J Food Sci Technol (March 2023) 60(3):820–834
https://doi.org/10.1007/s13197-021-05193-3

REVIEW ARTICLE

Functional foods and their impact on health

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Revised: 23 June 2021 / Accepted: 25 June 2021 / Published online: 8 July 2021

Abstract Functional foods play an important role in maintaining a healthy lifestyle and reducing the risk factors of various diseases. Most foods have a functional element which is responsible for improving the healthy state. All food substances such as fruits, vegetables, cereals, meat, fish, dairy contain functional ingredients. A wide range of naturally occurring substances from plant and animal sources having active components which play a role in physiological actions deserve attention for their optimal use in maintaining health. The market for functional food is keep on expanding, and the global market is projected to reach a value of at least 91 billion USD soon. Overwhelming evidence from preclinical (*in vitro* and *in vivo*) and clinical studies have shown that intake of functional foods could have an impact on the prevention of chronic diseases, especially cancer, cardiovascular diseases, gastrointestinal tract disorders and neurological diseases. Extensive research needs to be done to determine the potential health benefits for the proper application of these foods to improve health state and combat chronic disease progression. The aim of this review is to conduct a thorough literature survey, to understand the various classification of functional foods and their health benefits.

Keywords Functional food · Nutraceuticals · Plant food · Fruits · Vegetables · Nuts · antioxidants · Probiotics

Introduction

Functional foods are regarded as foods that have potential beneficial effect on health beyond their basic nutritional value. They promote good health and lower the risk of diseases. Functional foods have received widespread popularity across the globe, and they are commonly known as "nutraceuticals" and "designer food". The concept of functional food was started and regulated by the Ministry of Health and Welfare, Japan, in the year 1980s and then progressed to North America and other markets (Mellentin et al. 2014). Amount of biologically active compounds are

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very less in the food items and their beneficial effect have been studied in rodent models and clinical studies. Results from epidemiological studies have shown that consumption of specific fruits, animal products and vegetables that are rich in bioactive compounds reduced the risk of various metabolic disorders and cancer (Karasawa and Mohan 2018) (Fig. 1).

Natural bioactive molecules such as curcumin, resveratrol, quercetin, sulforphane, epigallocatechin, lycopene, and ellagic acid have been studied for their direct and indirect effects on various molecular pathways. Curcumin is the major bioactive constituent in *Curcuma longa* and is found in the spice turmeric as well as other sources. It has been studied for its antioxidant and anti-inflammatory properties (Sneharani 2019). Resveratrol (3,5,4-trihydroxystilbene) is found in grapes and pomegranates and studies have shown its benefits on vascular function, immunity and the gut microbiota (Chaplin et al. 2018). Apples are abundant in quercetin, which has shown potent neuroprotective properties in neurodegenerative diseases (Elumalai and Lakshmi 2016). Cruciferous vegetables such as broccoli, cabbage and kale are abundant in sulforphane, which is a. potent activator of the Nrf2-ARE pathway and promoter of redox, thereby protecting from oxidative stress. In addition, sulforphane modulates Phase I and II xenobiotic-metabolizing enzymes and directly inhibits binding of carcinogens to DNA, preventing DNA adduct formation (Juengel et al. 2017). Epigallocatechins are a group of compounds found in in tea leaves which have been shown to have widespread pharmacological properties. Recent studies have determined that epigallocatechins inhibits the expression and activity of indoleamine 2,3-dioxygenase in human colorectal cancer cells (Ogawa et al. 2012). (Table 1). Food production and eating habits have a pivotal role in the health, environmental and social life of human beings. The aim of this review is to conduct a thorough literature survey, to understand the various classification of functional foods and their health benefits.

Classification of functional foods

Functional foods are classified into three categories: (1) conventionally used food, (2) modified food, (3) food ingredients. Conventionally used foods have not undergone any modification and appear as a whole such as vegetables, fruits, fish, diary, pulses and grains that have potent health benefits. Modified foods are those foods which have been enriched or fortified with a specific nutrient in order to promote health benefits. Modified foods include calcium, anti-oxidants and vitamin fortified beverages, calcium and folate enriched bread, products enriched with plant fibers, sterols and omega 3 fatty acids are common examples of modified functional foods (Hasler et al. 2009).

Fortification is a common term that describes the practice of enhancing the amount of a specific micronutrient in a food item. This is a sustainable, cost effective solution to overcome micronutrient deficiencies. Similar to fortification another common term used in the food enhancement is fortificants, which are normally found in the raw food, but lost during food processing. In order to overcome this issue techniques have been developed such as biofortification, in which the nutrient content of the food source had been increased through genetic engineering and selective breeding (Hasler et al. 2009).

The third class of functional foods is prebiotics. Gibson and Roberfroid were the first to define prebiotics, they defined it as "food components which nurture the growth and activity of a single and/or a specific group of microorganisms residing in the gastrointestinal tract, thereby improving the health condition of host".The most common form of prebiotics is inulin and oligofructose. They selectively upregulate the useful gut microorganisms such as bacteria and fungi. The concept of prebiotics was first introduced in 1995 by Glenn Gibson and Marcel Roberfroid. Oligofructose such as fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and trans-galacto-oligosaccharides (TOS) are the most common prebiotics. Gut microbiota ferments these oligofructose to produce the short chain fatty acids (SCFAs) butyric acid, acetic acid and propionic acid which have potential health benefits. The major health benefits include improve cognition, immunity, Ca^{2+} absorption and decrease in the prevalence of irritable bowel syndrome (IBS) and colorectal cancer. The bacteria that aerobically ferment dietary fiber produce the short chain fatty acids which enhance the integrity of the colonic epithelium intestinal epithelium improving the gut blood barrier. Short chain fatty acids also readily enter the bloodstream and pass the blood brain barrier producing satiety. They also epigenetically improve the production of regulatory lymphocytes that are actively anti-inflammatory (Blaak et al. 2020).

Functional food of plant origin

Plants are the rich source of natural oxidants and help to strengthen innate immunity and protects from the toxic effects of oxidants. Many molecules in living cells are prone to oxidation and antioxidant molecules which are present in the body and which are obtained from plant sources help to fight against the oxidants and their deleterious effects on the body. Natural antioxidants are widely distributed in food and medicinal plants. Polyphenols are a key bioactive ingredient responsible for antioxidant

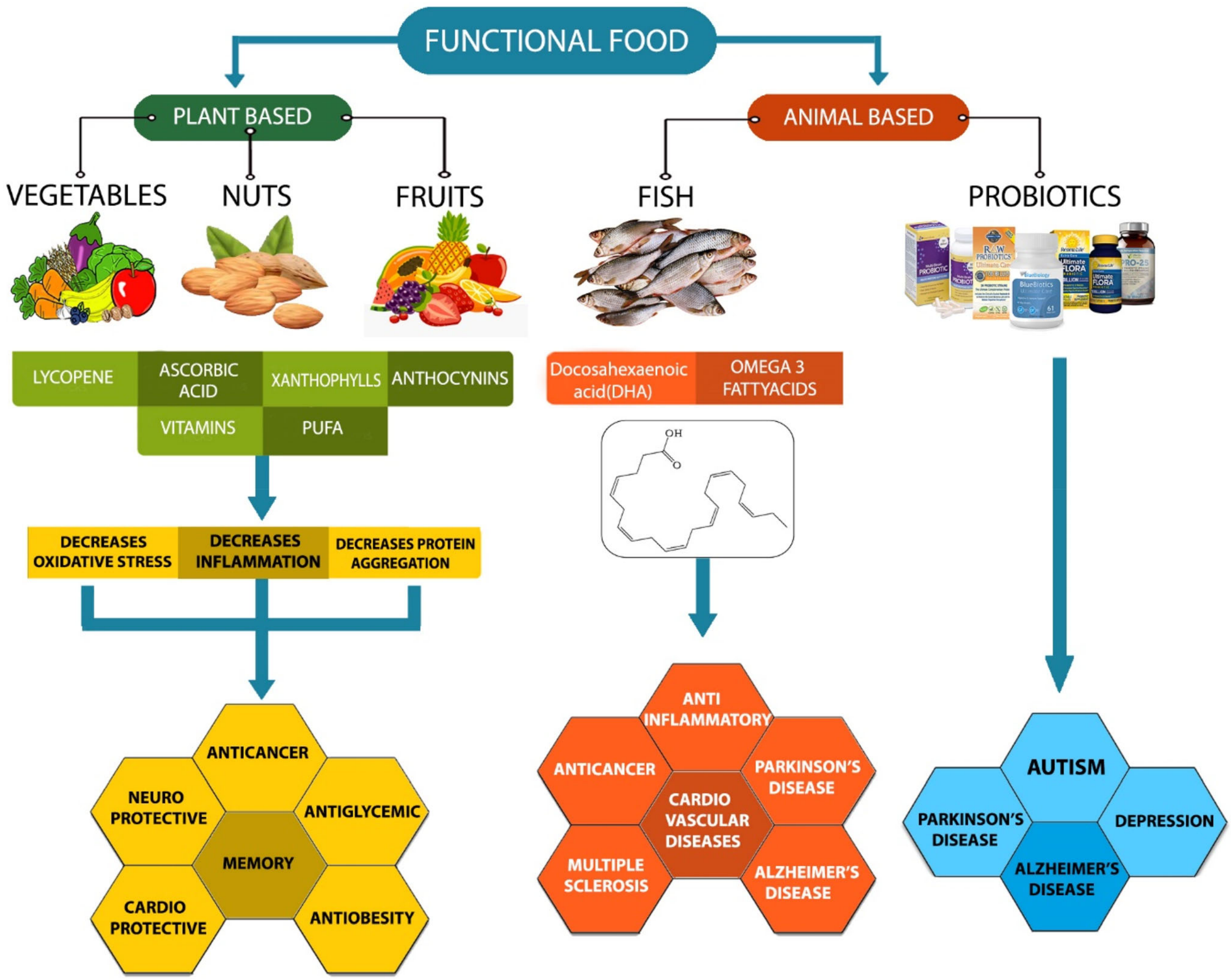


Fig. 1 Health benefits of functional foods

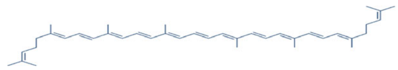
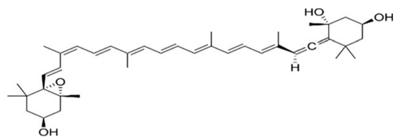
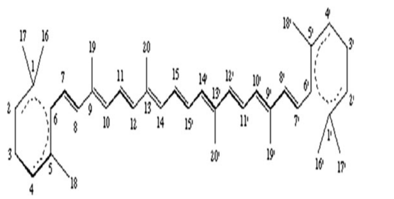
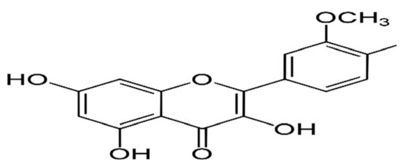
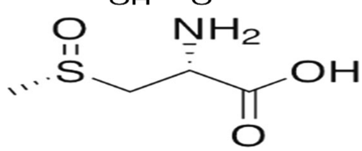
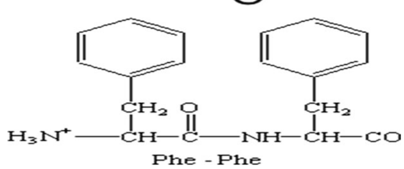
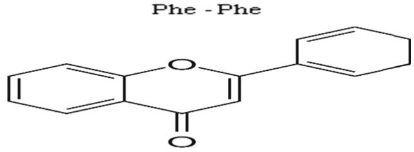
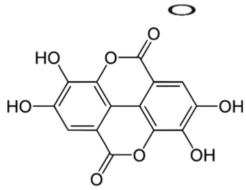
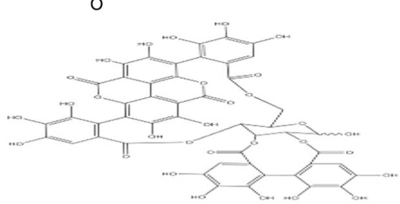
properties. Moreover, they are proven to have anti-allergic, anti-carcinogenic, anti-mutagenicity (Alshatwi et al. 2010) and neuroprotective properties (Yu et al. 2017). In this review, we discus some of the plant derived foods that are rich in polyphenols and other bioactive compounds.

Tomato

Tomatoes are the fruits of *Lycopersicon esculentum* and they originated in Mexico. They are regarded as vegetables and one of the highly consumed food products across the globe. The *Lycopersicon esculentum* has a deep red color which is associated with the carotenoid pigment synthesized during fruit ripening. Majority of the fruits and vegetables contain which phenolic molecules belongs to the flavonoid family. Tomato contains a plethora of bioactive compounds such as lycopene, neoxanthin, violaxanthin, α-cryptoxanthin, zeaxanthin, lutein, β-cryptoxanthin, β-carotene, γ-carotene, ζ-carotene, α-carotene, phytoene, phytofluene, cyclo-lycopene-neurosporene, and β-carotene 5, 6-epoxide (Burns et al. 2003).

Lycopene is the prominent bioactive compound in tomatoes and it has been widely studied over the past decade. Approximately 100 g of tomato contains 12 mg of lycopene. Chemically lycopene is acyclic carotene with 11 conjugated double bonds, these double bonds are contingent to isomerism and their isomers are reported to be found in blood plasma. The human body by itself is unable to synthesize carotenoids so the body is completely dependent on dietary sources. Studies have been reported that 85% of the lycopene in the human diet is obtained from tomato and tomato-based food products. Moreover, lycopene is a key intermediate in the biosynthesis of other essential carotenoids like β-carotene, and xanthophylls (Ruiz-Sola and Rodríguez-Concepción 2012).

Table 1 Chemical structures of some bioactive constituents

Bioactive constituent	Structure	Properties
Lycopene		Prevents DNA mutation (Lindshield et al. 2007), Improves lipid profile (Ibrahim et al. 2008), inhibits tumor growth (Tang et al. 2005)
Neoxanthin		Potent anti-oxidant properties (Lindshield et al. 2007)
Carotenoids		Potent anti-oxidant properties (Lindshield et al. 2007)
Isorhamnetin		Inhibits tumerogenesis (Damon et al. 2005)
S-methyl cysteine sulphoxide		Prevents DNA strand breakage. Inhibition of carcinogen activation by cytochrome P450 (H.Wiseman 2005)
peptide LPYPR		Reduces total cholesterol and LDL cholesterol (Yoshikawa et al. 2000)
Flavanoids		Potent antioxidant properties
Ellagic acid		Potent antioxidant and antiinflammatory properties (Akbar et al. 2015)
Punicalagin		Helps in reducing hypertension, arthritis, cancer, hyperglycaemia, oxidative stress and maintaining cholesterol levels (Zarfeshany et al. 2014)

It has been reported that consumption of foods that are rich in vitamins, carotenoids and tannins protect the body from oxidative damage. Lycopene is a potent antioxidant, and can protect DNA from free radicals and thereby prevent mutations that lead to cancer (Lindshield et al. 2007). In addition, higher lycopene (20 mg lycopene/kg diet) from tomato sauce and ketchup was reported to improve the lipid profiles of the hyperlipidemic rats

(Ibrahim et al. 2008). This result suggest that increase consumption of tomatoes is beneficial in hyperlipidemic patients. Lycopene is also noted to be a potent anti- carcinogen. A study from Alshatwi et al. (2010) had shown that lycopene can protect cells from chromosomal aberration. Lycopene traps the singlet oxygen, impairs the free radical formation and thereby protect DNA from oxidative damage. In addition, it improves gene functioning, carcinogen metabolizing enzymes, apoptotic pathways and immune function. Clinical research suggests that lycopene is beneficial in prostate cancer. Most of the *in vivo* and *in vitro* studies have concentrated on prostate gland cancer models. Studies from Tang et al. analyzed the effect of Lycopene on the growth rate of DU145 prostate gland cell lines in BALB/c nude mice. They had found that lycopene at 100 and 300 mg/kg inhibited the tumor growth by 56% and 76% respectively (Tang et al. 2005).

Dietary intake of tomato prevents the development of high fat diet induced hepatocellular carcinoma in BCO1/BCO2 double knockout mice by decreasing the mRNA expression of proinflammatory mediators, increased NAD^+ production by upregulating the expression of sirtuin 1 and nicotinamide phosphoribosyltransferase. This action is mediated by increased microbial richness and diversity and reducing the *Clostridium* and *Mucispirillum* abundance. Tomato seeds have also been found to reduce *Firmicutes/Bacteroidetes ratio, Rikenella, Enterorhabdus and increases abundance of Lactobacillusin mice* (Xia et al. 2018).

Several clinical trials have been conducted to evaluate the anti-cancer properties of the lycopene. Majority of the studies focused on the concentration of prostate specific antigen (PSA), which determines the risk of prostate cancer. A study from Chen et al. (2001), 32 prostate cancer patients where supplemented with tomato sauce for 21 days (30 mg lycopene/day). They found that tomato sauce consumption decreased the PSA level by 20%. Moreover, biochemical estimation of the prostate tissue revealed a decrease in the ratio of 8-hydroxy-2′-deoxyguanosine (8-OHdG) (oxidative stress marker associated with cancer) to 2′-deoxyguanosine (a marker of oxidative DNA damage) in patients supplemented with tomato sauce as compared to normal control patients. Similar results were found in the study from Grainger et al. (2008), they found that consumption of tomato products daily (lycopene 25 mg/day) for 56 days reduced the PSA levels in 34% of the patients. Phase 2 clinical trial of Lyc-o-Mato® 15 mg/day lycopene has also shown decrease in the PSA levels (Vaishampayan et al. 2007).

The protective effects of Lycopene are well studied in cardiovascular diseases. Potent free radical quenching properties of lycopene protects endothelial cells. Oxidative stress leads to endothelial damage due to decline in nitric oxide (NO) levels causing damage to endothelial cells. Lycopene reduces oxidative stress, enhances the availability of NO, promotes endothelial vasodilation, and alleviates DNA, lipids, and mitochondrial damage (Abdel-Daim et al. 2018). Hung et al. 2008 showed the beneficial role of lycopene in atherosclerosis and other inflammation induced cardiovascular events. They found that lycopene can inhibit Tumor Necrosis Factor (TNF-α) induced activation of Nuclear Factor Kappa B (NF-κB) and the expression of other molecules such as intracellular adhesion molecule-1 (ICAM-1). In addition, lycopene also inhibits the interaction between monocytes and endothelial cells, which may explain the beneficial role of lycopene in cardiovascular disease (Hung et al. 2008).

Some clinical studies have also reported the relationship between lycopene consumption and cardiovascular diseases. A randomized crossover study from Agarwal and Rao (1998) has reported significant decrease in the serum lipid peroxidation and LDL oxidation. The lipoprotein oxidation lag period, which is a measure of protection against oxidative stress was increased in healthy subjects consumed tomato soup for 15 days. Another clinical trial from Shen et al. (2007) treated 24 subjects with various tomato formulation (all the formulation delivering 40 mg lycopene/day) for 42 days, they found decrease in the triglyceride and LDL cholesterol levels and an increase in the High Density Lipoprotein levels.

Lycopene have been extensively studied in neurodegenerative diseases both in preclinical and clinical stages. Lycopene reduces oxidative stress, restores mitochondrial membrane potential and inhibited early apoptotic pathway activation in rat cortical neurons exposed to amyloid β. Lycopene administration in Tau Transgenic Mice increased the memory consolidation by reducing tau phosphorylation, malonaldehyde (MDA) concentrations and increased Glutathione peroxidase (GSH-Px) activities (Yu et al. 2017). Lycopene reduces neuronal damage and increased the expression of BDNF in hippocampus region of AD rats. Lycopene also inhibits depletion of dopamine in substantia nigra and striatum and prevents neuronal damage in rodent model of Parkinson's disease. In addition, lycopene have also been reported to have beneficial effects in Huntington's disease, depression, cerebral ischemia by reducing oxidative stress and inhibiting proinflammatory release (Chen et al. 2019) (Fig. 2).

Broccoli

Broccoli are the flowers of *Brassica oleracea var. italica*. Its flowering head, leaves and stalk are consumed as vegetables across the globe. Broccoli originated in the Roman empire by the primitive cultivators and then became popular in the Italian Peninsula and Sicily. Broccoli is commonly regarded as the "Crown Jewel of Nutrition" because, it is immensely rich in variety of nutrients such as vitamins, minerals, fibres and secondary metabolites. 100 g of broccoli contains: calories (31 g), protein (2.5 g), carbohydrate (6 g), sugar (1.5 g), Fiber (2.4 g) and fat (0.4 g). Broccoli is rich in sulphur containing compounds and their biometabolic products glucosinolates, isothiocyanates have been reported to have potent anti-cancer properties. Moreover, broccoli is also rich in polyphenols such as isorhamnetin, sinapic acid, quercetin and rutin. In addition, it is rich in Vitamin K, $B_{1,}$ B_2 (Damon et al. 2005) and minerals like Na, K, Ca, Mg, Cl, P and S. Dietary consumption of cruciferous vegetables is highly beneficial in preventing stomach, colon, thyroid, skin and prostate cancers. Anti—cancer property of broccoli is associated with sulforaphane, indoles, polyphenols, vitamins and minerals. It has been reported that sulforaphane prevents carcinogen induced tumorogenesis. It reduced incidence, multiplication and growth of breast cancer in dimethylbenzanthracene (DMBA)-treated rats. Moreover, sulforaphane or 4-methylsulfinylbutyl isothiocyanate induces phase 2 detoxification enzymes such as glutathione transferases, epoxide hydrolase, NAD(P)H: quinone reductase, and glucuronosyltransferases through inhibiting Nrf2-Keap 1 interactions and MAP Kinase activation (Bai Y et al. 2015)). In a clinical study where subjects consumed 250 gm/day (9 oz/day) of broccoli, it was found that broccoli consumption increased the urinary excretion of a potential carcinogen—2- amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP), which is commonly found in meat (Walters et al. 2004). Broccoli has also been reported to alter gut microbiome in humans.

Several studies have reported the cardioprotective properties of broccoli. Broccoli sprouts are rich in glucoraphanin which is a metabolic product of sulforaphane. It has been reported that glucoraphanin can induce phase II

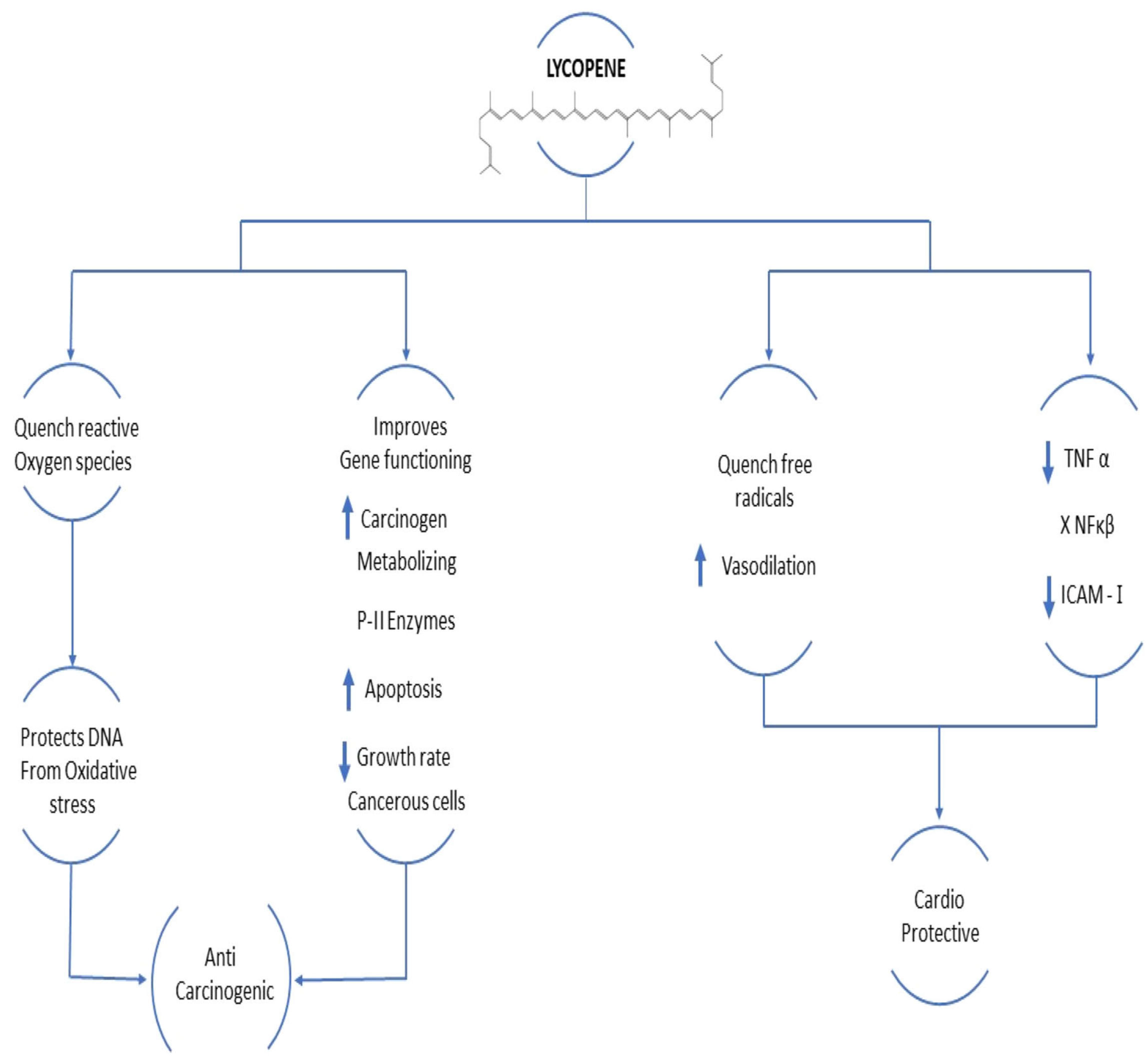


Fig. 2 Lycopene present in tomato is a potent antioxidant which provides several health benefits

proteins which in turn decreases oxidative stress and inflammation in both kidneys and the cardiovascular system. Thus, it lowers the risk of hypertension and atherosclerosis in spontaneously hypertensive stroke prone rats (Wu et al. 2004). In a clinical study where the subjects consumed broccoli sprouts (100 gm/day) for a week it was found that total cholesterol levels and escalated HDL cholesterol levels declined (Murashima et al. 2004). Broccoli reduces mRNA and protein levels of thioredoxin super family members which are commonly found following ischemic reperfusion injury, thus broccoli improves the cardiac function, reduces the risk of myocardial infraction, and cardiomyocyte apoptosis (Mukherjee et al. 2008).

Sulforaphane, bioactive compound of broccoli has been found to be beneficial in neurodegenerative diseases. Broccoli inhibits glial cell activation and improves the expression of GABA, AMPA, and NMDA receptors in hippocampus region of rats. Broccoli consumption inhibits NF-κB signaling cascade and proinflammatory cytokines which are responsible for neuroinflammation. Broccoli also upregulates the expression of Nrf2 pathway, inhibits neuronal apoptosis and enhances memory consolidation in mice (Subedi et al. 2019). Broccoli protects from Aβ-induced neurotoxicity in cell line model by mediating mitochondrial functioning, increased Hsp70 mRNA levels and improving the expression of Nrf2-ARE signalling (Masci et al. 2015).

Soya bean

Soya beans (*Glycine max*) are a legume species originated in Southeast Asia and it was first grown by Chinese farmers around 1100 BC. Soya beans consist of protein (35–40%), lipids (20%), and fiber (9%). The major bioactive fractions of soya beans include peptides, isoflavones, saponins, and protease inhibitors. The prominent protein fractions of soya beans are β-conglycinin (βCG, 7S) and glycinin (11S) which constitute around 80–90% of the whole proteins in the soya bean. Moreover, soya beans are also rich in isoflavones which have potent estrogenic and anti-estrogenic properties and saponins which are proven to have significant anti-inflammatory, anti-carcinogenic and cardioprotective properties (Guang et al. 2014).

The majority of the scientific studies have been focused on the hypolipidemic properties of soya beans. Yoshikawa et al. in 2000 have discovered the bioactive peptide LPYPR from the glycine fraction of soya beans. They found that administration of LPYPR (50 mg/kg) significantly reduced the total cholesterol and LDL cholesterol levels in rats (Yoshikawa et al. 2000). Further studies revealed that LPYP functions by inhibiting 3-hydroxy-3-methylglutaryl CoA reductase (HMGR) enzyme, which is the prominent rate limiting enzyme in cholesterol biosynthesis. In addition, other glycine derived peptides like IAVPGEVA and IAVPTGVA had shown potent inhibitory effects on HMGR enzyme, thus promoting hypolipidemic activity. Moreover, peptides derived from βCG like KNPQLR, EITPEKNPQLR, and RKQEEDEDEEQQRE had found to effective in inhibiting fatty acid synthase activity and thereby decreased serum triglyceride levels in rodents (Singh et al. 2014).

Bioactive peptides that are available in food products are well studied for their anti-hypertensive properties (Singh et al. 2014). The bioactive peptides isolated include: valyl-prolyl-proline (Val-Pro-Pro), isoleucyl- prolyl-proline (Ile-Pro-Pro) and (Tyr-Pro). These peptides elicit their action by inhibiting angiotensin-converting enzyme (ACE), which is a key enzyme in the regulation the blood pressure (Cam and de Mejia 2012). The marketed fermented soya bean food products like soya sauce, natto and tempeh are abundant in ACE inhibitory peptides (Hernández-Ledesma et al. 2004). Fermented Korean soya bean contain anti-hypertensive peptide HHL, also soya bean fermented with *Bacillus natto* or *Bacillus subtilis* contains two anti-hypertensive peptides VAHINVGZK and YVWK (Singh et al. 2014).

Soybean supplementation improve cholinergic transmission by increasing the levels of acetylcholine in cortex and hippocampus region of rats (Pan et al. 1999). Soybeans also promote the release of neurotrophic factors which have a critical role in brain development and functioning. Soyabean upregulates the expression of brain derived neurotrophic factor in cortical region of rats, nerve growth factor in cortex and hippocampus of rats (Pan et al. 1999) and improve memory performance in mice which is corroborated to decrease in high blood lipid levels and increased activity of neurotransmitters in mice. Clinical studies have also found that intake of soya improves both short term and long-term memory. Soybeans have also been found to improve the motor functions in Parkinson's disease by inhibiting the levodopa metabolism in humans (Liu et al. 2007).

Spinach

Spinach (*Spinacia oleracea*) is a leafy green vegetable belonging to the family *Amaranthaceae* and originated from Persia in the 7thcentury. Spinach is consumed in both raw and cooked form. Primarily the major chemical constituents are water (91.4), carbohydrates (3.6%), proteins (2.9%) and fat (0.4%). The lipid fraction mainly consists of poly unsaturated fatty acids (PUFA) (Park 1966). In addition, spinach is an abundant source of the carotenoid leutin, which is highly beneficial for patients with macular degeneration and cataracts (Olmedilla et al. 2003).

Compared to other leafy vegetables spinach is rich in flavonoids which includes patuletin, spinacetin, spinatoside, jaceidin, and flavone (Koh et al. 2012). These compounds are responsible for the potent antioxidant and anti-inflammatory properties of spinach.

Antioxidant properties of spinach are well established. Studies have reported that spinach scavenges 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; ABTS) radical, superoxide anion (O2-), Fe^{2+}, peroxyl radical, hydroxyl radical, and peroxynitrite thereby protecting cells from oxidative damages (Jaiswal et al. 2011). A water-soluble natural antioxidant (NAO) mixture extracted from spinach contains polyphenols and flavonoids. NAO was found to be effective in preventing malonaldehyde (MDA) formation (Bergman et al. 2001). The ant-inflammatory properties of spinach are also well established. Animals treated with spinach derived NAO and then challenged with lipopolysaccharide have shown reduced severity of lesions and alleviated the COX2 mediated inflammation (Bergman et al. 2001). In addition, leutin has potential free radical scavenging property and thereby decreased the levels of PGE2, TNF-α, and IL-1β in the LPS induced inflammatory model. Spinach intake reduces infarct volume, lowers caspase activity in cerebral cortex and increased locomotor activity in focal ischemic rat brain (Lingappan 2018).

Clinical studies have also proven the potential cardio-protective properties of spinach. In a A Randomized, Controlled Trial Jovanovski et al. (2015) had hypothesized that short term consumption of spinach, which is high nitrate content, this can affect arterial stiffness as well as central and peripheral blood pressure. The patients were supplemented with spinach (845 mg nitrate/day). They found postprandial reduction in augmentation index and concluded that spinach consumption contributes to hemodynamic properties, decreased arterial stiffness and central blood pressure.

Brown rice

Brown rice is a whole grain rice with the outer inedible husk removed. Green revolution in 1960's and 1970's has improved the crop yield and economy of the Asian countries like Japan and Korea. Since then, these countries focused on improving the taste, appearance and the texture of rice. A meta-analysis study from (Itani et al. 2002) has shown that increased consumption of sugar rich rice such as processed rice and sedentary life style raised the incidence of type 2 diabetes. This happened due to rice milling, which discards the micronutrients, proteins and fiber rich outer aleurone layer. Brown rice possesses prominent health benefits when compared to white rice. One cup of boiled brown rice has 216.4 cal of energy, monosaturated and polysaturated fat (0.64 g and 0.63 g respectively), 44.8 g of carbohydrates and 5.3 g of proteins. In addition, brown rice is also a rich source of fiber (3.5 g), thiamine (12%), riboflavin (15%), nicotinic acid, zinc (8%), iron (5%), magnesium (21%), phospherous (16%) and pantothenic acid (6%). The vitamin E component of brown rice consists of eight lipid homologues α, β, γ and δ tocopherol or tocotrienol these are having potent lipid peroxy radical scavenging properties thus preventing cellular ageing (Kim et al. 2015).

Lee et al., conducted a randomized 12-week clinical study where the type 2 diabetes patients were assigned to follow brown rice-based vegan diet. They found that brown rice-based vegan diet is more effective for glycaemic control in type 2 diabetic patients than conventional diet. In addition, they also found a reduction in the HbA1C levels among the vegan diet followed patients (Lee et al. 2016). Kozuka et al., have elucidated the underlying mechanism on how brown rice improves the glucose intolerance and impede the onset of diabetes. They investigated the effect of γ-oryzanol (orz) which is a major chemical constituent of brown rice on the feeding behavior and glucose homeostasis. They found that orz significantly improved the glucose intolerance and this was achieved by attenuating endoplasmic reticulum stress in mice fed with high fat diet. Using HEK293 cell line the revealed that orz prominently inhibits the transcriptional activity in the endoplasmic reticulum stress responsive element. In addition, they also found that orz significantly down-regulated the gene expression of endoplasmic reticulum stress related molecules in fetal mouse brain derived neuronal cells. Moreover, orz also has shown to improve glucolipotoxicity induced pancreatic islets disruption via enhancing glucose-stimulated insulin secretion and inhibiting excessive secretion of glucan (Kozuka et al. 2015).

Buckwheat

Buckwheat (BW) is a gluten free commonly eaten functional food belonging to family *Polygonaceae* genus *Fagopyrum*. It is considered as a food of high nutritional value due to the presence of protein, lipid, dietary fiber, minerals, phenolic compounds, and sterols. Buckwheat contains flavonoids such as rutin and polyphenolic compounds like hyperin, quercitrin, and studies showed that quercetin could be responsible for the beneficial effects. BW is also rich in amino acid lysine, arginine and vitamins (Giménez-Bastida and Zieliński 2015). Recently it has been found that buckwheat also contains γ-aminobutyric acid (GABA) and 2″-hydroxynicotianamine. BW has shown to possess strong antioxidant activity and prevents the DNA damage induced by oxidative stress (Zhou et al. 2012). Phenolic compunds and flavonoids present in BW exert anti-inflammatory effect by reducing the expression of IL-6, IL-1β, and TNF-α and inhibit NF-κB (Hole et al. 2009). BW consumption reduces body fat, low density lipids (LDL) and increases the content of high density lipids (HDL) and lowers cholesterol and triglycerides (TG) in rats (Kayashita et al. 1996), thus inhibiting the development and progression of cardiovascular diseases. BW intake also affects the mRNA expression of enzymes responsible for lipid metabolism. BW decreases the expression of glucose-6-phosphate dehydrogenase and fatty acid synthase and downregulates expression of PPAR -γ, peroxisome proliferator activated receptor-γ, CCAAT/enhancer-binding protein-α, sterol regulatory element-binding protein 1c, and carbohydrate responsive element-binding protein and of lipogenic genes acetyl-coenzyme a carboxylase 1 or 2 (ACC1 and 2), stearyl-coenzyme A oxidase, and FA synthase (Choi et al. 2007). Preclinical studies have shown that BW reduces the blood glucose levels in diabetic rats (Yao et al. 2008), inhibited α-amylase and α-glucosidase activity (Lee et al., 2015) and also modulates satiety, improve insulin sensitivity and glucose tolerance in hyperglycaemia patients (Qiu et al. 2016). Polyphenols present in buckwheat exert neuroprotection because of its free radical scavenging activity. Buckwheat has shown to improve spatial memory by inhibiting glutamate release and inhibiting production of nitric oxide in cerebral ischemia induced rat (Giménez-Bastida and Zieliński 2015). Buckwheat also improved the memory in *in vivo* model of AD by reducing oxidative stress in mice (Choi et al. 2007) (Fig. 3).

Several clinical studies have also shown potential health benefits of BW. He et al. (1995) has shown that daily intake of 100 g of lowered both total and LDL cholesterol in 850 people of ethnic minority in china. In a doube blind crossover study from Wieslander et al. (2011) samples were supplemented with normal BW (16.5 mg rutin/day) and tartary BW cookies (359.7 mg rutin/day) for two weeks. They found that tartary BW cookies consumption reduced the serum myeloperoxidase, total serum cholesterol and HDL-cholesterol. Moreover, they also found that tartary BW consumption improved the lung vital capacity. Hence, consumption of BW reduces the inflammatory markers and cardiovascular events in human beings.

Fruits as a source of functional food

Fruits are a rich source of fiber, vitamins and polyphenolic and anthocyanin compounds. These compounds have many physiological functions and delays the onset of ageing related changes, helps in fighting infections and chronic diseases, impedes cancer, osteoporosis and neurological disease progression. Some of the fruits which act as functional food discussed below.

Blueberries

Blueberries were known as 'super fruit' because of their strong antioxidant activity and rich content of polyphenolic compounds. Blueberries contain flavonoid and non-flavonoid. Anthocyanins (60%) are the major components. Malvidin 3-galactoside, delphinidin 3-galactoside, delphinidin 3-arabinoside, petunidin 3-galactoside, petunidin 3-arabinoside, malvidin 3-arabino-side, cyanidin 3-glucoside, cyanidin 3-galactoside, cyanidin 3-arabinoside and delphinidin 3-glucoside are the major anthocyanins present in blueberries. Proanthocyanidins, flavonols and chlorogenic acid are also present in blueberries. The commercially available blueberries species are *Vaccinium corymbosum* L., *V. virgatum* Aiton, *V. angustifolium*, *V. myrtillus* L. The association between the higher intake of anthocyanin and health benefits have been well studied. Higher intake of anthocyanin was associated with a decrease in hypertension risk in women, improved vascular function and helps in weight maintenance (Bertoia et al. 2016).Blueberries are also found to be beneficial in diabetes. Higher intake of anthocyanins improved insulin sensitivity, reduced inflammation and oxidative stress in diabetic patients (Li et al. 2015). Anthocyanin intake also reduced the risk of Alzheimer's disease, dementia and PD (Gao et al. 2012). *In vitro* studies have shown that anthocyanins improved viability and differentiation of human corneal epithelial cells (Song et al. 2010) and improve retinal photoreceptor sensitivity. Blueberries have been shown to reduce cancer progression by inhibiting production of pro-inflammatory molecules, oxidative stress and products of oxidative stress such as DNA damage, inhibition of cancer cell proliferation and increased apoptosis (Johnson and Arjmandi 2013).

Pomegranate

Pomegranate (*Punica granatum* L) fruits are rich source of phytochemical such as polyphenols, anthocyanins, tannins, flavonoids, lignans, terpenoids, and sterols. Ellagitannin which is broken down to ellagic acid is the main active constituent of pomegranate which is responsible for its strong antioxidant activity (Akbar et al. 2015). Punicalagin and punicalin are the two other ellagitannins having antioxidant and anti-inflammatory activity (Vučić et al. 2019). Numerous studies have claimed health benefits of pomegranates in preventing chronic diseases such as hypertension, arthritis, cancer, hyperglycaemia, reducing oxidative stress and maintaining cholesterol levels (Zarfeshany et al. 2014).

Khan et al. (2007) has revealed that pomegranate juice inhibits cell growth, induces pro-apoptotic proteins and downregulates anti-apoptotic proteins and suppresses the

Fig. 3 Mechanism by which buckwheat intake provides benefits in different disease conditions

progression of prostate cancer and breast cancer as well as lung and colon cancer (Khan et al. 2007). The pomegranate fruit extract (PFE) used in this study was rich in six anthocyanins (pelargonidin 3-glucoside, cyanidine 3-glucoside, delphinidin 3-glucoside, pelargonidin 3,5-diglucoside, cyanidine 3,5-diglucoside and delphinidin 3,5-diglucoside), ellagitannins and hydrolysable tannins. Invitro data has shown decreased cell viability in A549 following PFE administration. They found that PFE upregulates the cell cycle regulatory molecules like WAF1/p21 and KIP1/p27. WAF1/p21 and KIP1/p27 are regarded as the universal molecules of inhibitor of cyclin–cdk complexes. PFE administration has also significantly downregulated the cyclin–cdk associated molecules. In addition, the PFE administration declined progression of A549 human lung carcinoma cells in athymic mice. The potent anti-oxidant property aid to the chemoprotective nature of PFE.

Studies have showed the role of pomegranate juice in preventing hypertension and congestive heart disease (Esmaillzadeh et al. 2006). Pomegranate juice also promotes the expression of transcription factors such as CREB, and BDNF which play a critical role in brain development. Pomegranate juice reduces cerebral amyloid beta deposits by increasing the expression of CREB and synaptic proteins which were also found to be involved in the cleavage of amyloid precursor protein in transgenic mice model of Alzheimer's disease (Braidy et al. 2016). Decreased expression of amyloid beta in hippocampus due to pomegranate intake improves cognitive functions in mice. Pomegranate juice also enhances neuronal survival, protects from oxidative stress, reduces α-synuclein aggregation and could be able to increase mitochondrial activity in rotenone model of Parkinson's disease. Pomegranate administration also reduces the neuroinflammation and improved motor functions in mice (Kujawska et al. 2019).

Mango

Mango (*Mangifera indica* L.) is rich in polyphenols and other micronutrients which exert several health benefits. Mangiferin, gallic acid, gallotannins, quercetin, isoquercetin, ellagic acid, and β-glucogallin are the polyphenols present in mango. Mango parts have been used in traditional system in the management of various diseases. Mango extracts counteract the oxidative damage induced by the excessive production of free radicals and exert anti-inflammatory activity in mice model of colitis by reducing the expression of inflammatory mediators via IGF1R/AKT/mTOR pathway (Kim et al. 2016). Mango extract has beneficial effects in hypoglycaemia by inhibiting α-amylase and α-glucosidase activities (Gondi and Prasada Rao 2015). Bioactive compounds of mango have also shown to possess anticancer activity which is mediated by downregulating the anti-apoptotic factor Bcl-2 and activating caspase proteases. Mango intake reduces the risk of obesity and promotes endothelial function. Phytochemicals present in mango improve the lipid profile and reduced blood pressure surge in hypertensive rats (Liu et al. 2003). Mango intake also reduces the development of neurological diseases such as Alzheimer's disease. *In vitro* and *in vivo* studies have confirmed that magniferin protects the neurons by scavenges the ROS and restores mitochondrial membrane potential and improved cognitive performance (Bhatia et al. 2008).

Nuts as a source of functional food

Almond

Almonds are the most popular nut consumed by humans. They have a high nutritional value and are rich in poylphenols, vitamins, carbohydrates and polyphenols. Almonds are also rich in monounsaturated fatty acids such as oleic, linoleic and palmitic acids. Intake of almonds reduce chronic disease such as diabetes, hypertension and help in weight maintenance. Invitro and animal studies have reported that almonds reduce oxidative stress and DNA damage. Epidemiological studies have shown that higher intake of almonds in Mediterranean countries contributes to lower incidences of coronary heart disease, reduce inflammatory diseases and improve endothelial functions (Kamil and Chen 2012). Dietary elements present in almonds improve memory consolidation in rodent models of amnesia (Batool et al. 2016).

Walnut

Walnuts are one of the most nutritive nuts belonging to family *Juglandaceae.* They are rich in proteins, fats, vitamins, minerals, and polyphenols. The major triacylglycerols; free fatty acids found in the walnut kernel are oleic, linoleic, linolenic acids (Poulose et al. 2014). They also contain high quantity of omega-3 fat [alpha-linolenic acid] which has been linked with numerous health benefits. Walnuts also contain amino acids such as lysine and arginine which are converted to nitric oxide, which acts as a potent vasodilator, inhibiting platelet adhesion and aggregation, and reducing the progression of atherosclerosis. Ellagic acid present in the walnut reduces the risk of congestive heart disease and suppresses cancer progression. Melatonin present in walnut is a powerful antioxidant and regulates circadian rhythm. Dietary supplement of walnut improves memory consolidation and has been reported to delay the progression of neurological disorders. Moreover, walnut supplementation provided neuroprotection and improved motor functions in rodent model of Parkinson's disease (Choi et al. 2016). Taken together, evidences suggest that integration of nuts in a healthy diet could be an effective measure to maintain a health state and delay the onset of diseases.

Functional foods of animal origin

Fish

The chief bioactive component present in fish products are polyunsaturated fatty acids. Eicosapentaenoic acid and docosahexaenoic acid (DHA) form the major components of polyunsaturated fatty acids. DHA forms an essential component of cellular membranes in brain and retina. DHA is critical for normal functioning and development of organs in children. Preclinical and clinical studies have shown the beneficial effects of fatty acids in inflammatory diseases such as arthritis, psoriasis, Crohn's disease, and chronic diseases such as cancer and cardiovascular diseases. DHA have also been found to provide protective effect in neurological diseases (Wergeland et al. 2012).

Probiotics

Probiotics are the viable microorganisms that improve the intestine functions in the host organisms. Probiotics are known for their anti-carcinogenic, hypocholesterolemic and antagonistic action against enteric pathogen in the intestines. Dairy products are the best source of calcium. Probiotics have been incorporated in milk products, mayonnaise, edible spreads (Begum et al. 2017). Probiotics constitute around 65% of functional food market. Probiotics inhibit pathogen growth by synthesizing biochemical compounds which possess antimicrobial activity, altering the pH, receptor binding of pathogens, and initiating immune response. Probiotics have also been found to be useful in the management of neurological disorders. Alteration in gut microbiome have been reported in autistic children. Lower levels of *Bifidobacterium* have been found in autism. Similarly, fecal matter of autistic children has higher levels of *Clostridium spp.* In case of Alzheimer's disease *Oscillospira* were found to be reduced while as *Enterobacter*, *Shigella* and *Roseburia* increased. Various clinical and animal studies have confirmed the beneficial effects of probiotics in autism. The key mechanism by which probiotics have an impact on the gut microbiome are by competing for dietary ingredients production of end products having inhibitory property increased innate immunity reduced inflammatory response. Some of the commonly used microorganisms in probiotics are *Lactobacillus rhamnosus, Lactobacillus reuteri, Bifidobacteria, Lactobacillus casei Lactobacillus acidophilus, Bacillus coagulans, Escherichia coli, Saccharomyces boulardii.*

Probiotics may contain a single strain or mixture of these microorganisms.

FDA perspective on functional foods

The Federal Food Drug and Cosmetic Act (FFDCA) does not provide a specific definition for the functional food. Hence, FDA does not have an established regulation for the functional foods. Therefore, marketing functional foods come under the existing regulatory options. There is a rising concern to develop regulations to document the safety of the dietary ingredients and dietary supplements. Nutrition Labeling and Education Act which was developed (NLEA) in 1990 introduced food labels, this explains the relationship between food or a food component with disease or health conditions. These potential health benefit claims should be approved by FDA before marketing. In 1997, the FDA Modernization Act (FDAMA) had been implemented. This act smoothened the FDA preapproval process by implementing the "authoritative statements" on food labels as health claims. These statements should be published by US government bodies which are responsible for the public health like National Institute of Health (NIH). Manufacturers who intend to use the authoritative statement should notify the FDA 120 days prior to the marketing (Affairs 2019 p. 1).

The most significant change in the food regulation was implemented by Dietary Supplement Health and Education Act of 1994 (DSHEA). This act considered the food additives as vitamins, minerals, amino acids used by man to improve the health conditions. They introduced "significant Scientific agreement" which includes the reports of the safety and efficacy of these compounds in living system. This includes the role of the bioactive compound that affects the functioning of living systems and the mechanism by which the compound induces pharmacological effect. In addition, if the compound claims to treat any conventional nutrient deficiency diseases then the prevalence of the disease in the United States should be produced. Manufacturers who are using structural and functional claims on the label should notify the FDA within 30 days of marketing and the following statement should be kept as a disclaimer ("Dietary Supplement Health and Education Act of 1994," n.d.).

Conclusion

Functional foods have been receiving considerable global attention because of their nutritional value and the presence of constituents which are critical in regulation of physiological processes. Functional foods have all the ingredients necessary for a healthy diet and have been found to possess health benefits. Recommendation of functional foods is evolving and will be an essential strategy for maintenance of healthy sate and delaying or preventing the onset of diseases.

Acknowledgements The authors wish to thank their institutions for continued support. The language and technical editing support provided by The Editing Refinery, MD, USA is highly acknowledged. The financial support in the form of internal grant from SQU Oman to MME is highly acknowledged. The project was also supported by Alfaisal university by INTERNAL RESEARCH GRANTS IRG20314.

Author contributions MB, and AB performed literature research, gathered and analyzed information, and generated short preliminary write-ups. SBC, BB, HH and NG provided research insight, content examination and supported wide ranging aspects of the manuscript development process. MME, RPF and MWQ conceptual work, framework, final draft write-up, critical reading and editing. All authors read and approved the final manuscript.

Funding MME highly acknowledge the funding support provided by SQU, Oman in the form of Internal Grant. The support provided to HH by Al-Faisal university, KSA as INTERNAL RESEARCH GRANTS IRG20314 is highly acknowledged.

Availability of data and materials All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest Authors declare no conflict of interest.

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