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Medicinal Plant-based Functional Foods for the Management of Neurological Health

Md. Nasir Ahmed

Biotechnology & Natural Medicine Division, TechB Nutrigenomics, Dhaka, Bangladesh

Author (s) email id:

nasir.ahmedbd@hotmail.com ; nasir.ahmed@tech-b.org

Correspondence: Md. Nasir Ahmed, Biotechnologist

Mobile: +8801722599279;

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Abstract

Plants and plant-derived food products have been used for medicinal purposes since the ancient. Medicinal Plant-based functional foods or plant-based dietary compounds are a re-emerged interest for their therapeutic benefits and nutritive supports which has implicated in healthcare systems across the world.

Neurological disorders are one of the greatest threats to public health and according to the World Health Organization, about 100 million people are affected globally by several neurological and mental ailments. In a traditional medication system, medicinal plants have been applied as both neuro-therapeutic purposes and micro-macro nutrients provider for the wellbeing of psychological states e.g. anti-depressant, anti-anxiety, anti-convulsions, anti-dementia, anti-psychotic, etc.

Herein, it is a topic of great interest to present a conceptual aspect by reviewing relevant scientific literature about the plant-based functional foods or bioactive phytochemicals for the prevention and treatment of mental and neurological disorders. From the literature assessment, we have found that nutritional neuroscience is becoming an advanced research discipline and there has been a growing pile of evidence concerning the therapeutic use of plant-based functional foods and/or plant-derived food compounds for the management of neurologic health, evolving with promising impact over the time.

Keywords: functional food, dietary supplement, phytochemicals, nutritional neuroscience, gut microbiome, personalized nutrition, Bangladesh

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1. Introduction

"To eat is a necessity but to eat intelligently is an art" – La Rochefoucauld

plants are the primary source of food for humankind. Consumption of food provides nutrition to the human body, improves their wellbeing, and on the other side foods can also be responsible for arising of ailments. The concept of "functional foods" is an emerging field in food science to reflect the philosophy- "food as medicine" beyond the basic nutrition needs **[1]**. The term "functional food" first came into sight in 1993 in the nature news magazine under the heading 'Japan explores the boundary between food and medicine' **[2].** Bioactive compounds or functional components in food provide beneficial influences on body functions to help improving health and can be exerted in the treatment, reduction, and prevention of chronic diseases **[3-4].**

Functional foods and dietary supplements can be developed and produced by the addition of health-promoting bioactive components, reduction or elimination of harmful bioactive components, and even modification of the bioavailability of specific bioactive **[5].** These active food/or bioactive components can derive both from phytochemicals (plant) and zoochemical (animal) and besides, the scientific evidence for functional foods and their bioactive components can be categorized into 4 following distinct areas **[6]**:
(1) clinical trials
(2) animal studies
(3) *in-vitro* laboratory studies, and
(4) epidemiologic studies.
The American Dietetic Association (ADA) classifies all foods as functional at some physiologic level and functional foods can be broadly grouped and categorized into the flowing table 1 & table 2 **[1,7]** & table 3:

Group	Examples
Conventional food	β-glucan in oat bran to lower blood cholesterol
Modified food	Fortified margarines that contains added phytosterol and stanol esters that is known to lower serum cholesterol
Synthesized food	some specialized carbohydrates intended to have probiotic effects

Table 1: Groups of functional foods

Category	Examples
Basic Food	Carrots (containing the anti-oxidant b-carotene)
Processed foods	Oat bran cereal
Processed foods with added ingredients	Calcium-enriched fruit juice
Food enhanced to have more of a functional component	Tomatoes with a higher levels of lycopene
Isolated, purified preparations of active food ingredients (dosage form)	Isoflavones from soy; b-Glucan from oat bran

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Table 2: Categories of functional foods adapted from Arvanitoyannis and Van Houwelingen-Koukaliaroglou [7].

Category	Selected examples
Conventional foods (Whole foods)	Garlic Nuts Tomatoes
Modified foods:	Calcium-fortified orange juice, Iodized salt
Fortified	
Enriched	Folate-enriched breads
Enhanced	Energy bars, snacks, yogurts, teas, bottled water, and other functional foods formulated with bioactive components such as lutein, fish oils, *ginkgo biloba*, St John's wort, saw palmetto, and/or assorted amino acids
Medical foods	Phenylketonuria (PKU) formulas free of phenylalanine
Foods for special dietary use	Infant foods Hypoallergenic foods such as gluten-free foods, lactose-free foods, Weight-loss foods

Table 3: Categories of functional foods along with selected food examples adapted from Hasler and Brown [8].

2. Ethnomedicinal Plant-based Functional Foods

Plants have been utilized traditionally as therapeutic purposes or as food supplements in various cultures for centuries. Plants have a combination of secondary metabolites, also known as phytochemicals that are naturally occurred, gives therapeutic benefits with the supply of nutrition to the human body. Both medicinal plants and commonly consumed plants or plant products having the additional properties of promoting health or preventing diseases in addition to their property of supplying nutrients to the body can be considered as functional foods or nutraceuticals **[9-10].**

A vegetable can also contain different nutrients and phytochemicals **[3],** and numerous ethnomedicinal plants and their active phytochemical compounds have also been investigated for their role in disease prevention **[6].** A study reported that leaves of *Adenophora triphylla,* a wild plant of Korea, is a potential source for functional foods that are commonly used for its analgesic, anti-inflammatory, and antitussive properties as well as a natural source of antioxidants **[11].** A Cohort Study showed that consumption of onion (*Allium cepa*) has an inverse relationship to the prevalence of stomach carcinoma **[12]**. In Bangladesh, some medicinal plants such as *Aegle marmelos, Coccinia grandis, Hyptis suaveolens, Mangifera longipes, Nymphaea nouchali, Terminalia chebula,* and *Syzygium cumini* used as food supplements by the Chakma tribe for treating several ailments like indigestion, piles, respiratory problems, diabetes, sex stimulant, cancer, liver diseases, hypertension, eyes diseases, tuberculosis, etc. **[10].** Leaf juice of *Mentha arvensis* was used as a functional food by the Kavirajes of Dinajpur district, Bangladesh for dysentery, indigestion, and stomach pain **[13].** In Chazuta valley (Peruvian Amazon), plants used

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traditionally in strict diets (where plant remedies are consumed with nearly fasting and with some sort of social seclusion), can contribute to the main effects through anti-inflammation, anti-infective actions, psycho-activity and depurative related activities **[14].** The traditional Amazonian medicinal plants diet has globally become increasingly popular as complementary and alternative therapy practiced by *shaman* in Peru for the healing of various physical and mental conditions **[15].** A systematic review **[16]** study reported that plants like *Coccinia indica, Gymnema sylvestre, Aloe vera*, and *Momordica charantia*, which are taken as food supplements show promise for glycemic control in diabetes. A study conducted in Turkey revealed that various Turkish herbs, that are used for edible purposes, contain bioactive principles for generating better human health and for the prevention of cancer **[17].**

Functional foods that are potentially beneficial in the prevention and treatment of cardiovascular disorders (CVD) include soybeans, oats, psyllium, flaxseed, garlic, tea, grapes and nuts **[18],** and the use of functional foods as potent drugs for the prevention of CVD due to inhibition of the inflammatory process, prevention of endothelial dysfunction, and vasodilator production **[19].**

The Allium genus, especially garlic (*Allium sativum*), onion (*Allium cepa*) and Chinese chive (*Allium tuberosum*) is rich in sulfur compounds, steroidal saponins, flavonoids, and so on, have anticancer, antioxidant, anti-platelet aggregation, anti-atherosclerosis, and antimicrobial activities **[20]** A study conducted in Taiwan, found good antioxidant and antimicrobial activity in several Zingiberaceae plants commonly known spices like ginger, turmeric **[21].** Curcumin, a principal ingredient of turmeric (*Curcuma longa)* has antioxidant, anti-inflammatory, antiviral, and antifungal actions **[22].**

Beetroot (*Beta vulgaris*) has a long ethnopharmacological history in the treatment of tumors of the intestine, breast, stomach, and uterus **[23]** and consumption of beetroot leaf improves antioxidant capacity, reduces lipid peroxidation, and enhances glutathione levels **[24]**.

3. Medicinal Plant-based Foods and Phytochemicals for Neurologic Health

Studies on the impact of plant-based functional foods or phytochemicals on brain function are still advancing. Effects of plant-based foods on brain health, cognitive functions, mental and neurological health as well as the underlying mechanisms remain largely unexplored **[25].** Nevertheless**,** there has been a pile of reports in Bangladesh regarding the usage of medicinal plant-based functional foods as traditional phytotherapy for the maintenance of mental health **[9,10,13].** Ahmed and Azam **[26]** have evaluated 15 plant species that were reported to use by the traditional medicine practitioners of Bangladesh for the treatment of schizophrenia-like psychosis and accompanying symptoms like depression, insomnia, forgetfulness. In Ghana, thirty-two plant species have been identified to use as traditional medicine for treating mental and neurological disorders. Most of these plant species have reported anxiolytic, antidepressant, anticonvulsant, antipsychotic, sedative, anti-Alzheimer's, cognitive enhancement, motor coordination, and neuroprotective properties **[27].** Plant-based traditional medicine is very common for treating neurological

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disorders in the West African region and sixty-seven plant species of Guinea Bissau flora were reported for the maintenance of several neurological and mental disorders e.g. epilepsy, convulsions, insanity, and depressant used by the traditional healers of West Africa **[28]**.

Table 4: List of some medicinal plants which can be classified as functional foods, used by Bangladeshi traditional medicine practitioners for the management of neurologic and gut health [9-10,13,92]

Serial Number	Plants name	Part(s) utilized
1	*Abroma augusta* (L.)	roots
2	*Aegle marmelos* (L.)	Whole plant, leaf, root, bark, fruit
3	*Amaranthus spinosus* L.	Leaf, stem
4	*Amaranthus viridis* L.	Leaf stem
5	*Amomum subulatum* Roxb.	Seed
6	*Asparagus racemosus* Wild.	Whole plant
7	*Artocarpus heterophyllus* Lam.	Seed
8	*Bacopa monnieri* (L.) Pennell	Leaf
9	*Bixa Orellana* (L.)	Fruit
10	*Carissa carandas* L.	Fruit
11	*Cayratia trifolia* (L.)	Leaf
12	*Chenopodium album* L.	Leaf, steam
13	*Centella asiatica* (L.) Urb.	Leaf
14	*Cinnamomum tamala* (Buch.-Ham.) T.Nees	Leaf
15	*Cinnamomum zeylanicum* Blume	Bark
16	*Clitoria ternatea* (L.)	Flower
17	*Coccinia grandis* (L.) J. Voigt	Whole plant, leaf, stem, root, flower
18	*Colocasia esculenta* (L.) Schott.	Leaf, stem, tuber
19	*Corchorus capsularis* L.	Leaf
20	Dillenia indica L.	Fruit
21	*Glinus oppositifolius* (L.) Aug. DC.	Leaf
22	*Gmelina arborea* Roxb.	Bark, fruit

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23	*Hyptis suaveolens* (L.) Poit.	Whole plant, leaf, bark, root, fruit, seed
24	*Mentha arvensis* L.	Leaf, stem
25	*Moringa oleifera* Lam.	Leaf, fruit
26	*Musa x sapientum* L.	Fruit
27	*Nymphaea nouchali* Burm.f.	Leaf, stem
28	*Spilanthes acmella* (L.)	Leaf
29	*Syzygium aromaticum* (L.) Merr.	Flower bud
30	*Syzygium cumini* (L.) Skeels	Leaf, bark, fruit, seed, seed kernel
31	*Terminalia chebula* Retz.	Leaf, bark, fruit, seed
32	*Vitex negundo* (L.)	Leaf

Foods containing phytochemicals like alkaloids, anthocyanins, carotenoids, and polyphenols, etc. are capable of improving cognitive function, learning, general brain, and wellbeing **[29].** Zhang **[30]** identified extracts and constituents from 85 individual medicinal plants that have demonstrated potential efficacy for treating psychiatric disorders based on animal behavioral models. A bioactive component called Linalool, isolated from the leaf oil of *Cinnamomum tamala* has been reported to possess anti-inflammatory and anti-nociceptive properties including attenuation of allodynia in neuropathic pain induced by spinal nerve ligation in mice **[31]**. Phytochemicals like resveratrol, curcumin, and salvianolic acid derived from traditional Chinese herb *Salvia miltiorrhiza*, have reported protecting neurons *in-vivo* and *in-vitro* by activation of PI3K/Akt pathways **[32].** Phyto-compounds like Amentoflavone, bilobalide, hesperetin, luteolin, naringenin, quercetin, and resveratrol derived from the leaf of *Ginkgo biloba* has been reported to protect neurons from cell death and memory deficits via binding to the ATP-binding site on enzymes and receptors and via activating PI3K/Akt and PKC **[33].**

Aegle marmelos, commonly known as Bael, can be classified as a functional food and in India, it is a highly reputed Ayurvedic medicinal tree that has been used in nervous disorder and as a tonic for brain **[34-35].** Methanolic extract of *A. marmelos* leaf possessed potential anxiolytic and antidepressant activities in albino mice and also may be served as a potential resource for natural psychotherapeutic agents **[36]**. The neuroprotective potential activity of ethanolic extract of *A. marmelos* leaf against streptozotocin-induced oxidative stress and cognitive deficit in rats indicated its therapeutic action in Alzheimer's diseases **[37].**

Peppers (*Capsicum spp*), is an important vegetable, widely consumed as a spice is rich in various phytochemicals like phenolics, alkaloids, and carotenoids, a natural pigment **[38-40]**. Water extractable phytochemicals from *Capsicum chinense* and *Capsicum annuum* var. *acuminatum* inhibited acetylcholinesterase and butyrylcholinesterase

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activities and also exhibited antioxidant activities by scavenging free radicals and inhibiting pro-oxidant induced lipid peroxidation in rat brain homogenate in vitro **[41]**.

Rosmarinic acid and its derivatives from *Melissa officinalis* plays a vital role for its antioxidant and neuroprotective actions and exhibited neurotrophic effect in the mechanisms that underlie memory-enhancing function by improving cholinergic activity **[42]** and the authors concluded that a variety of dietary phytochemicals that regulate neurodegenerative diseases by targeting neurotrophins might be a promising future **[43].**

Herbal coffees prepared from *Phoenix dactylifera* showed the highest enzyme inhibitory effects among the tested coffees obtained from *Gundelia tournefortii*, *Nigella sativa*, *Phoenix dactylifera*, and *Ceratonia siliqua* as well as a sample of instant coffee (Nescafe, green blend) **[44]**. The fruits of *Pistacia terebinthus* consumed in Turkey were explored for neuroprotective and antioxidant effects through enzyme inhibition tests against acetylcholinesterase, butyrylcholinesterase, and tyrosinase **[45]**.

Rhizomes of *Zingiber officinale*, commonly known as ginger and used as a spice, reported having the ability to inhibit enzymes like acetylcholinesterase and butyrylcholinesterase that linked to neurodegenerative diseases **[46].** It is also demonstrated **[47]** that ginger reverses behavioral dysfunction and prevents Alzheimer's like symptoms in the rat model. Sharma et al., **[48]** suggested that neuroprotective actions of zinger roots are mediated via its anticholinesterase activity and the experiment has been done for the treatment of Huntington's disease. The extract restored behavioral and biochemical changes induced by a neurotoxin, 3-nitropropionic acid.

An edible plant *Morinda citrifolia,* known as Noni, popularly used as food **[49]**. The antipsychotic-like activity of *M. citrifolia* in mice demonstrated the anti-dopaminergic effect, suggested that this plant has an antipsychotic-like activity that can be utilized in the treatment of psychiatric disorders **[50].** Another finding **[51]** suggested that Noni exhibits more obvious inhibitory effects on hydrocephalus-induced neurodegenerative disorder than memantine (has been used for the treatment of Alzheimer's disease) in periventricular tissue of the fourth ventricle. The neuroprotective effect of the Noni extract might occur partly via the improvement of oxidative stress status in the cortex **[52]**.

Silva and Pogacnik **[53]** stated that polyphenols are promising molecules for the prevention and treatment of neurodegenerative diseases and antioxidant-based mechanisms of polyphenols can modulate several cell-signaling pathways and mediators. Plant-derived polyphenols such as curcumin, resveratrol, propolis, ginsenoside, rosmarinic acid, and polyunsaturated fatty acids have been applied to numerous neurodegenerative diseases for their anti-oxidative and anti-inflammatory effects that have been widely confirmed *in-vivo* and *in-vitro* **[54].** Flavonoids belonging to the group of polyphenols, which are rich in vegetables, fruits, grains, and teas, have been investigated about their ability to prevent or reverse cognitive related deficits by numerous mechanism **[55-56].**

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Resveratrol has been reported to have powerful neuroprotective effects by several different studies and confirmed in neurodegenerative disorders like traumatic brain injury **[57-58]** and Alzheimer's disease, Parkinson's disease **[59].** Supplementation of resveratrol might enhance memory performance in older people, potential mechanisms have been addressing underlying this effect **[60].** Kennedy et al., **[61]** suggested that a single dose of orally administered resveratrol can modulate cerebral blood flow variables**.**

4. Discussions

In sum, the therapeutic effects of whole foods and plants as neuroprotective agents are becoming the attention of research by neuroscientists **[62-63]**. Kennedy and Wightman **[64]** in his review, have assessed the available evidence for the efficacy of plant-based extracts and phytochemicals that may improve brain function and also reach a conclusion to their potential effectiveness as nootropics. A review done by **Naoi et al. [65]** has studied multiple neuroprotective activities of phytochemicals via targeting oxidative stress, neuroinflammation, mitochondrial dysfunction, neurotrophic factor deficit, apoptosis, and accumulation of abnormal-modified protein**.** The authors in another study **[66]** also proposed phytobioactive polyphenols as one of the most promising mitochondria-targeting medicine to preserve the activity, structure of mitochondria, and neurons**.** Data accumulation **[67]** suggested that phytochemicals from fruits, vegetables, herbs, and spices may exert relevant immunomodulatory and anti-inflammatory activities in the context of brain aging and randomized controlled trials should be performed in humans to invent the real impact of dietary phytochemicals which can play a pivotal role in the prevention and treatment of neuro-inflammaging **[68]**.

4.1 Microbes, brain and food

The human intestinal microbiota (gut microbiome) has an important role in shaping brain functions and behavior **[69]**, and changes of the gut microbiome in people experiencing psychological illness such as schizophrenia and depression, as well as neurological disorders such as Parkinson's disease **[70],** and recent research has been reported on the role of gut microbiota in the development of autism spectrum disorders **[71].** Because of the food we eat can also influence the structure and activity of the gut microbiota **[72].** Different gut microbiota thrives on different foods to play multiple important roles in human physiology via extracting nutrients and energy from ingested foods and contributes to the immune function of the host **[73-74].** Dietary polyphenols have an important impact on brain modulation **[75]** and the biotransformation of polyphenols is needed to obtain metabolites (the small byproducts of microbial digestion, those can send signals to the brain) active in brain processed by the gut microbiota **[76]**.

4.2 Interaction between gut microbiome and medicinal plants

An et al., **[77]** has found two pathways while investigating the interaction between the gut microbiota and herbal medicines. One is the digestion of herbal medicines into absorbable active small molecules that enter the body to induce physiological changes and another pathway is the change of gut microbiota composition and its secretion by herbal medicines which induce pharmacological effects. Another review **[78]** study has summarized the interactions between gut microbiota and ethnomedicine constituents via highlighting the modulation of the gut microbiota profile by ingested natural compounds and the gut

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microbial conversion of natural products into the "daughter molecules" with potent bioactivities. Recent studies **[79-80]** are also suggesting that certain foods or the Mediterranean diet are associated with friendly gut microbiota that aids the biosynthesis of essential nutrients and the production of short-chain fatty acids. The influx of review studies indicates that the role and utilization of gut microbiome as therapeutic purposes and their correlations with the diet components in the management of neurologic disorders has become a fascination over the time for the research **[81-91].**

To be concluded, it is essential to emphasize on doing more research to outshine the insights of the role of medicinal plant-based foods and/or plant-derived bioactive components to the gut microbiota and their interaction mechanisms that impact on the brain function and to also elucidate the nutrition-gene interactions that exert neurological benefits, to optimize cognitive function and promote the plant-based personalized nutritional diets or personalized nutrition practices in the management of multiple devastating neurologic disorders that lead to mental wellness as well.

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