Role of Nutraceuticals in Neurodegenerative Diseases

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ABSTRACT

Nutraceuticals are food-derived compounds considered beneficial for human health. It has been recently shown that nutraceuticals play an important role in the regulation of brain physiology and in the prevention of neurodegeneration and cognitive decline. Nutraceuticals differ structurally and therefore act at different biochemical and metabolic levels and have shown different types of neuroprotective properties which include mitochondrial dysfunction, intracellular calcium overload, oxidative stress and inflammation. Nutraceuticals have recently gained importance owing to their multifaceted effects. These food-based approaches are believed to target at multiple pathways in a slow but more physiological manner without causing severe adverse effects.

Keywords: Nutraceuticals, neurodegeneration, mitochondria, calcium, oxidative stress.

INTRODUCTION

Neurodegenerative disease indicates a range of conditions which primarily affect the neurons. Neurons are building blocks of the nervous system and don’t reproduce or replace themselves. Neurodegenerative diseases are characterized by progressive degeneration or death of the neurons. Neurodegenerative diseases occur as a result of damage to the neurons. These diseases are associated with mutated genes, accumulation of abnormal proteins, increased reactive oxygen species or destruction of neurons in specific part of brain.

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(Received 13 May 2019, accepted 12 August 2019)
TYPES OF NEURODEGENERATIVE DISEASES

There are four types of neurodegenerative diseases which are shown in Figure 1.

Neurodegenerative diseases

Amyotrophic lateral sclerosis (ALS)

ALS is a disease of motor neurons of the anterior horns of spinal cord and motor neurons in the cerebral cortex. It is a specific disease which causes the death of neurons controlling voluntary muscles. It is characterized by stiff muscles and muscles twitching. It begins with weakness in the arms or legs or with difficulty in speaking or swallowing\(^1\). Excitotoxicity mediated by glutamate and elevated calcium ion is considered to be a major mechanism of neuronal death in ALS\(^2\).

Parkinson’s disease (PD)

It is an extrapyramidal motor disorder characterized by rigidity, tremor and hypokinesia with secondary manifestations like defective posture and gait, mask like face and sialorrhoea\(^3\).

It is characterized by,

- Degeneration of dopaminergic neurons that produces dopamine in basal ganglia.
- An imbalance between acetylcholine and dopamine in brain.
- Formation of lewy bodies.
- Loss of dopamine results in akinesia, rigidity and bradykinesia.
- Excess amount of acetyl choline result in tremor and sialorrhoea.

Alzheimer’s disease (AD)

AD is a neurological brain disorder which is the most common form of dementia and it is a group of disorders which impairs mental functioning\(^4\). It is progressive and irreversible. Memory loss is the earliest symptoms, along with gradual decline of other intellectual and thinking abilities, called cognitive functions and changes in personality or behavior.
It is characterized by,

- Decrease in acetylcholine levels in cerebral cortex and hippocampus which results in progressive and significant loss of cognitive and behavioral function.
- Deposition of amyloid plaques and neurofibrillary tangles.
- Microglial and astroglial activation which finally leads to neuronal dysfunction and death.

**Huntington’s disease (HD)**

HD is an inherited disease which results in death of the brain cells. As the disease advances, uncoordinated and jerky body moment become more apparent. Physical abilities gradually worsen until coordinated movement become difficult and the person is unable to talk. Mental abilities generally decline into dementia. The disease is caused by autosomal dominant mutation of a gene called huntingtin.

**MECHANISM OF NEURONAL DAMAGE**

There are several mechanisms recognized which leads to neurotoxicity as shown in Figure 2.

**Mitotoxicity mediated neuronal damage**

Pathophysiology of neurodegenerative diseases such as AD, ALS, PD and HD involves damage to mitochondria. Mitochondrial function is under the control of two genomes i.e. nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Mutation in either of these genomes can result in mitotoxicity-mediated neurodegeneration.

The neurotoxicant, 1 methyl-4-phenylpyridium(MPP+), generated from the mono amine oxidase MAO)- catalyzed oxidation of 1-methyl-4-phenyl-1,2,3,6-...
tetrahydropyridine (MPTP) within the brain which is concentrated inside the mitochondria of dopaminergic cells and inhibits complex I of the respiratory electron transport chain (ETC), which leads to the development of PD10.

Mutant huntingtin, the gene which is responsible for the development of HD, directly impair mitochondrial functions11. Defective mitochondrial complex I, II, III and IV were found in the postmortem tissue of HD patients12. Mitochondrial abnormalities also result in the neuronal damage in AD and ALS.

**Calcium overload-mediated neuronal damage**

In general, calcium in extracellular space remains in millimolar range, while inside the cell it remains in micromolar range13. Maintenance of intracellular Ca$^{2+}$ is very important for the survival of neuronal cells. If there is a sudden rise in intracellular Ca$^{2+}$, it triggers a cascade of neurotoxic events, including mitochondrial toxicity and cessation of ATP synthesis, over activation of several Ca$^{2+}$ dependent hydrolytic enzymes such as proteases, phospholipases, nuclease, nitric oxide synthase and phosphatases. These events lead to the onset of neurotoxicity, impaired neuronal functions and eventually death of the neuronal cells.

Accumulation of Ca$^{2+}$ in neuronal cells occur through several routes such as activation of voltage-sensitive Ca$^{2+}$ channel, receptor operated Ca$^{2+}$ channel (N-Methyl-D-Aspartate (NMDA)), ATP-dependent Ca$^{2+}$ channel, cyclic nucleotide-gated Ca$^{2+}$ channel, Ca$^{2+}$ channel coupled to G protein receptors. Plasma membrane, endoplasmic reticulum and mitochondria can only handle rise in intracellular Ca$^{2+}$ up to a certain extent but if there is a persistent rise in intracellular Ca$^{2+}$ it will lead to disturbances in endoplasmic reticulum and mitochondrial Ca$^{2+}$ homeostasis which results in neurodegenerative diseases14.

In AD, amyloid beta induced neuronal cell death is associated with deregulation of Ca$^{2+}$ dependent pathways15. In PD deregulation of intracellular Ca$^{2+}$ lead to the selective destruction of dopaminergic neurons16. In HD mutant huntingtin releases Ca$^{2+}$ from endoplasmic reticulum which results in neuronal death17.

**Oxidative stress-mediated neuronal damage**

Excessive production of reactive oxygen species (ROS) due to the imbalance of cellular biochemical process results in a condition known as oxidative stress18. ROS and reactive nitrogen species (RNS) mediated damage to cellular macromolecule is involved in the pathogenesis of neurodegenerative disease.

Neuronal degeneration and amyloid neurotoxicity in AD patients are associated with oxidative damage to DNA, RNA, proteins and lipids19. Oxidation of dopamine to a reactive 6-hydroxy dopamine results in the development of
Oxidative stress induced mutations in the gene encoding for ubiquitous Cu/Zn-superoxide dismutase (SOD-1) enzyme and damage to protein, lipid and DNA is associated with familial and sporadic forms of ALS. Increased incidence of oxidative DNA strand breaks and exacerbated lipofuscin, a pigment which is produced by the reaction of cellular amino compounds with aldehydic products of oxidative damage to the tissue macromolecule, is associated with HD.

**Inflammation mediated neuronal damage**

Macrophages are present in the brain near glia and microglia and plays a fundamental role in inflammation-mediated neurodegenerative diseases. In disease state, the activated microglia mediate neuronal injury through the production of pro-inflammatory factors such as cytokines and chemokines. Production of the cytokines and chemokines lead to the trans-endothelial migration of immune cells across the blood brain barrier.

There are several mechanisms identified for the microglia-mediated phagocytic and cytotoxic action which is responsible for neuronal damage. One of the major mechanisms is phagocytic oxidase mediated oxidative stress-induced neurotoxicity. Inflammatory activation of phagocytic oxidase results in activation of microglia which in result in production of TNF-α, IL-1β and inducible NO synthase (iNOS). iNOS results in increased NO production leading to neuronal death.

**CURRENT THERAPY FOR NEURODEGENERATIVE DISEASES**

The drug treatment for neurodegenerative diseases is shown in the Table 1. Though there are many pharmaceuticals available that improves the neuronal health, but the major disadvantage is that the chronic use of these pharmaceuticals is associated with multiple adverse effects as shown in Table 1. As a result nutraceuticals are used over pharmaceuticals which are cost effective, beneficial and include lesser or no adverse effects. Hippocrates the father of medicine said that “let food be your medicine and medicine be your food.”
Table 1. Drugs used in various neurodegenerative disease along with their mechanism of action and adverse effects.

| Neurodegenerative Disease | Drug             | Mechanism of Action                                                                 | Adverse Effect                                      |
|---------------------------|------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------|
| Amyotrophic lateral sclerosis (ALS) | Endaravone (Radicava) | Decreases the effect of oxidative stress                                              | Hypersensitivity reaction, respiratory failure, eczema |
| Parkinson’s disease       | Levodopa/Carbidopa (Sinemet) | Levodopa-metabolic precursor of dopamine, a neurotransmitter depleted in PD, crosses BBB and get converted to dopamine by striatal enzymes Carbidopa-inhibit aromatic amino acid decarboxylase which in turn inhibit the peripheral breakdown of levodopa | Edema, anxiety, ataxia, dyskinesia, confusion         |
| Alzheimer’s disease       | Rivastigmine (Exelon) | Reversible acetylcholinesterase inhibitor that cause increase in concentration of acetylcholine and enhances cholinergic neurotransmission | Tachycardia, seizure, allergic dermatitis, anorexia, headache, dizziness |
| Huntington’s disease      | Tetrabenazine (Xenazine) | Reversibly inhibit vesicular monoamine transporter type 2 resulting in decrease uptake of monoamine into synaptic vesicles and depletion of monoamine stores from nerve terminal | Sedation, fatigue, insomnia, depression, extrapyramidal events, anxiety, nausea |
**NUTRACEUTICALS**

Nutraceuticals is a term coined in 1979 by Stephen De Fliece. It is a term combining the word nutrition (a nourishing food or a food component) and pharmaceutical (a medical drug) as shown in Figure 3.

![Figure 3. Concept of Nutraceuticals](image)

Nutraceuticals is defined as a food or a part of food that provide medical or health benefit including the prevention and treatment of disease.

Food and nutrient play an important role in the normal functioning of body. They are helpful in maintaining the health and reducing the risk of various disease. They are medicinal foods that play a role in maintaining wellbeing, enhancing health, modulating immunity and thereby preventing as well as treating specific diseases. Thus, the field of nutraceuticals are emerging as one of the missing block in the health benefit of an individual and it has been scientifically proven that nutraceutical are efficacious to treat and prevent various disease condition.

**BENEFITS OF NUTRACEUTICALS**

The major benefits of nutraceuticals include lesser or no adverse effects.

- They help us to avoid taking medications.
- They are economically affordable, easily available and has multiple therapeutic effect.
- They increase the health value by improving medical condition of the individuals.
- They act on multiple pathways linked to the neuronal cell death.
CLASSIFICATION OF NUTRACEUTICALS

Nutraceuticals are classified on the basis of food source and chemical nature. Nutraceuticals are classified into seven different types based on food source as shown in Figure 4.

Dietary fibers
Plant origin substances present in food which are not digested and add bulk to the intestinal contents. Examples: Fruits, barley, oats, lignin, cellulose, pectin.

Probiotics
These are live microbial feed supplements which when administered in adequate dose, helps in improving the intestinal microbial balance of the host. Examples: Lactobacilli, bifidobacilli, sacromyces cervicea.

Prebiotics
These are the dietary ingredients that benefit the host by selectively altering the composition or metabolism of gut microbial flora. Examples: Chicory roots, banana, tomato and beans.

Polyunsaturated fatty acids
These may be,
Omega 3 fatty acids Examples: α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid.
Omega 6 fatty acid Examples: arachidonic acid found in sunflower, soyabean and corn.

Antioxidant
These include vitamin C, vitamin E and carotenoids. These vitamins are abun-
dant in many fruits and vegetables and possess singlet oxygen quenching and lipid peroxidation preventing properties.

**Polyphenols**

These phytochemicals are produced by plant for protection against photosynthetic stress and reactive oxygen species. Examples: Flavonoids, anthocyanins and phenolic acids.

**Species**

These are food adjuncts used to enhance sensory quality of foods. Most of the components of spices are terpenes and essential oils.

**Classification of nutraceutical based on chemical nature**

Table 2 shows the classification of nutraceuticals based on their chemical nature.

| S. No | Class/component | Source |
|-------|-----------------|--------|
| 1     | Fatty acids     | Milk and meat |
| 2     | Omega-3 fatty acids (DHA, EPA) | Fish oils, maize, mustard and grape seed |
| 3     | Polyphenols     | Fruits |
|       | - Anthocyanidine | Tea, mustard seed, grape seed |
|       | - Catechins     | Citrus fruits |
|       | - Flavonone     | Fruits, vegetables, soyabean |
|       | - Flavones      | Cocoa, chocolate, tea, grape |
|       | - Proanthocyanidine | |
| 4     | Saponins        | Soya bean, chick pea |
| 5     | Phytoestrogen   | Soya bean, flax, lentil seed, maize |
|       | - Diadzein, Zenistein | Flax, rye, vegetables |
|       | - Lignans       | |
| 6     | Carotenoids     | Carrot, maize, oats |
|       | - β-carotene    | Fruits, vegetables |
|       | - Luteine       | Eggs, citrus fruits, corn |
|       | - Zeoxanthine   | Tomatoes |
|       | - Lycopene      | |
| 7     | Isothiocyanate  | Broccoli |
|       | - Sulforphane   | |
ROLE OF NUTRACEUTICAL IN NEURODEGENERATIVE DISEASES

Docosahexaenoic acid

- It is an essential omega 3 polyunsaturated fatty acid that is found in marine fish. Mechanism of action:
  - It produces anti-inflammatory effect by decreasing the production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α and inhibits NF-κβ transcriptional activity.
  - It decreases Aβ secretion from neuronal cells
  - It is an important modulator for dopaminergic neuron in basal ganglion.

Resveratrol

- It is a polyphenolic phytoalexin, present in grapevines and legumes such as peanuts and tea. It exists in two geometric isomers, cis resveratol is unstable while trans resveratrol is biologically more active.
  - It has a strong ability to remove free radicals due to the presence of OH group in position 3, 4 and 5 aromatic rings and a double bond in the molecule.
  - It reduces Aβ induced neuronal loss and memory impairment through reduction of iNOS expression.
  - Acts as a free radical scavenger
  - Increases 5-HT activity

Epigallocatechin gallate

- It is also known as epigallocatechin-3-gallate. It is the ester of epigallocatechin and gallic acid and is a type of catechin. It is mostly abundant in tea and also trace amount are fond in apple skin, plum, onion and hazel nut.

Curcumin

Curcumin is a diaryl heptanoid polyphenol isolated from the rhizomes of Curcuma longa L. (Zingiberaceae) and it is one of the most commonly used natural remedies in traditional medicine. The main constituent found in Turmeric is curcumin, which has numerous health benefits, including anti-inflammatory, antioxidant and neuroprotective properties. It has been extensively studied in the context of Alzheimer’s disease and Parkinson’s disease. The mechanism of action includes the modulation of various signaling pathways involved in neurodegeneration, such as the inhibition of NF-κβ, reduction of inflammatory cytokines, and modulation of oxidative stress and mitochondrial function. Additionally, curcumin has been shown to enhance synaptic plasticity and improve cognitive function in various preclinical models of neurodegeneration. Its neuroprotective effects are likely due to its ability to cross the blood-brain barrier and directly interact with neuronal cells. Overall, curcumin offers a promising therapeutic strategy for the management of neurodegenerative diseases.
Cuma longa. It has multiple activities and it is effective against wide variety of diseases due to its anticarcinogenic, hepatoprotective, cardioprotective and neuroprotective properties.

**Mechanism of action:**
- It is a potent antioxidant because of its capacity to scavenge free radicals due to the presence of its unique structure which can donate H atoms or transfer electron from the phenolic sites.
- It also has anti-inflammatory activity as it inhibits lipopolysaccharide induced morphological changes of microglia and decreases the production of pro inflammatory factors.
- Restores glutathione levels which protect neurons against protein oxidation and preserves mitochondrial complex-I activity.

**Sulforphane**

Sulforphane is a compound within the isothiocyanate group of organosulfur compounds. It is obtained from cruciferous vegetables such as broccoli and cabbages.

**Mechanism of action:**
- In AD it increases acetylcholine levels and decreases acetylcholinesterase activity and also increases acetylcholine transferase expression in hippocampus and frontal cortex.
- It decreases ROS and inhibit pro inflammatory signaling through NF-kβ.

**Anthocyanin**

- It is a polyphenol. Plants rich in anthocyanin include blueberry and raspberry. Mechanism of action:
  - It negatively regulates pro inflammatory cytokines signaling pathway.

**Apigenin**

Apigenin is a flavonoid found in the flower of chamomile plants and also in celery, parsley and peppermint.

**Mechanism of action:**
- It shows potent antioxidant antipoptotic activity by protecting neuronal cells that are subjected to oxygen and glucose deprivation.
Coenzyme Q 10

It is also known as ubiquinone. It is a coenzyme that is ubiquitous in animals and most bacteria.

Mechanism of action:

Potent antioxidant that can reduce oxidized form of α-tocopherol to prevent lipid peroxidation.

Maintain proper transfer of the electrons in electron transport chain of mitochondria and ATP production.

α-lipoic acid

It is chemically synthesized, but also considered as a natural compound as it is a naturally occurring precursor of essential cofactors for mitochondrial enzymes including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. It is a low molecular weight compound which easily crosses blood brain barrier (BBB). After crossing BBB, it is absorbed into the cells and reduced to dihydrolipoate acting as a potent antioxidant.

Mechanism of action:

- It increases acetylcholine production in AD
- It inhibits the formation of hydroxyl radicals and ROS and increases the level of reduced glutathione.
- It can scavenge lipid peroxidation products.

Vitamin C

It is also known as ascorbic acid, is a water-soluble vitamin which is naturally present in some foods and also available as a dietary supplement. It is an important physiological antioxidant and has been shown to regenerate other antioxidants within the body.

Mechanism of action:

- Free radical scavenger in the cytosol.

Vitamin E

Vitamin E is a fat-soluble vitamin that plays a role as an antioxidant in the body.

Mechanism of action:

- It prevents lipid peroxidation.
**Ginsenoside**

It is a phytoestrogen, which belongs to a class of molecules extracted from several species of ginseng.

**Mechanism of action:**
- It maintains glutathione levels.
- It prevents elevation of iron levels by regulating the expression of iron transport proteins.

**Genistein**

It is a phytoestrogen found mainly in soy and peanuts.

**Mechanism of action:**

It increases the levels of malondialdehyde, superoxide dismutase and monoamine oxidase and exhibit antioxidant activity.

**CONCLUSION**

In recent years there is a growing interest in nutraceuticals which provide health benefits and are alternative to modern medicine. By using nutraceuticals, it may be possible to reduce or eliminate the need for conventional medications and reducing the chances of any adverse effects. Nutraceutical is demonstrated to have a physiological benefit and provide protection against neurodegenerative diseases.

**CONFLICT OF INTEREST**

There is no conflict of interest between the authors.

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