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Chapter

Disease Modifying Potential of Functional Foods for Neurodegenerative Disorders: Status Update on Regulatory Compliance

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Abstract

Progressive loss of functional neurons is typically characterized as neurodegeneration. This is particularly pronounced during aging and results in debilitating conditions such as Parkinson's disease and Alzheimer's disease. Symptoms appear typically after 70–80% neuronal loss, resulting in irreversible damage. Several drugs have been clinically approved but they only alleviate symptoms and additionally lead to undesirable side effects. Hence there is a dire need for drugs and/or supplements which address this lacuna. Functional foods are known to offer health benefits beyond their attributed nutritional values. Unlike dietary supplements which are made from foods or food-like substances with enriched nutritional value, functional foods are foods that are modified for greater nutritional value. Conceptually, as an expansion of dietary supplements, functional foods are known to be neuroprotective. Here we discuss functional foods which can potentially be used as adjunctive therapy, with a note on the regulatory compliance.

Keywords: Neurodegenerative diseases, neuroprotection, functional foods, adjunctive therapy, regulatory compliance

1. Introduction

Since 1900 the global average life expectancy has more than doubled and is now 70 years. This is expected to further increase over the coming years. This can be mainly attributed to better healthcare systems, access to timely medical and emergency services, lifestyle changes, decrease in infant mortality, and to a large extent higher income. A corollary to this is an increase in the geriatric population, which brings with it several age-related health concerns. Not surprisingly, diseases of the aging brain are also rampant. The brain is the most privileged organ. Yet, what appears to be an advantage could also classify as a drawback as early detection of brain disorders always poses to be challenging. Age associated progressive deterioration of the neuronal structures typically results in a group of conditions called

Sl No	Physiological Effect	Food source	Phytochemical/ Bioactive compound	Regulatory compliance (RC)	References
1	Multiomic alterations	1. Green tea 2. Turmeric	1. Butyrate, flavonoids, and genistein 2. Caffeine and theanine 3. Curcumin	F, K, P, R, HH	[3, 4]
2	Epigenetic changes	1. Soy products 2. Broccoli 3. Brazilian nuts 4. Green tea 5. Garlic 6. Grapes 7. Cruciferous vegetables 8. Blueberry, fish, olive oil, diet rich in vegetables	1. Genistein 2. Sulforaphane 3. Selenium 4. Catechins epigallocatechin-3-gallate 5. Resveratrol Dihydrocaffeic acid, malvidin-3′-O-glucoside 6. Folic acid, isothiocyanates, docosohexanoic acids 7. Vitamin B12, choline, folate, methionine, betaine, biotin, pantothenic acid, curcumin	C, D, B, E, F, K, L, M, O, P, S, W, AA, GG, HH	[5–13]
3	Mitochondrial health enhancing	1. Red meat, dairy products, avocado, chicken, fish, beans 2. Organ meat, muscle meat, fatty fish, spinach, cauliflower, broccoli, orange, strawberries, sesame seeds and pistachios. 3. Protein rich meats such as beef, turkey, pork and limited in chicken 4. cherries, berries, eggs, milk, fish, nuts	1. L-carnitine 2. Co-enzyme Q [#] 3. Carnosine 4. Green tea catechins 5. Melatonin	C, D, G, H, K, O, P, T, U, R, X, Z, HH	[14–18]
4	Anti-inflammatory function	1. Turmeric, Berries, kale, grapes, spinach, bell peppers, cocoa, broccoli 2. Soybeans 3. Peanut oil, corn, peas and beans 4. Olive oil 5. Mint	1. Flavonols 2. Flavans 3. Palmitoyl ethanolamide 4. Hydroxy-benzoic acid 5. Patchouli alcohol	A, I, K, P, S, U, AA, EE, HH	[19–26]
5	Antioxidant function	1. Tea, grapes, lentils, cocoa, apples, apricots, cherries 2. Flax seeds [#] 3. Walnuts	1. Flavanols 2. Alpha-linolenic acid 3. Flavonoids and Alpha-linolenic acid	D, G, J, K, P, S, EE	[27–32]

Sl No	Physiological Effect	Food source	Phytochemical/ Bioactive compound	Regulatory compliance (RC)	References
6	Improved cognitive function	1. Grape seeds, soy products 2. Barley grass 3. Fermented foods 4. *Ginkgo biloba*	1. Isoflavones 2. Saponarin 3. Ginkgolides	B, G, K, N, P, Q, V, FF	[33–38]
7	Neuroprotective role	1. Grape fruit, lemons, oranges 2. Olives, plums, chickpeas, herbs and spices 3. Coconut 4. Mushroom	1. Flavonoid glycoside 2. Tannins/Proanthocyanidin 3. Phenolic acids 4. Polysaccharides	D, K, P, S, V, Y, AA, BB, DD, FF, HH	[27, 39–48]
8	Mitigation of neuroinflammation and microglial activation	1. Peaches, 2. Blackberries, 3. Black grapes 4. Strawberries	Flavanols	B, D, G, K, P, V, EE	[49–51]
9	Free radical scavenging property	1. Grape skin 2. Peanuts 3. Red wine 4. Cranberries	Trihydroxy-stilbenes	B, D, K, P, S, V, CC, EE, FF, HH	[52–54]
10	Suppression of oxidative stress	1. Celery 2. Fresh parsley 3. Olives 4. Oregano 5. Peppers 6. Rosemary	Flavones	D, K, P, S, V, CC, EE	[55–57]

A*: Belgium-Federal Agency for the Safety of the Food Chain (FASFC);* **B***: Canadian Food Inspection Agency (CFIA);* **C***: Center for Food Safety and Applied Nutrition (CFSAN);* **D:** *China-National People's Congress (NPC);* **E***: Council of Europe (Flavouring substances and natural sources of flavouring);* **F:** *Dietary Supplement Information Expert Committee (DSIEC);* **G***: European Food Safety Authority (EFSA);* **H:** *European Medicine Agency (EMA);* **I***: Europe-Center for Food Safety and Applied Nutrition (CFSAN);* **J***:Flax Council of Canada (FCC);* **K***: Food and Drug Administration, USA (USFDA);* **L***: Food for Special Dietary Use (FSDU);* **M:***Food Safety and Standards Regulations (FSSR);* **N***: Food Standards Agency, UK (FSA);* **O***: Food Standards Australia New Zealand (FSANZ);* **P***: FSSAI- Food Safety and Standards Authority of India;* **Q;** *Hong Kong-Centre for Food Safety (CFS);* **R***: International Alliance of Dietary/Food Supplement Associations (IADSA);* **S***: Japan- Ministry of Health, Labour and Welfare (MHLW);* **T***: Korean Food and Drug Administration (KFDA);* **U:** *Malaysia-Food Safety and Quality Division (FSQD);* **V:** *Malaysia-Ministry of Health;* **W:** *Medicines and Healthcare products Regulatory Agency, UK (MHRA);* **X:** *Natural health product (NHP) in Canada;* **Y:** *Nepal-Department of Food Technology and Quality Control (DFTQC);* **Z***: NIH- Office of Dietary Supplements (NIH-ODS);* **AA***: Norway-Norwegian Ministry of Agriculture and Food (NMAF);* **BB***: Philippines-Food and Drug Administration (PFDA);* **CC***: Portugal-Economic and Food Safety Authority (EFSA);* **DD***: South Korea-Ministry of Food and Drug Safety (MFDS);* **EE***: Taiwan FDA (TFDA);* **FF***: UK-Department for Environment, Food, & Rural Affairs (DEFRA);* **GG***: UK-Food Standards Agency (FSA);* **HH***: United States Department of Agriculture (USDA).*#*Not approved by FDA.*

Table 1.
Table depicting a comprehensive list of the various physiological effects exerted by functional foods, their dietary sources, and status of their regulatory compliance.

neurodegenerative disorders; Alzheimer's Disease (AD) and Parkinson's Disease (PD) being classical examples. These debilitating disorders negatively impact neuronal functions in a progressive manner. Although age is the predominant risk factor, environmental influences play a significant role. Pharmacological and surgical approaches are being rampantly used as therapy. While these strategies address the clinical symptoms and provide relief to the patients with minimal side effects, they fail to prevent disease progression. Further, there could be additional risk involved due to chronic drug administration. Owing to these serious lacunae, there is a dire need to investigate novel approaches which are disease modifying, neurorestorative, possibly curative, and have minimal side effects. Adopting a nutritional approach is being increasingly considered for its protective function and has already proven effective in several patients. Special diets and a dietary plan have been investigated for their neuroprotective roles. Increasing the nutrient value and quality of the diet and adherence to the dietary plan are being emphasized for long term benefits.

Foods that we consume have three functions: primary, secondary, and sometimes tertiary functions. While the primary function would be to meet the body's energy requirement, the secondary function is attributed to the flavor, smell, appearance, texture, etc. In addition, certain foods have been known to modulate human physiology and hence prevent disease. This function is sometimes regarded as the tertiary attribute and includes anti-carcinogenic, anti-inflammatory, antioxidant, anti-mutagenic, and anti-ageing, to list a few. Foods that possess such attributes are classified as 'functional foods'. Functional foods are known to offer health benefits beyond their traditional nutritive values. Physiologically, they help reduce the risk of contracting chronic diseases. These are conventional foods which can be consumed like a normal diet, but are fortified with a specific or cocktail of well-balanced health promoting nutrients. Good examples of such fortified foods are iron-fortified cereal, iodized salt, vitamin D-fortified milk etc. Functional foods contain the required amounts of antioxidants, carbohydrates, vitamins, proteins, fats, and other components so as to boost the immune system and improve cell survival. Functional foods overlap with nutraceuticals, medical foods, probiotics, designer foods, pharmafoods, and vitafoods. The health benefits and physiological effects attributed to functional foods and nutrients such as polyphenols are also relevant in the context of brain health but are relatively under investigated. Consumption of foods containing natural antioxidants such as legumes, fruits, herbs, whole grains, and vegetables, or processed foods enriched for natural antioxidants such as vitamin C and E, omega 3-fatty acids, carotenoids, polyphenols, stilbenes, etc. can provide the desired protection against neurodegenerative and metabolic disorders [1, 2]. Here, we discuss the various biological effects modulated by functional foods in the context of neurodegeneration, with a note on the regulatory guidelines and regulatory status of such functional foods (**Table 1**).

2. 'Omic' and physiological effects exerted by functional foods

2.1 Multiomics

Advancing technology has made possible the study of entire gene sets or protein complements as one unit resulting in the 'omics'-era. High throughput investigations allow access to huge amount of data and aid in understanding biology in an interactive and holistic manner. Diet offers many health promoting and disease preventing factors which target not just one gene/protein/cell type/pathway, but can affect multiple entities resulting in a cumulative outcome. The influence of bioactive food components on the gene expression is termed as 'nutrigenomics' and the response of gene variants to a particular nutrient is called 'nutrigenetics'. Nutrients

from the diet can interact with the genetic material by functioning as co-factors or substrates for processes that regulate DNA metabolism and gene expression. Early life exposure to nutrients and environmental factors both during the prenatal and postnatal period has a significant influence on gene expression, cellular plasticity, and susceptibility to various adult diseases [58].

The first and most widely employed omics technology is transcriptomics which is highly efficient and provides high-throughput data. It provides a snapshot into the mRNA complement of the tissue at a particular time. It allows us to understand the influence of bioactive dietary compounds on gene sets and biological processes. Microarray technology offers the possibility of understanding the change in gene expression patterns after exposure to a particular nutrient. Using a wide range of bioinformatic tools one can build interaction networks and pathway for the observed gene profiles [59, 60]. An accumulation of large - scale nutritranscriptomic microarray data has necessitated the need for integrated web-based databases which have been built on open-source platforms and ensure efficient organization, storage, and analysis of the humungous data [61].

The proteome represents the protein complement of the genome that is expressed at a particular time in response to a particular stimulus and is more complex, dynamic, and subject to spatio-temporal changes. While the genome is constant, the expression of the gene is largely dependent on several parameters; alternative splicing and post translational modifications included. Protein identification technologies have largely evolved from simple gel-based techniques to mass spectrometry and multiplexed immunoassays which are further assisted by powerful bioinformatic tools. Nutritional proteomics hence allows us to examine the effect of food components on protein expression and also offers a platform for biomarker identification in relation to dietary interventions. *In vitro* and *in vivo* studies have revealed the impact of dietary component such as butyrate, flavonoids, and genistein on the proteome [62–66]. One study identified thirteen candidate proteins as potential biomarkers of neuroprotection in response to grape seed extract supplementation [67].

Metabolomics is the newest addition to the omics family in nutritional research. Metabolome is the complete set of metabolites synthesized as a result of the genome-environment interactions under a given environmental condition. Similar to the other omics approaches advanced techniques such as mass spectrometry and Nuclear Magnetic Resonance (NMR) in addition to powerful bioinformatic tools enables us to detect the biochemical changes in response to nutritional interventions and also understand the impact of genetically modified foods on food safety [68].

Studies regarding the effect of functional foods with metabolomic effects related to neurodegenerative disorders are limited. Green tea and curcumin are among those that have been reported to exert metabolome changes. Use of green tea polyphenols on aging rats resulted in metabolomic alterations. Dysregulation of lipid metabolism was moderated by consumption of caffeine and theanine enriched green tea [69]. NMR and MS based metabolomics showed the effect of curcumin on hyperlipidaemia mice induced by high-fat diet [70].

2.2 Epigenetics and functional foods

Unlike what was popularly believed a few years ago, somatic heritable states need not necessarily depend on the DNA sequence alone. There could be environmental influence resulting in DNA methylation, histone modifications, and chromatin remodelling. Both external and internal factors could bring about such epigenetic changes which can in turn control the gene expression pattern. These changes are also heritable and hence provide a framework for the quest

of etiological factors governing several diseases including neurodegenerative diseases. It is aptly said 'you are what you eat'. Nutrition and the bioactive food components can influence the epigenetic mechanisms and bring about changes at the transcriptional level. Vitamin B12, choline, folate, methionine, betaine all of which are constituents of the diet, mediate 1-carbon metabolisms involved in DNA and histone methylation. Biotin is a substrate for histone biotinylation; niacin and pantothenic acid facilitate histone ADP-ribosylation, acetylation, and deacetylation processes [71–73]. Several phytochemicals like tea catechins, resveratrol, sulforaphane, curcumin, etc. affect epigenetics [74, 75].

Natural products from tea, garlic, soy products, herbs, grapes, and cruciferous vegetables have epigenetic targets. Selenium in Brazil nuts, sulforaphane in broccoli, epigallocatechin-3-gallate in green tea, resveratrol in grapes, and genistein in soy beans have been shown to be dietary inhibitors of DNA methyltransferases [76, 77]. While epigenomic alterations owing to dietary interventions are well documented in carcinogenesis, their effects in neurodegenerative diseases are limited. Vitamin B12, folic acid, dietary polyphenols, isothiocyanates, docosohexanoic acids, olive oil, blueberries, fish, and a diet rich in vegetables have been suggested to modify the epigenetics of AD [78]. Dihydrocaffeic acid from grape juice and malvidin-3′-O-glucoside from grape seed extract, reduced proinflammatory cytokines via down-regulation of DNA methyltransferase 1 and upregulation of histone deacetylase 2 respectively, hence attenuating depression-like behaviour in mice [79].

2.3 Neuroinflammation and functional foods

Inflammatory processes localized to the central nervous system (CNS) are categorized as neuroinflammation. It can be regarded as a double edged sword as it is deleterious but at the same time triggers the repair and recovery mechanisms. Glia, the CNS specific immune cells play a major role in this process. A cross talk between the CNS and the inflammatory cells mediates an inflammatory response involving the production of mediators such as cytokines, chemokines, reactive oxygen species (ROS), and second messengers, by the latter. Recruitment of immune cells, edema, tissue damage, and possibly cell death are some events that follow inflammation. The positive responses of neuroinflammation can involve immune surveillance, injury induced remodelling, immune preconditioning, development, memory, and learning; all of these leading to tissue repair, neuroprotection, and enhanced plasticity [80]. Hence, even though neuroinflammation is one of the most evident consequence of neurodegeneration, therapeutic strategies could be evolved so as to potentiate the positive effects of inflammation and concomitantly mitigate the negative effects.

Neuroinflammation in the context of AD and dementia were mitigated by functional foods. Mediterranean diet such as fruits, vegetables, whole grains, nuts, and legumes; moderate intake of fish, poultry, and alcohol; and low intake of red and processed meat improved cognitive function in elderly, probably due to the anti-inflammatory mechanisms [81]. Dietary components categorized as functional foods encompassing carrots, tomatoes, cranberry, grape seeds, papaya, pomegranate, curcumin, ginger, green tea, PUFA, dark chocolates, and cocoa have shown antioxidant and anti-inflammatory properties [82].

2.4 Mitochondrial health and functional foods

Mitochondria are the seat of cellular energy metabolism and several key housekeeping activities. Neuronal functions are highly energy demanding and the presence of healthy mitochondria is indispensable. Several evidences suggest a link between dysfunctional mitochondria and neurodegenerative diseases. Mitochondrial

glucose metabolism, oxphos enzyme activities, mitochondrial dynamics, motility, fusion and fission have all been implicated in neurodegeneration. TCA enzymes such as pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase, were impaired in post-mortem AD brain and fibroblasts from AD patients [83]. Mitochondrial electron transport chain complexes I, III, and IV showed reduced activities in platelets and lymphocytes and post-mortem brains from AD patients [84, 85]. Additionally, aberrant expression of Drp1, a protein associated with mitochondrial dynamics was reported in AD brains, AD mouse models and APP cell lines [86]. Likewise, deficiency in mitochondrial complex I in the SNpc of the brain, lymphocytes, platelets, and muscle from PD has been well established [87]. Several genes related to genetic forms of PD such as phosphatase and tensin homolog-induced putative kinase 1 (PINK1), DJ-1, α-synuclein, parkin, and leucine-rich repeat kinase 2 (LRRK2) are associated with mitochondria. Parkin and PINK1, implicated in mitochondrial quality control, mitophagy, and mitochondrial dynamics are reported to be abnormal during PD [88, 89]. Knockout mice for mitochondrial transcription factor A (*Tfam*), associated with mitochondrial copy number, maintenance and transcription of mitochondrial DNA, survive to adulthood and display Parkinsonian phenotype such as intracellular inclusions within dopaminergic neurons, dopaminergic cell degeneration, and loss of striatal dopamine [90, 91]. Considering the significant role of mitochondrial health in neuronal function, use of functional foods that protect and/or preserve mitochondrial health and in turn its function is a promising approach. L-carnitine and co-enzyme Q10 play a key role in mitochondrial biogenesis and health. L-carnitine exhibits antioxidant function within the mitochondria by scavenging ROS and prevents inflammation. It drives ATP production, lowers cholesterol, and helps build lean muscle. Acetyl L-carnitine enhances mitochondrial health [92]. Carnitine exerts neuroprotection by acting on the NrF2 inhibitor, keap1, and activating the phase II antioxidant system [93]. Unites States and Japan are marketing L-carnitine and carnosine fortified foods as energy boosting and health promoting products. Green tea catechins have antioxidant function and improve cellular energy production and mitochondrial health [94]. Melatonin has antioxidant properties and is neuroprotective [95].

2.5 Oxidative stress and functional foods

Increased reactive oxygen species (ROS) can potentially harm cellular macromolecules such as lipids, proteins, and nucleic acids. While moderate production of ROS is essential for normal cellular function, excess production is countered by a battery of antioxidants within the cell. A normal cell maintains this homeostasis but if this balance is disturbed a cell experiences oxidative stress. Mitochondria are the primary site of ROS production and also its principal target. Increased ROS beyond the threshold and/or a failure of the antioxidant defence contributes to mitochondrial dysfunction, cellular damage, and oxidative stress contributing to a series of events resulting in neurodegeneration. The dopaminergic neurons associated with PD are particularly vulnerable to oxidative stress due to their increased iron content, which catalyzes the Fenton reaction leading to the generation of superoxide. Dietary intervention can effectively manage oxidative stress [96–98].

Polyphenols in fruits, vegetables, cereals, dry legumes, chocolate, and tea have antioxidant potential and prevent neurodegenerative diseases. Flavonoids from fruits and vegetables such as spinach, pepper, asparagus walnut, sunflower seeds, and chia seeds have the highest antioxidant capacity [99]. Additionally, α-lipoic acid, anthocyanin, *Ginkgo biloba*, garlic, black cumin, and green tea prevent neurodegenerative disorders through antioxidant mechanisms [100]. Black raspberries, rich in the antioxidants anthocyanin and ellagitannin, have successfully been

used in clinical trials and are reported to reduce the risk of cancer [101]. Preclinical research demonstrated the use of berries in preventing neurodegeneration owing to their anthocyanin, caffeic acid, catechin, quercetin, kaempferol, and tannin content. They have been shown to reduce oxidative stress, have anti-inflammatory function, alter levels of brain–derived neurotrophic factor, and enhance memory and cognitive function [42]. However, their clinical uses have not been reported.

2.6 Gut microbiota, neurodegeneration and functional foods

Recent research points to the microbiota-gut-brain-axis as a novel contributing factor for neurodegeneration and mood disorders, by directly affecting the neuroimmune, neuroendocrine, and direct neural pathways such as the vagus nerve. Microbial metabolites which include but not limited to bioactive constituents, neurotransmitters, and epigenetic regulators cross the blood–brain-barrier (BBB) exerting physiological effects. A dysbiosis in this microbiota causes dysregulated gut-brain signalling resulting in oxidative stress, neuroinflammation, immune disturbances, and metabolic imbalance [102, 103]. Indeed, altered gut microbiota and metabolites like butyrate and amyloid are associated with neurodegeneration [104]. The gut of AD patients was shown to have decreased levels of Bacteroidaceae, Veillonellaceae, and Lachnospiraceae family members, which contain several key butyrate producers, but increased abundance of microbes from Ruminococcaceae, Enterococcaceae, and Lactobacillaceae. Pathogenic gut residents such as *Escherichia coli*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Salmonella enterica*, *Salmonella typhimurium*, and *Staphylococcus aureus*, are known to produce amyloid proteins, implicated in AD [105]. Stools from patients with Amytrophic Lateral Sclerosis (ALS), had increased content of potential inflammatory pathogens such as *Escherichia coli* and members of Ruminococcaceae and Enterobacteriaceae family [106, 107]. PD gut showed reduction in the relative abundance of *Prevotella*, which may be associated with reduced metabolism of high-fiber foods, mucin production, gut barrier function, and small chain fatty acid (SCFA) levels [108–110]. Reduced levels of butyrate producers such as *Blautia*, *Coprococcus*, *Faecalibacterium,* and *Roseburia* species in PD stools suggests increased intestinal permeability and inflammation. These observations support emerging evidences of neuroinflammation in neurodegenerative conditions probably induced by peripheral circulating inflammatory products [111].

Considering the role of gut microbiome dysbiosis in neurodegeneration, strategies for modulation of gut microbiota are under investigations. The use of probiotics, synbiotics, and prebiotics either as isolates or herbal supplements appear to be promising avenues. Prebiotics are particularly carbohydrates that are selectively fermented by gut microbes and modify the microenvironment favourably to the microbes and in turn offer health benefits to the host [112, 113]. SCFA such as butyrate, of microbial origin are known to modulate histone acetylation pattern and inflammatory responses via altered gene expression, induction of T-regulatory cells, BDNF expression, and function as signalling molecules between the gut-brain axis [114, 115]. Probiotics, contrary to prebiotics, are a cocktail of live intestinal bacteria and yeasts which are consumed to improve gut health. They improve the permeability of the intestinal wall and the BBB. A randomized, placebo controlled clinical trial using pre and probiotics helped improve PD associated bowel dysfunction [116]. In the peripheral blood mononuclear cells (PBMC) of PD subjects given probiotics the expression of pro-inflammatory cytokines was reduced. Reduced oxidative stress was noted in probiotic treated PD subjects as indicated by a decrease in C-reactive protein (CRP), malondialdehyde (MDA), and increased glutathione levels [117]. Likewise, a double blind placebo controlled clinical trial in AD subjects using probiotic

cocktail of *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum* showed improved learning and memory as scored by Mini Mental Score Examination (MMSE) and a reduction in oxidative stress markers such MDA levels [118]. Clinical trials using selenium containing probiotics improved the MMSE score, antioxidant capacity, reduced serum triglycerides and LDL cholesterol, reduced CRP level, and improved insulin sensitivity in AD subjects by altering the gut microbial composition [119]. Probiotic Annurca apple puree minimised plasma lipid profile and trimethylamine-N-oxide levels, hence offering cardioprotection [120]. However, their efficacy in neurodegeneration needs further investigation. Likewise, Danone, a French company markets its dairy products enriched with *Bifidobacterium lactis* as a gut health promoting probiotic product [121]. Yet, no studies exist till date indicating its role in improving brain health. Several studies in *in vivo* models as well as in clinical subjects indicate promising outcome. Nevertheless, the use of pre/probiotics as neuroprotective agents is in its infancy as many unanswered questions remain. Their therapeutic use is constrained by the absence of (1) strong translation of preclinical studies, (2) thorough elucidation of pertinent mechanisms, and (3) larger cohort studies.

2.7 Calcium as functional food

Calcium forms a major macronutrient which serves multiple functions in our body. Some of them are bone and skeleton formation, coagulation, enzyme functions, nerve conduction, and cardiovascular functions. The source of calcium in our body is solely through the diet hence malabsorption or inadequate intake could lead to myriad of altered functions in our body. On account of the key physiological functions of Calcium, the use of Calcium/Vitamin D supplementation is rampant particularly in the elderly and post-menopausal women. Occasionally, regular consumption of calcium causes nausea, constipation, and indigestion. Hence, consumption of calcium fortified foods is gaining popularity. Examples of calcium fortified foods include milk and related products like cheese, yoghurt, and probiotics [122]. Several studies have demonstrated the effect of calcium fortified milk and milk products with or without Vitamin D on osteoporosis in the elderly [123]. Non-dairy food products rich in calcium are seeds (poppy, sesame, celery and chia seeds), edible bones of sardines and salmon, beans and lentils, almonds, and vegetables (broccoli, kale, spinach, okra and greens). Although green leafy vegetables are rich sources of calcium, their absorption in the gastrointestinal tract depends on the presence of inhibitory factors, such as oxalates, phytates, and tannins which bind with calcium, rendering it insoluble and therefore unavailable to the body. Therefore, the bioavailability of calcium via functional foods is a key factor for consideration [124].

3. Regulations of functional foods

The health benefits of food have always been a subject of discussion from ancient times. While most initial claims regarding the disease-preventing attributes of foods lack scientific evidence, foods such as green tea have been extensively investigated for their health promoting role. The modern concept of functional foods was born in Asia, and Japan was one of the earliest countries to fund research for the systematic analysis and development of functional foods. Research in the recent past has clarified that food can be designed not just to meet primary functions, but also to adjust the human body's homeostasis so as to regulate health and wellness. This idea of physiologically relevant functional foods led to the

Sl. No	Country	Regulatory Policy	Governing body	Coverage	References
1	Japan	FOSHU	Ministry of Health and Welfare	Dietary fibers, lactic acid bacteria, oligosaccharides, soy proteins, sugar alcohols, peptides, calcium/ iron, polyphenols, glycosides, sterol esters, 4-Aminobutanoic acid	The Nutrition Improvement Law Enforcement Regulations, (1996)
2	Taiwan	Health Food Control Act (HFCA), Regulations for food labeling	The executive Yuan, Department of Health	Foods containing bioactive compounds, foods with specific healthcare abilities, disease preventing, health improving foods	Health Food Control Act, (1999), Food Administration Act. 2007., Yen GC. 2003.
3	Hongkong	No specific regulation on nutrient fortified foods but referenced from the Codex Alimentarius, which issued a general principle for the 'Addition of Essential Nutrients to Foods' in 1987 and subsequently amended the principles in 1989 and 1991	Director of health, Health and Welfare Bureau	Dietary supplements, nutraceuticals, designed foods, functional foods, and natural health products	Regulatory ordinances: 1. Pharmacy and Poisons Ordinance (PPO; Cap. 138) 2. Chinese Medicine Ordinance (CMO; Cap. 549) 3. Public Health and Municipal Service Ordinance (PHMSO; Cap.132) 4. Undesirable Medical Advertisements Ordinance (UMAO; Cap. 231)
4	India	Food Safety and Standards Authority of India (FSSAI)	Ministry of Health & Family Welfare, Government of India	Dairy products, Fats, oils and its emulsions, Fruits and vegetable products, Sweets & confectionery Sweetening agents including honey Salt, spices, condiments and related products Beverages, s Other food product and ingredients Proprietary food Irradiation of food Fortification of staple foods i.e. vegetable oil, milk, salt, rice and wheat flour/maida	Food Safety and Standards Act, 2006

Sl. No	Country	Regulatory Policy	Governing body	Coverage	References
5	Sri Lanka	Drug Regulatory Authority (DRA) or Food Administration Unit		Dietary items based on the traditional wisdom of their ancestors as treatment for certain illness	Food and Nutrition Policy of Sri Lanka (2004–2010)
6	China	State Food and Drug Administration (SFDA)	The Chinese Food Composition Tables (FCT)	Enhancing the immune function, lowering blood cholesterol and sugar, lowering blood pressure, improving sleep and assisting in memory improvement. Chinese foods and traditional Chinese medicines	Approved by SFDA from July 2003 till July 2004
7	USA	Food and Drug Administration	US government	Conventional foods, supplemented foods, and natural health products	The Federal Food, Drug, and Cosmetic Act (FFDCA)
8	Canada	Natural Health Products Directorate	Canadian and US government	Conventional foods, supplemented foods, and natural health products	Food and Drugs Act, 2005
9	South Korea	Korea Food and Drug Administration (KFDA), The Korea Health Functional Food Act (HFFA), Food Sanitation Act (FSA)	1. Food headquarters 2. Nutrition and Functional food headquarters: both under the Korean Ministry of Health and Family Welfare (MHW)	Phenols (green tea, aloe extracts, Co Q10, soya isoflavones), terpenes (ginseng, red ginseng, chlorella, spirulina), fatty acid and lipids (omega-3-fatty acids, linolenic acid, lecithin, squalene, polysterol, lutein), sugars and carbohydrates (gaur gum, glucomannan, soybean fiber, wheat fiber, barley fiber, corn bran), fermented microorganisms (probiotics, red yeast rice), amino acids and proteins (soy proteins), aloe gel, chitosan etc.	The Presidential Decree issued in 2003, Ministerial Ordinance issued in 2004

Table 2.
Table depicts a list of the countries along with their functional food regulatory acts.

formulation of the Japanese regulatory systems. The label and labelling information such as the nutrient content or health claims, accompanying the product would be a primary determinant of its regulatory status. Thus, if the label claims that the

product is intended for use in diagnosis, cure, mitigation, treatment, or prevention of a disease, it would be regulated as a 'drug'. However, if the claim relates to any alteration of the structure and function of the body, with no specific reference to a disease it would be regulated as a dietary supplement [125].

One of the earliest regulatory guidelines was established by the Ministry of Health and Welfare in Japan under a policy termed 'Food for Specified Health Use (FOSHU), under which health claims for few selected functional foods was made legal (The Nutrition Improvement Law Enforcement Regulations, (1996)). The repertoire of functional foods has now expanded to include over 800 FOSHU products [92]. Following the Japanese example several countries have scripted regulatory guidelines for the health enhancing claims of functional foods and nutraceuticals. Nevertheless, regulations for functional foods have not been well established in most countries. Also, the legislations widely vary from country to country.

In the Indian context, the Food Safety and Standards Authority of India (FSSAI) under the Ministry of Health and Family Welfare, Government of India, has framed the guidelines and regulations for health supplements, nutraceuticals, foods for special dietary use, foods for special medicinal purpose, functional foods and, novel foods. The quality requirements and general monograph for such foods are defined in the Indian Pharmacopoeia, which provides guidelines on the usage of food coloring agents, flavours, quantity of nutrients to be added as per Indian Council of Medical Research (ICMR) recommended daily allowance. Interestingly, FSSAI clarifies that mere foods such as vegetables, fruits, cereals, legumes, spices, and other plant or botanicals with minimal processing such as cleaning, de-husking, de-weeding, sorting, drying, or powdering, cannot be considered as 'health supplement', 'nutraceutical', 'food with special dietary use', or 'food for special medical use'. However, the formulation of articles of food must be based on the principles of medicine of nutrition and must be supported by validated scientific data, wherever applicable. More importantly, the label and or leaflet must specify details including the specific use, intended target consumers, the physiological or disease conditions which they address, recommended duration of usage etc. [126].

A list of the countries along with their regulatory acts has been provided in **Table 2**.

4. Conclusion

Age related neurodegenerative disorders pose a serious healthcare challenge to the medical fraternity worldwide. This is a cause for concern, particularly because symptoms are evident largely during advanced stages of the disease. Presently available monotherapy and pharmacotherapy only provide symptomatic relief. Hence there is an urgent need for improved therapeutic approaches. Also, currently available pharmaceuticals are not free from adverse effects. Therefore, the world is now embracing natural sources as health promoting and disease modifying agents. Towards this objective, the use of nutraceuticals and functional foods is on the rise (**Figure 1**). While several scientific reports prove their neuroprotective functions, extensive clinical validations are lacking. Further, while some functional foods and foods for medical purposes have been evaluated by preclinical and clinical studies, the regulatory guidelines for their labelling and use are still evolving. Increasing awareness among consumers has brought the functional food market to the forefront. It is hence inevitable for authorities to formulate regulatory guidelines with respect to their labelling and usage. While some countries worldwide have put forth

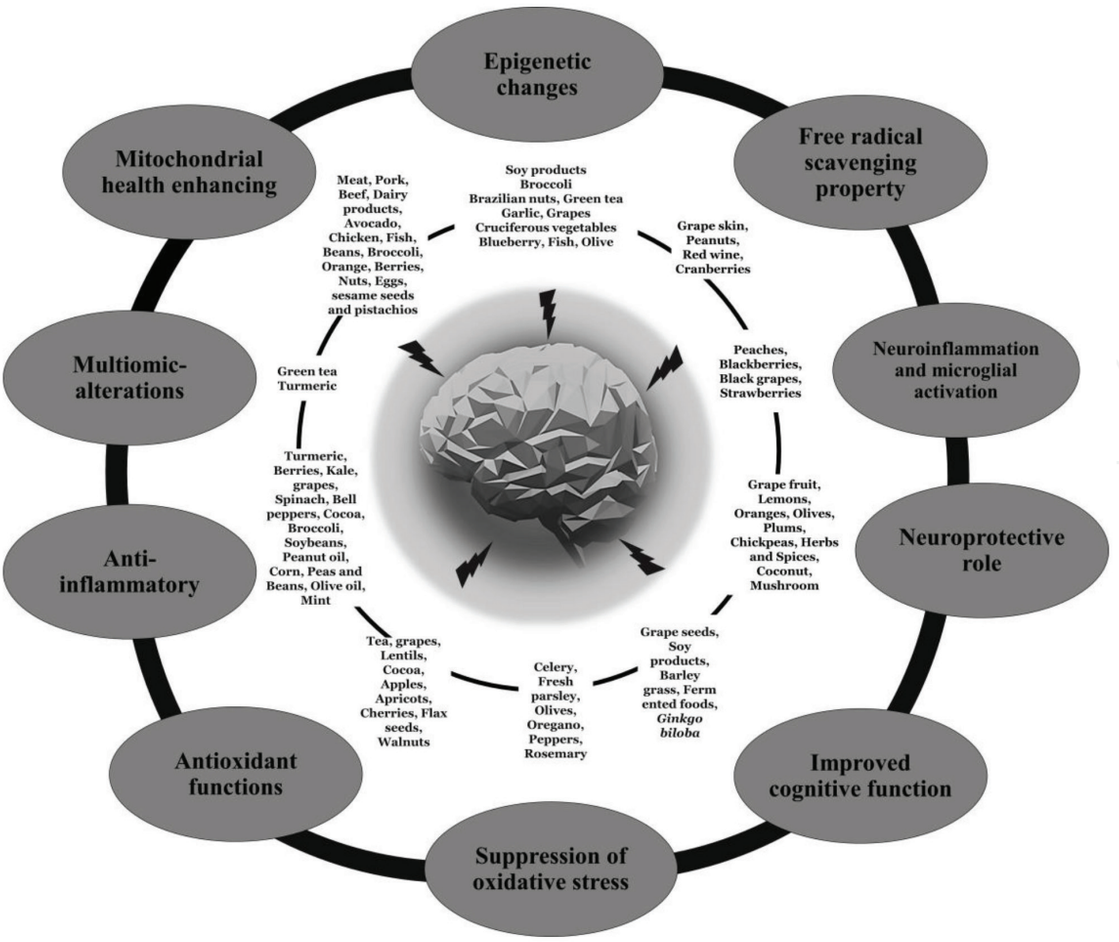

Figure 1.
Neurodegeneration, Physiological Effects, and Functional foods. Image indicates the various physiological dysregulations observed during neurodegeneration (outer circle) and an illustration of functional foods which positively modulate these effects (inner circle).

legal guidelines, many more are lagging. In addition, a unified set of guidelines across nations is absent.

Conflict of interest

The authors declare no conflict of interest.

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