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THERAPEUTIC AND PREVENTIVE ROLE OF FUNCTIONAL FOODS IN PROCESS OF NEURODEGENERATION

H. Kaur [1], S. Agarwal [2], M. Agarwal [2], V. Agarwal [2] and M. Singh [* 2]

Amity Institute of Biotechnology [1], Amity University, Noida - 201304, Uttar Pradesh, India.
Department of Biotechnology [2], Jaypee Institute of information Technology, Noida - 201307, Uttar Pradesh, India.

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Correspondence to Author:
Dr. Manisha Singh

Assistant Professor,
Department of Biotechnology, Jaypee Institute of Information Technology, A-10, Sector 62, Noida - 201307, Uttar Pradesh, India.

E-mail: manishasingh1295@gmail.com

ABSTRACT: Diet and dietary habits of an individual are considered to be an essential factor based on biologically active compounds extracted or modified from either known or unknown natural sources, contributing to completing the dietary and nutritional needs beyond the traditional supplements. Moreover, the latest research information about their supportive and therapeutic utility suggests that they play a potential role in promoting the overall sensory and motor synergies in the brain, reducing cognitive decline and activating neuronal receptors. Many of the functional food items are reported to have many effective bioactive compounds such as – polyphenols, flavonoids, stilbenes, terpenoids, carotenoids, alkaloids, omega 3, PUFA, *etc.* Also, various phyto-compounds (ginseng, vitamin B12, alpha-lipoic acid, berry anthocyanins, trans-resveratrol, *Ginkgo biloba*, *Bacopa monniera*, Huperzine A, *Centenella asiatica*, vinpocetine, tocotrienols and palm oil, selenium) are noted globally for incrementing the cerebral health and its upkeep, listed as functional foods. This review study focuses on the direct co-relation and various effects of functional foods in reducing or preventing the neurodegeneration process. Authors have also summarized details of functional foods in supplementing the diet using the neuroprotective pathway and many newly discovered natural substances as functional foods along with their mechanism related to the expression of disease-promoting genes.

INTRODUCTION: Functional foods are known to exhibit health properties beyond the traditional nutrients it contains. They display physiological benefits and higher capacities to reduce the risk of chronic diseases beyond its basic nutritional functions, including maintenance of gut health [1].

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They are the conventional food and are consumed like a normal diet, but they do support the body with the balanced number of vitamins, fats, proteins, carbohydrates, *etc.*, required for its healthy survival [2].

The study of such a category of food supplements has become a necessity in today's world, and thus, recent researches have introduced the various components of food which have a useful and advantageous impact on host health. This concept is widely used for the expansion of dietary supplements which aim to affect activities and composition of gut microbes, reducing cognitive

decline and activating neuronal receptors [3]. Initially, more vitamins and calcium supplementation was used during the first generation of functional foods due to their health attributes; later they were transformed into their fortified version with nutrients to help prevent specific nutritional deficiencies like - iron-fortified cereals, vitamin D-fortified milk and iodized salt [4, 5].

In today's time, these functional foods are aimed to formulate in such a way so that they can enhance immunity, strengthen up the gut microbiota, increasing the content of phytochemicals to curtail the risk for chronic diseases like cancer, neurological heart diseases and diabetes [6]. Furthermore, in the recent past, it has been observed that the ideology of including additional nutrition into our daily diet schedule to produce a positive result on gut microbiota composition has evolved immensely. This resulted in higher production of probiotics / prebiotics [7].

They are either living microorganisms or food substrates that produce valuable effects by improving microbial balance in the intestine of the host. Probiotics like lactic acid excretors bifidobacteria and lactobacilli are majorly used in lyophilized or fermented forms of milk products [8]. Secondly, prebiotics, which is known to be a non-viable component that aids in microorganism activity (fungi and bacteria) or promoting growth, helps in specific fermentation and moves along the colon [9]. This gives the benefit to the host by stimulating the activity of colonic bacteria. They are the specific substrate for colonic bacteria and may not be absorbed or hydrolyzed in the upper gastrointestinal tract. They are capable of inducing systematic or luminal effects, hence, provoking healthy composition in the host.

Lactobacilli or/and bifidobacteria are considered to be suitable organisms for target [10]. The symbiotic effect produced from the mixture of prebiotic and probiotic benefits the host by cultivating implantation and survival of microbial supplements [11]. Nowadays, the intensive examination of foods is taking place with the aim of optimizing health and reduce or prevent chronic diseases [12]. However, according to several organizations, the definition of functional food is different. In the United States, organizations like the National Academy of Sciences Food and Nutrition Board proposed a new definition of functional foods as "any modification in food ingredient or food that is beneficial in providing health benefits beyond any traditional use" [13]. However, in 2016, American Dietetic Association (ADA) described functional foods as "fortified, enriched, enhanced and whole foods" [14,] and according to International Life Sciences Institute, they are the foods having active physiological components providing benefits that are beyond basic nutrition.

It is often seen that "Functional food" are commonly interchanged with "Nutraceuticals", although this term is less favored, latter invented by Foundation for Innovation in Medicine in 1991. Further, another associated term is – "Bioactive components", which are seen as extra nutritional elements that aim to deliver health benefits, and are present in less quantities in foods [15]. They exhibit varied functions and chemical structures, for example, phenolic components including flavonoids which are present in plants and extensive research is being carried out in nuts, red wine, fruits, legumes, cereals, vegetables, and tea.

These phenolic compounds possess antioxidant properties and establish favorable effects on tumorigenesis and thrombosis. Similarly, phyto-estrogens are present in flaxseed oil, vegetables, soy, fruits, and whole grains [16] and have shown promising results in controlling the further proliferation of cancer cell lines and various risk factors associated with cardiovascular diseases (CVD) [17]. The commercial market placement for functional food has risen a lot in last two decades, which can be assured from the higher count of functional foods based products launched in these years and their presence in the supplement market.

According to the food industry worldwide, the vogue of functional foods is more inclined to be heterogeneous rather than homogenous in nature, growing and evolving at diverse rates across and within the countries. The core reason for this scenario is the economic acceptance and awareness of the consumers across the globe for benefits rendered by functional foods, which are as good as drugs. Likewise, due to the increasing growth rate in current years US has become the largest supplier of probiotics [18,] whereas use of probiotics remained

underdeveloped in terms of value and volume in countries like UK, French, Spanish, and German. Also, on the outskirts of Japan and the U.S. sports drink category is observed to be underdeveloped whereas, the same drinks are fortified and dominated the European markets [19].

Origin of Functional Foods from Animal Sources: The active elements that are derived from animals are (n-3) fatty acids mainly discovered in fatty fish like tuna, herring, salmon, mackerel, and sardines. Docosahexaenoic acid (DHA) and eicosatetraenoic acid (EPA) are the two other essential primaries (n-3) fatty acids [20]. DHA is a vital element of phospholipids of retinal cell membranes and the brain, essential for their normal physiological functioning [21]. Further, DHA is responsible for the development of retina and brain in infants [22]. Nowadays, the use of arachidonic acid and DHA using formulas have been cleared by the Food and Drug Administration (FDA) [23] for full-term infants feeds. Studies are now being conducted to know the physiological effects of (n-3) fatty acids in rheumatoid arthritis, cancer, CVD, Crohn's disease, psoriasis, cognitive dysfunction. Simultaneously, the reduction in death and mortality in myocardial infarction patients has been observed due to the intake of (n-3) fatty acids [24].

According to the American Heart Association, Dietary Guidelines intake of two portions of fatty fish per week leads to a healthy heart [25]. These dietary supplements are FDA authorized involving the intake of DHA, (n-3) fatty acid, and EPA to lower the risk of coronary heart diseases.

TABLE 1: LIST OF FUNCTIONAL FOOD SOURCES FROM ANIMAL ORIGIN AND THEIR CHARACTERISTICS

Functional food	Key component	Potential health benefits	Scientific evidence	Regulatory evidence
Low fat diet (*e.g.*, meats, fish and dairy)	Low in saturated fat	Reduce risk of cancer and heart disease	Clinical trials	FDA approved health claim
Milk	Calcium	Reduce risk of osteoporosis	Clinical trials	FDA approved health claim
Fermented dairy Products	Probiotics	Reduce cholesterol, Reduce risk for cancer, Control enteric pathogens	Epidemiologic studies	No health claim
Fish	N-3 fatty acids	Reduce risk for heart disease	Epidemiologic studies	No health claim
Beef, Dairy and Lamb	Conjugated linoleic acid	Reduce risk for maminary tumors	Animal studies	No health claim
Eggs with n-3 fatty acids	N-3 fatty acids	Reduce cholesterol	Clinical trials	No health claim

Origin of Functional Foods from Plant Sources: Various physiologically active components derived from plants have been examined in curing diseases.

FDA authorizes the sale of products like - soy protein, stanol-ester-fortifies margarine, soluble fiber from husk of psyllium seeds, oat soluble fiber (β-glucan) [26] that claims to provide enormous health benefits under this category.

Other examples of plant-based resources are - chocolate, cranberries [27], grapes [28], nuts [29] and garlic [30,] *etc.* in eliminating the pathological signs. Consequently, since 1920s cranberries have been acknowledged to be efficient in treating urinary tract infections (UTIs) [31] due to the presence of proanthocyanins (condensed tannins) in cranberries that softens the epithelial line by inhibiting *E. coli* from adhering [32] on the walls of the urinary tract as it has anti-adhesion [33] properties.

Also, since age's garlic has been used for various medicinal purposes (lowering blood pressure, treating cancer) as it contains allylic sulfides, allicin as major active components that help in the reduction of total cholesterol by 4-6% in CVDs patients. It is believed that fat-rich food components are not "heart-healthy", except for fatty fishes, nuts, *etc.* that have shown evidence on attaining higher cardiovascular benefits.

Clinical trials, which have specifically examined the effect of almonds on blood lipids, have found that these tree nuts significantly reduced total cholesterol by 4–12% and LDL cholesterol by 6–15%. More recently, a collective review of six clinical intervention trials with walnuts consistently demonstrated decreases in total and low-density lipoprotein (LDL) cholesterol that should lower the risk of coronary heart disease (CHD) [34].

TABLE 2: LIST OF FUNCTIONAL FOOD SOURCES FROM PLANT ORIGIN AND THEIR CHARACTERISTICS

Functional food	Origin	Bioactive compound	Health benefits	Type of evidence	Strength of evidence	Recommended amount	Regulatory status
Fortified margarines	Plant	Stanol esters and plant sterol	Lowers LDL and total cholesterol	Clinical trials	Very strong	1.7 g/d for stanols and 1.3 g/d for sterols	Health claim
Psyllium	Plant	Soluble fiber	Lowers LDL and total cholesterol	Clinical trials	Very strong	1g/d	Health claim
Soy	Plant	Protein	Lowers LDL and total cholesterol	Clinical trials	Very strong	25g/d	Health claim
Whole oat products	Plant	β-glucan	Lowers LDL and total cholesterol	Clinical trials	Very strong	3g/d	Health claim
Cranberry juice	Plant	Proanthocyanidins	Reduced UTIs	Less clinical trias	Moderate	300 ml/d	Conventional food
Fatty fish	Animal	(n-3) fatty acids	Lowers heart disease	Clinical trials	Strong	2/wk	Claim for Dietry fibres
Fermented dairy products	Animal	Probiotics	Good for gastrointestinal tract	*In-vitro* and *in-vivo* studies	Weak	Daily	Claim for Dietry fibres
Lamb, beef, turkey	Animal	Conjugated linoleic acid (CLA)	Prevents breast cancer	*In-vitro* and *in-vivo* studies	Weak	Unknown	Conventional food

Functional Foods as Health Enhancing Ingredients: Functional foods stand for a new category of remarkably promising foods bearing properties (*i.e.*, low cholesterol, antioxidant, anti-aging, anticancer, *etc.*) that have already rendered them quite appealing [34]. There are many classes of functional foods pro- and pre-biotics, dietary fiber, low fat, etc. The bioactive ingredient found in vegetables, fruits, other plant products, and grains mainly "phytochemicals" associated in lowering major chronic diseases [35].

According to studies, only five thousand phyto-chemicals are known but a large percentage of them have not been identified till now, and research is being carried out to identify its functions [36]. Cells of humans and other organisms are exposed to several useful and harmful oxidizing agents that mainly occur in water, air, food.

Having a balance between anti-oxidants, oxidants and presence of flavonoids in food products leads to optimization of body's physiology against certain infections like parasitic, bacteria, virus, fungi, *etc.* oxidative damage produced by oxidative stress causes impairment of biomolecules like DNA, RNA, lipids resulting in cardiovascular diseases (CVD) and cancers. To decrease oxidative stress produced by free radicals' antioxidants need to be consumed. Antioxidants are present in vegetables and fruits such as carotenoids and phenolics, which help in reducing aging, preventing chronic disorders, cervix, cataract, cancers of colon, esophagus, oral cavity, pancreas, ovary, breast, and lung. GI tract acts as an interface between the diet and other metabolic functions as it's an obvious target for the development of functional foods [37]. The function of GI tract totally depends upon the balance of healthy bacteria, which further prevents the invasion of harmful bacteria/antigens. The composition and the metabolic activity of the gut microflora can be modified by using the ingredients present in the functional food, and thus it acts as the most promising area for its development.

Probiotics, prebiotics, and synbiotics [38] have certain health benefits ranging from reducing the incidence of GI infections, alleviation of lactose intolerance, improvement in overall gut functions, reduction in constipation, and diarrheal episodes. However, Functional foods are more related to improving and promoting the optimal mental state and performance [39]. It largely influences the cognitive performance, attention and vigilance, changes in memory, and other mental processes that occur during aging.

Glucose helps in improving mental performance, which includes memory and decision time. Sucrose reduces pain perception; caffeine leads to improvement in cognitive performance with effects on vigilance, reaction time, and memory [40]. The amino acid tryptophan reduces the time taken to fall asleep, while tryptophan and tyrosine help in recovering from jet lag [41].

Several ingredients, such as n-3 fatty acids, S-adenosylmethione (SAMe), and folic acid, have attracted attention as potential functional ingredients to improve depression [42].

Neurodegeneration Mechanism and Role of Functional Food: Neurodegenerative diseases (NDDs) are characterized by the disintegration of neuronal cells leading to declined cognitive functions [43]. The most integral and eminent part of the brain is CNS as it has the potential to drive vital sensory and motor synergies in the body.

Any modulations, discontinuity or blockage in the smooth conduction of transmission process occurs, leads to triggering of neurodegeneration process resulting in many neuronal disorders like - Alzheimer's disease (AD), Parkinson's disease (PD) and Multiple sclerosis (MS), Huntington's disease (HD), *etc.* These neurodegenerative conditions are characterized by increased inflammation leading to disruption in cell signaling and extending to mitochondrial DNA (MtDNA) damage. Any damage in MtDNA contributes or triggers oxidative phosphorylation and aberrant functions in respiration [44].

MtDNA comprises complex IV, and I, and the modifications in complex IV are observed in patients suffering from AD whereas, latter mutations are observed in PD. Mitochondrial damage due to the presence of free radical reactive oxygen species (ROS) and reactive nitrogen species (RNS) that results in initial damage in MS [45]. So, it's the most logical and suitable approach to restore the neuronal functioning by protecting the mitochondrial functioning. Many phytocompounds are reported for the restoration like - L-carnitine and coenzyme Q10 have a major role in mitochondrial bioenergetics.

The role of L-carnitine (an antioxidant) is to scavenge free radicals chemically, biologically and physically [46]. Also, this antioxidant, shuttles molecule of fatty acid for beta-oxidation in mitochondria. Thus, protecting tissues from ionizing radiations by quenching ROS in a chemical way and biologically inducing TFs (NrF2) to allow expression of genes mainly phase II detoxifier gene. L-carnitine provides protection against inflammation [47]. It also transfers a long chain of fatty acids in the mitochondria, wherein these acids get oxidized to produce energy.

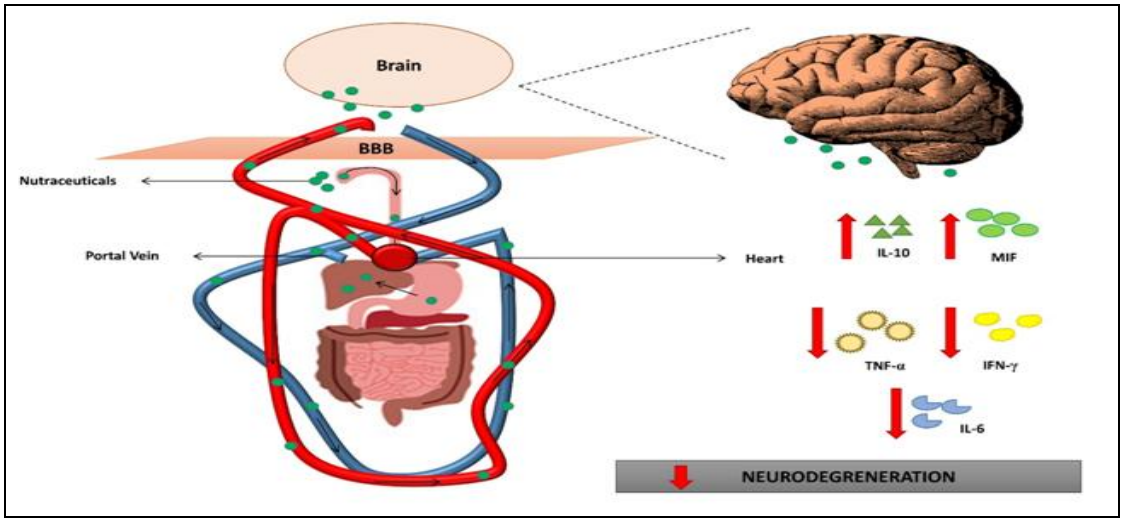

FIG 1: VARIOUS PATHWAYS IN PROCESS OF NEURODEGENERATION AND THERAPEUTIC INTERVENTIONS BY FUNCTIONAL FOODS

TABLE 3: LIST OF VARIOUS FUNCTIONAL FOOD AND THEIR IMPACT

Functional foods	Active ingredient	Impact
Hemidesmus indica roots and Vanilla planifolia pods	The phenolics 2-hydroxy-4-methoxybenzaldehyde	Inhibitory potential against acetylcholinesterase For treating AD and other neurological problems
Pepper (*Capsicum spp*)	Phytochemicals (phenolics and alkaloids) and natural pigments (carotenoids)	Capsaicin works as a chemical signal, activating peripheral terminals of the sensory neurons by increasing membrane permeability to cations such as calcium and sodium signals and are transmitted to CNS and releases neuropeptide substance P.

TABLE 4: REPRESENTING VARIOUS TYPES OF FUNCTIONAL FOODS WITH THEIR CHARACTERISTIC FEATURES AND MODE OF ACTION.

Functional food	Bio-active compound	Therapeutic implications	Mechanism of action
Walnut and polyunsaturated fatty acids	Ω-3 fatty acid α-linolenic acid (ALA), Ω-6 fatty acid linoleic acid (LA)	Neurotransmitter communication, synaptic vesicle fusion, maintaining membrane fluidity.	ALA and LA are metabolized to produce lipid messengers like eicosapentaenoic acid (EPA), docosahaenoic acid (DHA), prostaglandins *via* arachidonic acid thereby, enhancing cognitive functions.
Curcuminoids	Curcumin	Decrement in cognitive deficits, oxidative damage, Aβ42, pro-inflammatory cytokines.	It is direct repressor of fibril formation and Aβ oligomer that can prevent formation of plaques and Aβ42 in the brain
The canine antioxidant diet	Carotenoids, selenium, vitamin E, C, A	Improved visual discrimination, behavioral enrichment,	Helps in reduction of reactive oxygen species or reactive nitrogen species (ROS/RNS)
Green tea	Epigallocatechin-3-gallate (EGCG), other polyphenolic compounds	Anti-oxidant, prevents or reduces aging, increases fat burning and cancer, improves physical performance.	Catechins play a major role in scavenging free radicals.

Functional Food Benefits in Neurodegeneration: The treatment options in CNS for treating neuro-degeneration remain unsatisfactory ever since a long time. According to studies, natural compounds like carotenoids, Vitamin-D, polyphenols, cur-cumin, coenzyme Q10, acetyl –L-carnitine, and other nutraceuticals are reported to possess neuro-protective properties due to their multiple targeting ability for maximum neural pathways48. Likewise, for oxidative metabolism of lipids and carbohydrates vitamin B5 (pantothenic acid) is required and is used in neurotransmitter and hormone synthesis. Lack of vitamin B5causes fatigue [49], increase in neuropathy, insomnia, headache, and deficiency of vitamin B6 (pyridoxine) results in anemia, rashes on mouth or skin dermatitis. Therefore, it results in affecting the cognitive process and neuronal functions, which are dependent on the synthesis of cellular energy metabolism and hormones/neurotransmitters.

Deleterious Effect of Free Radicals on Cellular Mechanism: If hormones/neurotransmitters or cellular compounds are used in deficiency and particular stress or at a higher dose than normal additional functions for these compounds are found [50]. Example: detoxification or apoptosis observed as free radical in stress, *e.g.*, ROS and RNS or both. Therefore, substances in this particular group are classified as anti-oxidants Catechins, which is a polyphenol, belongs to this group and is found in green tea. Due to its antioxidant property, it exerts neuroprotective action [51]. And thus, they are able to protect cellular energy production and mitochondrial function. Another compound against neuro-degeneration is melatonin, which is also an anti-oxidant and contains a neuroprotective role.

Cellular Bioenergetics: Coenzyme Q10 and metabolic agents [52] that protect mitochondrial biogenesis and nicotinamide and antioxidants such as alpha-lipoic acid have a good effect on brain [53]. Acetyl-L-carnitine is a type of carnitine that exerts neuro-protective actions and enhance the function of mitochondria54. According to studies, the action of carnitine can be produced via gene modulation. Inhibitor of NrF2 family of transcription factors (TF) *i.e.* keap 1, carnitines are able to act on it biologically on them to reduce oxidative stress by generating expression of phase II detoxifier genes [55].

Nutrigenomics: Nutrigenomics is the combined approach for the study of signaling (proteic), and metabolic pathways in the cell have led to the discovery of treatment of neurodegeneration [56, 57]. The study of metabolic pathways is known as metabolomics and it provides a fuller image of various processes when pooled with transcriptomic. Also, metabolomics and proteomics have a varied range of applications in nutrigenomics [58].

Their function is to provide data on metabolic alteration, which is produced by bioactive foods or by the effects of nutrients in the various metabolic pathway. Sequencing based technologies, bioinformatics, and microarray technology are some of the vital applications of nutrigenomics [59].

Role of Epigenetic Modulation in Nutritional Requirements: Chemical compounds that can cross-talk to the genome for an alteration of its biology and biochemistry as well as physiology and metabolism to achieve capability for the survival of the fittest which can easily control the protein production in cells is defined as the epigenome. Epigenetic modulation can alter the composition of the function of foods for both animal and plant origin because of alteration in the nutrient content of the water and feed or soil, which are important for the growth of plants and animals, respectively [60]. The epigenetic mechanism acts as mediators in affecting the nutrition of the body. These three are: histone modification, non-coding RNAs, DNA methylation [61].

Induction of epigenetic mechanisms by nutritional factors is via three pathways 1) ligands activating nuclear receptors 2) modification in membrane receptor signaling cascades 3) influence on gene expression [62]. Therefore, this mechanism must deliver time responsive and adapting system in an organism. This has led to research in various fields of nutrigenomics, which aims to target the role of the expression of gene and power for other compounds for modulating the health of cell [63]. The study for the prevention of disease by nutraceuticals is an extremely important, challenging, and promising task. Any type of modulation in food to provide health benefits aids in the prevention of disease, and it can be incorporated in the future as neuroprotective roles.

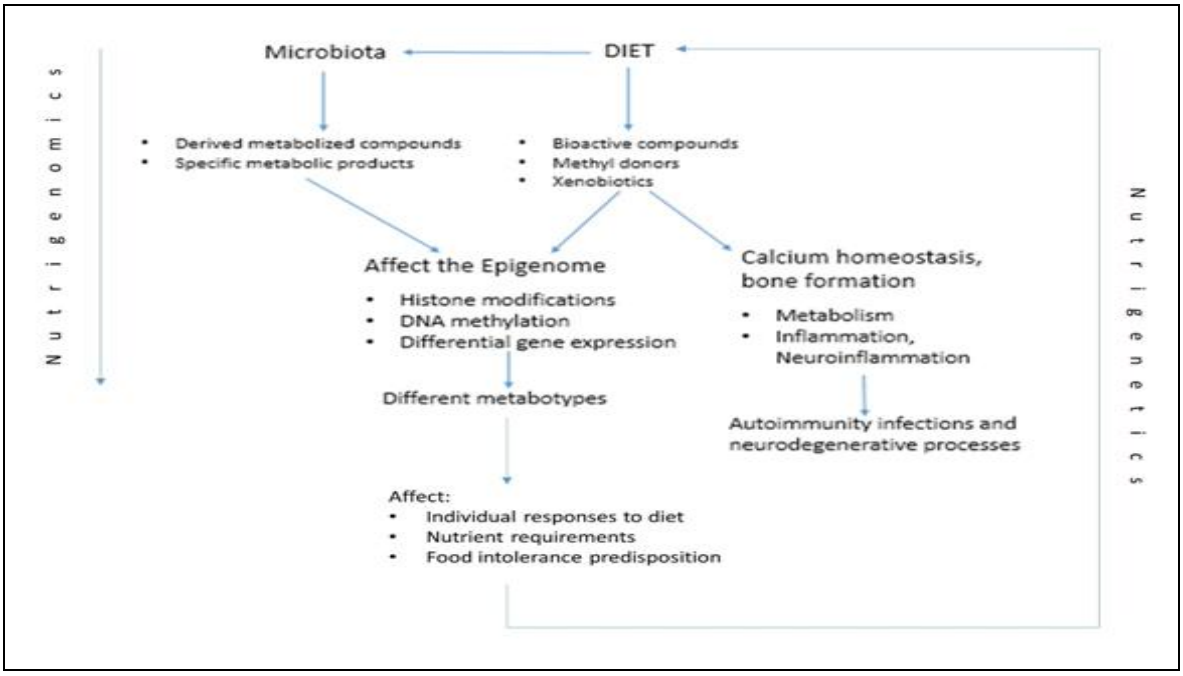

FIG. 2: SCHEMATIC REPRESENTATION OF THE VARIOUS ASSOCIATED MECHANISMS SUPPORTING FEATURES OF NUTRIGENETICS AND NUTRIGENOMICS STUDIES

Process of Aging and Nutrigenomics: The area of nutrition that uses molecular tools to search, access and understand the severe; responses obtained through a certain diet applied between individuals is termed as nutrgenomics [64]. It studies the interaction between dietary components of food and genes. The process of aging links nutrigenomics with neurodegenerative diseases. Advancement in sciences now has made it possible to apply nutrigenomics in the field of anti-aging and customized nutritional solutions in the form of supplements to meet the optimal nutrition required by the body, which prevents aging of cells by the formation of free radicals [65]. Dysfunctional or accelerated aging is the same as neurodegeneration. Due to less ability to respond to other stresses like environmental leads to more prone to vulnerable diseases [66]. Aging is linked to dysfunctional modulation of cells caused by three signaling networks that end in cell cycle arrest, apoptosis and RNS/ROS detoxification, and these signals act on hormonal signaling, oxidative stress, dietary restriction [67]. In general, the first is modulated by resveratrol (polyphenol) and acts in sirtuins family of proteins. The next act is through SGK/AKT represented by TGF (tumor growth factor) or IGF

(insulin growth factor), as they are receptors primary. At foxO gene, this network ends.

Alteration in Genes Related to Aging: Dietary restrictions and anti-oxidant (resveratrol, melatonin, lipoic acid, green tea) are vital modulators belonging to the gene family. It is the sir (information regulator) gene family [68]. Sirtuins are NAD+ dependent histone deacetylases coded by gene "sir" [69]. For the de-acetylation of DNA [70], these enzymes are motivated (Martins, Lithgow, & Link, 2016). According to many studies, these sir genes are also known as longevity genes. Positive modulation of gene family is permitted by sir family of gene known as pepsinogen Cpgc (progastricsin) into PGC-alpha protein [71]. This protein encourages detoxification of ROS and allows mitochondrial biogenesis [72]. Dietary restrictions and sirtuins [73] alters neurodegeneration and biological processing that causes aging [74]. These agents motivate the longevity of genes.

CONCLUSION: The concept of dietary recommendations in the treatment prescriptions is evolving and may prove to be an essential strategy for the overall growth and wellbeing of patients suffering from NDDs. Although the compensatory and prognostic mechanism of these functional foods needs to be established, and detailed studies are required. Also, the toxicity and its abuse need to be systematically evaluated. After evaluating the facts and findings of the functional foods, it can be concluded that in today's modern-day lifestyle, they have emerged as an essential part of our standard daily diet and preferred in required quantities. Apart from its proven health benefits and biological advantages, it has exhibited many interesting facts about reducing and treating certain specific chronic diseases.

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