. It is prebiotic in nature which supports the digestion and eliminates toxic substances. Ghrelin, a hormone secreted in the small intestine called 'hunger harmone' is reduced by the intake of oligo-fructose in rats and helped to reduce their obesity.[96] Inulin, a dietary soluble fiber present in garlic, banana, onion, asparagus, parsley and cinnamon is found to be highly useful in regulating lipid metabolism, lowering blood sugar, weight loss, reducing the risk of colon cancer, improving mineral absorption and constipation.[97] Gluten -free pearl millet was reported to be a good source of DFs. It also contains low-glycemic complex carbohydrates which are helpful in managing diabetes and blood sugar levels.[98] As there is a link between colorectal cancer and gastrointestinal diseases like Inflammatory Bowel Disease (IBD), dietary fibers have been discovered to be protective against colorectal cancer. This is possibly due to fermentation effect of the fibers followed by the production of SCFA. Despite the small number of studies, they all supported the inverse association between fiber consumption and the risk of colorectal cancer.[99] Consuming fiber from fruits, legumes, vegetables, and nuts has been reported to help lower the risk of cardiovascular disease. On the contrary, no such benefits were observed by the intake of grain fibers.[100]

Mechanism of Action of DFs in the Gut

Fibers have the property of holding large quantity of water and capable of acting as a laxative. Lactulose is an example and studied in detail in constipation investigations. DFs have the ability to induce gut hormones and stimulate the release of insulin. DFs may restrict the postprandial glycemic and insulinemic responses which are directly linked to hunger and energy intake. SDFs (soluble DFs) are water holding, viscous and gel like which may delay intestinal absorption and gastric emptying. IDFs (Insoluble DFs) induce motility of the gut, bulking the fecal and prevent constipation by binding with water. DFs are converted by polysaccharide lyases and glycoside hydrolases, the specialized enzymes which are already present in the gut microbiome. They break the glycosidic bonds of DFs and produce monosaccharides and oligosaccharides. Most of them are fermentable. As a result, SCFAs are produced inside colon by the fermentation of DFs.[101]

Vitamins

Vitamins are one of the essential nutrients present in almost all vegetables, fruits and animal food products. They are organic compounds useful for the development and well-being of the humans. Since humans cannot synthesize the majority of vitamins, they must be ingested in the form of functional meals or supplements. Deficiency of vitamins is one of the major concerns for the humans because of the mal nutrition or alternative food habits or unbalanced diet. The deficiency of the vitamins cause several health issues to the human and affect proper functioning of the body. They fall under the categories of fat-soluble and water-soluble vitamins. Vitamins C and B complex (containing B1 through B12) are water soluble, while vitamins A, D, E, and K are fat soluble. Fat soluble vitamins can

be stored in the body generally and water soluble vitamins cannot be stored and hence they need to be consumed everyday through food. Daily requirement of Riboflavin is 43.3 mg/day, vitamin B5 is 200 mg/day and B12 is 2 g/day. 28 In a case study involving 1253 Chinese individuals, a deficiency in intake of riboflavin is observed for the 5 years period and resulted in anemia.[102] The list of vitamins, their sources, and their uses are displayed in Table 4.

Table 4: List of vitamins, sources and their functions

Classification of vitamin	Source	Functions	Reference
Vitamin A	Orange fruits, dark green vegetables, eggs, liver, fish	Bone and embroyonic development, immunity, eye health	[103]
B1 (Thiamin)	Pork meat, legumes, cereal grain	Regulates metabolism, enhances mental health, balances nervous system	[104]
B2 (Riboflavin)	Dairy products, animal products	Essential for cellular development	[105]
B3 (Niacin)	Legumes, eggs, whole grains, and olive oil	Regularization of metabolism, cellular development, better nervous system	[106]
B5 (Pantothenic acid)	Peanuts, Yolk and liver	Antioxidant, lipid metabolism	[107]
B6 (Pyridoxine)	Meat, nuts, whole grain, and vegetables	Improves immunity by synthesis of antibodies, healthy liver, improves the energy level, lower blood pressure, enhances metabolism of amino acids, fatty acids and sugars	[108]
B7 (Biotin)	Legumes, dairy products, grains, eggs	Helps to cure skin disorders, balances metabolism and improves hair growth.	[109]
B9 (Folic acid)	Broccoli, spinach, citrus fruits, leafy vegetables, celery & lentil	Works against anemia, cures indigestion, birth defects, alleviate skin disorders	[110]
B12 (Cyanoco -balamin)	Whole milk, meat, eggs, fish	Improves antibodies, reduction in homocysteine, gastrointestinal health	[111]
C	Citrus fruits, & Green vegetables	Improves the production of collagen, increases metabolism, enhances immunity by raising T cells and mental health	[112]
D	Milk, egg yolk, fish, butter, ghee, & meat	Immune functions, modulating cellular growth, reduce inflmmation	[113]
E	Almonds, avocado, nuts, spinach, sunflower seeds, olive oil, shrimp, bell peppers	Protection of body from oxidative damage, help to stabilize lipid bilayers of the cells & skin care	[114]

Encapsulation of various vitamins using nanoliposomes was found to be an effective method in the application of fortification agent in beverages. The nutritional value of the orange juice is enhanced by the encapsulation of vitamins E and C by liposomes. The purpose of liposomal protection is to avoid destruction of vitamin C by the heat applied during pasteurization. Same kind of liposomal

protected vitamins C and E were used to enhance the flavor of cheese, chocolate milk and soy milk. These encapsulations were generally stabilized by stearic acid and calcium stearate.[115] When functional food in the form of probiotics or yogurt is consumed, vitamins are produced in-situ with the help of Lacto Acid Bacillus kind of microorganisms. In a particular investigation, probiotic strain B. animalis subsp. lactis HNO19 (DR10™) was used as a supplement for the pregnant women. Due to this, blood levels of vitamins B6 and B12 rise during the second and third trimesters.[116] Nano carriers are other interesting vehicles for carrying bioactive components such as vitamins in functional food. Sodium caseinate nanocomplexes were used to carry vitamin A. Pea protein-stabilized nanoemulsions and whey protein-stabilized nanoemulsions and composite gels were used as carriers for vitamin D3. Cellular upatake, intestinal absorption and bio accessibility were studied to test the efficiency of these carriers for functional food applications.[117]

Table 5: List of Fatty acids, sources and their functionalities

Type of fatty acid	Sources	Functions	Reference
Monounsaturated fatty acids	Olives, whole milk, canola oil, tree nuts, macadamia nut, avocados	Coronary heart diseases are prevented. Serum lipid profiles will be healthier	[119]
Omega n-3 fatty acid (α-Linolenic acid)	Flax seed oil, canola, hemp, walnuts	Provide anti-clotting and anti-inflammatory effects; improves heart health; balances mental function	[120] [120]
Long chain Omega -3 fatty acid (DHA/EPA)	Fish oil, tuna, salmon, algae oil	Reduce auto-immune diseases, CHD, rheumatoid arthritis, helps cognitive development of the child	[120]
Conjugated linoleic acid	Meat items, a few mushroom species, cheese	Helps to build body, enhances immunity	[121]

Fatty Acids

Fatty acids are macronutrients. Oils from olive, sesame, fish, flaxseed, sun flower and others contain large quantities of fatty acids. They are available both as monounsaturated and polyunsaturated forms. Extensive use of these oils in food products helped to enhance human health and protect from heart diseases, immune response disorder and diabetes. Additionally, lipid-soluble bioactive substances like phytosterols, tocopherols, polyphenols, and carotenoids are abundant in unsaturated fatty acids. However, these unsaturated fatty acid components are easily oxidizable and because of that nutritional values and sensory properties of the oils will be affected. Three particular bioactive polyunsaturated fatty acids (PUFAs) are eicosapentaenoic acid (EPA), gamma linolenic acid, and docosahexaenoic acid (DHA). It has been shown that pumpkin seeds contain 95% of the total amount of fatty acids, the majority of which are unsaturated fatty acids such linoleic acid, palmitic acid, stearic acid, and oleic acid.[118] Table 5 lists a few important types of fatty acids and their functions.

It has been reported that linoleic and α -linolenic acids are not synthesized by humans. They can only be supplemented through functional food. Omega n-3 fatty acid or α-Linolenic acid is found in large quantities in flax seeds and small quantities in hemp, canola, and soybean. It reduced arrhythmias and serum triacylglycerol levels, which helped to prevent heart disease. Indian Council for Medical Research suggests an intake of Omega n-3 fatty acid about 1.1g/day in the case of females and 1.6 g/day in the case of males.[28] Sunflowers, corn, sesame, almonds, and other foods contain the polyunsaturated omega-6 fatty acid linoleic acid. It helped to decrease cholesterol levels in blood.[122]

For the functional food applications, encapsulation of bioactive components is widely used. It has helped to coat sensitive components so that they can be protected in variety of environments such as high temperature, oxygen exposure and freezing conditions to perform their functionalities. Encapsulation is designed for the maximum retention of bioactive components with small outer surface oil microcapsules. Multiple materials of encapsulator such as carboxymethyl cellulose and lecithin added to extra- maltodextrin (derived from virgin olive oil) were found to be better encapsulators with good yield and efficiency.[123] γ-Cyclodextrin was used to encapsulate *α*-linolenic acid present in the Perilla frutescens seed oil. The bioavailability of this component was found to increase in the inclusion diet provided to rats.[124] Nutritional requirements of omega-3 fatty acids were attained when encapsulation was used in fortification applications of food. Emulsion gels are additionally employed in the process of food fortification to give beneficial unsaturated fatty acids as opposed to saturated fatty acids. In an investigation, water in oil emulsion was prepared using Gum Arabic as an encapsulating material with tween 80 as an emulsifier to protect the omega-3 fatty acids. Further these nanocapsules were incorporated into the fermented milk. The results showed that the increase in Lactobacillus plantarum viability, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) leads to enhanced nutritional benefits.[125] Microalgal derived food products are attractive in the recent studies because of their immense health benefits. Omega-3 fatty acids were incorporated into foods like eggs and salmon by adding microalgal feed.

Mechanism of Action in Cardio Health

Omega-3 fatty acids, for instance, significantly reduce the triglyceride-rich lipoprotein (TGRL) when short chain fatty acids are consumed. These fatty acids integrate into the plasma membranes, stabilize, resist oxidation and protect against arrhythmias. Prostanoids which are produced through omega-3 fatty acids exhibit anti-inflammatory actions. Proresolving mediators which are used to prevent inflammation are synthesized through the precursors produced by omega-3 fatty acids. Combination of these steps results in the protection against cardiovascular diseases.[126]

Applications of Bioactive Substances as Functional Foods and their Role in the Remedy of COVID-19

The crucial role of bioactive substances in the physiological functions of the body systems has led to a significant increase in demand for functional foods. In this scenario, the recent epidemic Coronavirus disease (Covid 19), caused by SARS-CoV-2 has traumatized the world because of its severity in spread and life-threatening in nature. It has become a serious contagious illness especially in the case of people with diabetics, cardiovascular issues, cancer or other chronic illness.[127] It is a general finding that the data is insufficient for the use of any kind supplements including vitamins, or minerals or herbs for the prevention or treatment of covid 19. However, it is a well-known fact that a high quality diet including all kind of these bioactive substances, supports the body with the immune cells and antibodies which can fight against diseases such as covid-19.[128]

COVID-19's Fundamental Mechanism

It is currently unclear how COVID-19 pathogenesis works. SARS-CoV-2 typically spreads by the exhalation of infected persons or fomites through aerosolized viral particles, where the virus attaches to the ACE2 (angiotensin-converting enzyme 2) receptor (an X-linked gene) to enter lung's epithelial cells before going after type-II ACE2+ alveolar cells.[129] On the contrary, in a recent study, a synthetic DNA tether is introduced to replace receptor binding in order to elucidate the fusion mechanism. The fusion with synthetic DNA tether was triggered by an exogenous protease. It confirmed that the conformational transitions of the glycol protein influence the fusion compared to ACE2 receptor binding.[130] However, It has been proposed that the fusion takes place through the spike glycoprotein split into receptor binding (S1) and membrane fusion (S2).[131] The virus interacts with the host through binding of S1 and ACE 2 receptor. S2 promotes cleavage event in the membrane site. Consequently, innate immune response for the antiviral defense mechanism led to the production of inflammatory cytokines at the elevated levels.[132] Early defense mechanisms of the innate immune system consist of mucosa-associated lymphoid tissues (MALT) protecting mucosal surfaces. The

Pattern Recognition Receptors (PRR) like TLR7 is used to identify the Pathogen-Associated Molecular Patterns (PAMPS). Additionally, when transcription factors like nuclear factor b (NF-B) and activator protein 1 (AP-1) are activated, pro-inflammatory cytokines including TNF-, IL-6, and AP-1 are produced.[133] While this is happening, neutrophils near the site of the infection use phagocytosis, oxidative burst, and neutrophil extracellular traps (NETs) to try and eradicate the virus. In addition, it has been found that microbes and stress-sensing pathways also induce immunological functions. It includes both antimicrobial activity and inflammatory modulation. Host proteins, interacting viral particles and stimulants of stress played the crucial role in immunological activities. These include protein envelopes, N, S proteins, single stranded RNA, nucleic acids released from dead cells and host molecules.[134] Further, antigen presentation starts the phase of the adaptive immune response that depends on T cells. Helper T cells stimulate B cells to produce SARS-Cov-2-specific antibodies whereas cytotoxic T cells kill infected cells. According to studies, 80% of cell infiltration in COVID-19 patients is caused by cytotoxic T cells.[135] The release of pro-inflammatory cytokines becomes uncontrollable and causes a cytokine storm if the illness lasts longer and cytotoxic T cells are unable to eliminate infected cells. Infected patients eventually experience a number of negative effects, such as acute respiratory distress syndrome (ARDS) and organ failure, all of which have the potential to cause death.

Possible Roles of Functional Foods for Relieving COVID 19

A combination of a few basic foods is enough to fend off many illnesses and even to ease patients' symptoms. For instance, including herbs like garlic in everyday meals may improve their flavour and practicality.[136] The primary protease in SARS-CoV-2 can be inhibited by bioactive chemicals in garlic, preventing the virus from spreading throughout the patient's body. Garlic was found to suppress the secretion of cytokines and stimulate immunity by increasing T cells.[137] In a report, garlic along with other species such as ginger, lemon, eucalyptus, chamomile, papaya, etc., were found to counteract infections due to covid-19 in rural regions of Colombia. However authors concluded that phytochemical activities need to be validated with the support of scientific studies.[138] This fact is elucidated by a recent study which found that although garlic cannot prevent COVID-19, its antiviral properties can certainly support the immune system in fighting against the disease.[139] Furthermore, the simple addition of liquids like green tea can be quite helpful in the avoidance of serious, life-threatening illnesses. As a result, many patients, especially those who cannot afford conventional medical treatments, may discover that the best course of action is to supplement expensive medications and therapies with inexpensive, straightforward food ingredients. Keflie and Biesalski reported the potential role of bioactive substances and micronutrients in the prevention of infections. In general, the bioactive substances and minerals present in various food items such as garlic, green tea, curcumin, etc, have the ability to interfere with spike glycoproteins and ACE2 receptors. They support to prohibit the entry of viral particles into the host and inhibit the activities of protease, 3CLpro, and RdRp. They are identified to complement the existing therapies to combat Covid-19 by daily intake.[140]

Non-Conventional and Non-Specific COVID-19 Therapy Methods and their Effects

Numerous local and international businesses are utilizing a range of technologies to create vaccinations, immunotherapies, and antiviral medications with varying degrees of precision. Antiviral medications are typically administered to patients with early infection to lower viral load. Anti-inflammatory medications are, nevertheless, provided to patients who have severe and late infections only likely subsequent bacterial infections are treated and prevented with the use of these antibacterial and anti-inflammatory medications.[141-142] As a result, they cannot guarantee a direct or guaranteed recovery from the infection itself. Intensive and fast paced research in the vaccine development especially for the SARS-CoV2 during the period of covid-19, provided immediate solace to the spread. However variations in viral particles, replicatory features of SARS-CoV2 demand the need for continuous development of vaccinations. In addition to traditional vaccines, other vaccines such as RNA based, DNA based, recombinant protein based and viral vector vaccines were produced mainly targeting S protein. However antibody dependent enhancement (ADE) was not considered

during the rapid vaccine development. It was found that antibody dependence increased after covid-19 infection. So, vaccine development should be used effectively along with other evidence based health measures.[143] The side effects created by the vaccines are still unclear.[144] In order to reduce the severity of COVID-19 infections in public, functional food can be utilized as a therapeutic alternative rather than relying on expensive pharmaceuticals. One of the primary symptoms of COVID-19 is an unpleasant dry cough, which can discharge virus particles into the air and raise the risk of infection.[145] Some individuals have breathlessness as a result of coughing that becomes more intense. Foods that fight infection, like ginger, can lessen coughing. Furthermore, other compounds like 6-gingerol and 8-gingerol would relieve the smooth muscles in the upper air tracts, which lessen the likelihood of coughing.[146] Additionally, Treg cells have been found to protect against cytokine storm. Also, the adverse effects of COVID-19 have been found to be reduced in patients. Generally, people with COVID-19 have suffered from thrombotic issues linked to a vitamin D shortage. Therefore, ingesting foods high in vitamin D such egg yolk, milk and mushrooms can aid in avoiding the related complications.[147] Zinc is one of the potential minerals required to inhibit COVID-19 infections. It also impairs autophagy and allows in vitro RdRp activity. Eggs and other foods high in zinc influence cytokine synthesis, immune cell function and abundance, promote autophagy, enhance the effectiveness of antiviral medications, and prevent the processing of viral polyproteins.[148] Usually, the SARS-CoV-2 alters the body's redox equilibrium, gathers an excessive amount of reactive oxygen species (ROS), and causes oxidative stress, which harms the lungs and endothelium, triggers a cytokine storm, and results in insulin resistance. Patients with COVID-19 were given broccoli seeds, which significantly improved cough, gastrointestinal problems, and other cytokine storm-related symptoms Various foods, including cabbage and fermented vegetables, have nutrients that interact with nuclear factor (erythroid-derived 2)-like 2 (Nrf2). These nutrients can reduce the oxidative stress linked to the disease.[149-150] Essentially, there is a possibility of post-COVID-19 complications such as weakness in bones, pains in muscles overall fatigue, the symptoms of nausea, vomiting, diarrhoea, and neurological symptoms of loss of taste and smell and strokes in the infected persons. These symptoms can be treated with a variety of functional foods, such as Astragali radix for exhaustion, sumac extract and pomegranate juice for muscle pain, ginger for nausea and vomiting, ginger supplements for diarrhoea, supplement of omega-3 fatty acids to reduce the possibility of stroke, and supplements of liposomal lactoferrin are recommended for the loss of taste and smell. Active components present in a traditional Chinese medicine of Rhizoma polygonati were detected in 23 targets in SARSCoV-2 after active compounds were screened from several databases. It has proved that Rhizoma polygonati can be used for the treatment. Ten active substances from this herb also demonstrated excellent molecular docking scores with a variety of SARSCoV-2 therapeutic targets, including Spike protein S1, ACE2, RNA-dependent RNA polymerase RdRp and 3CL hydrolase.[151] Furthermore, active ingredients present in stingless bee honey exhibited antibacterial action which helps to prevent secondary bacterial infection. The antioxidant capabilities and down-regulation of IL-6 which help to shorten the viral endurance in the body were also stimulated by these active ingredients. Through the assessment of their efficacy, safety, and toxicity, novel functional foods can be investigated, identified, isolated and used as supplements or preventive drugs in the case of COVID-19.[152]

Conclusion

The bioactive components present in variety of food products are elaborated and the significance of those components is highlighted. Recommended daily intake levels of the components are specified. The deficiency of the bioactive components induces various difficulties in a human in the form of illness or disorders such as obesity, cardiovascular diseases, hypertension, diabetes etc. Daily consumption level of the bioactive components is narrated and how they relieve the humans from various disorders. Control of blood sugar levels by the supplementation of polyphenols, cholesterol by omega-3 fatty acids, blood pressure by peptides, development of immunity and cellular function by mineral absorption, role of polyols, prebiotic and probiotics in maintaining gut health, antioxidant properties of the carotenoids, anti-tumor, anti-viral, anti-inflammatory properties of the flavonoids, digestive improvement of the fibers are discussed in detail. The physico-chemical

properties and the interactions between diverse bioactive components in the gut, their influence over gut-microbiome and biochemical changes created largely benefit the humans. Research studies try to establish the biochemical response of the gut with reference to the action of particular bioactive component. The bioavailability and absorption of the components are found to be enhanced by nano encapsulations. The availability and feasibility of nano delivery carriers is also discussed over their benefits. Significance of functional food in our daily consumption is comprehended especially after global pandemic of Covid-19 infection. The role of functional food in the enhancement of immunity, work against pandemic such as Covid-19 is clearly elucidated and shows the importance of such food over expensive medications with side effects. Direct correlation between the intended benefit and the action of a particular bioactive component is yet to be clearly understood. Further investigations must be done to study, whether the particular ingredient works effectively as an isolated component or only in conjunction with one or more other bioactive components. In this scenario, commercialization of functional food should focus not on consumerism, but on being health-specific, safe to use without side effects from overconsumption, and realistic in the claims made by the manufacturer. A regulatory framework is needed to monitor the claims made by the manufacturers.

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Author Contributions

- **Revathi Chandran:** Contributed in the literature survey and drafted the manuscript.
- **Senthilkumar Obuliraj:** Contributed in conceptualizing and framing the idea, and critically reviewed multiple times
- **Soundeswaran Sundararajan:** Contributed to writing the review and editing,
- **Sridevi Baskaran:** Contributed to the discussion, and improvement in content.
- **Muralisankar Margabandhu:** Contributed to the editing, referencing and formatting.

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