Plants and phytochemicals for Huntington’s disease

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ABSTRACT

Huntington’s disease (HD) is a neurodegenerative disorder characterized by progressive motor dysfunction, including chorea and dystonia, emotional disturbances, memory, and weight loss. The medium spiny neurons of striatum and cortex are mainly affected in HD. Various hypotheses, including molecular genetics, oxidative stress, excitotoxicity, metabolic dysfunction, and mitochondrial impairment have been proposed to explain the pathogenesis of neuronal dysfunction and cell death. Despite no treatment is available to fully stop the progression of the disease, there are treatments available to help control the chorea. The present review deals with brief pathophysiology of the disease, plants and phytochemicals that have shown beneficial effects against HD like symptoms. The literature for the current review was collected using various databases such as Science direct, Pubmed, Scopus, Sci-finder, Google Scholar, and Cochrane database with a defined search strategy.

Key words: Brahmi, Celastrol, Ginkgo biloba, Sesamol, Withania somnifera

INTRODUCTION

George Huntington, an Ohio physician, first described Huntington’s chorea or Huntington’s disease (HD). It is an autosomal dominant inherited neurodegenerative disorder characterized by progressive motor dysfunction, including chorea and dystonia, emotional disturbances, memory, and weight loss.[1-3] The pathological alterations mainly affect the medium spiny neurons (MSNs) of striatum, and to lesser extent of cortex. There is also loss of γ-amino butyric acid (GABA) and enkephalin neurons of basal ganglia in HD, along with modifications in the number of N-methyl-D-aspartate (NMDA) receptors.[2-4] HD is also caused by expansion of the Cytosine-Adenine-Guanine (CAG) repeats which leads to the formation of polyglutamine stretch. The CAG repeat length and the onset age for HD are inversely correlated to each other.[1] Death normally occurs 15–20 years after the first appearance of symptoms.[6] Various biochemical alterations [Figure 1] found in the caudate of patients with HD include decreased GABA and acetylcholine (ACh) levels, and their synthesizing enzymes glutamate decarboxylase (GAD), and choline-acetyl transferase (CAT), respectively. There is also a decrease in the concentration of certain peptides that are present specifically in middle-sized spiny neurons.[7,8]

HD currently occurs in many different countries and ethnic groups across the globe.[9] It has a worldwide prevalence of five to eight per 100,000 people with no gender predominance. Europe and countries of European origin have utmost frequencies of HD. In the USA, estimates of the prevalence of HD range from 4.1 to 8.4 per 100,000 people.[10,11] In India, pervasiveness of HD is higher and is closer to that occurs in Western Europe.[12] In the present review, an attempt has been made to highlight various plants and phytochemicals that have shown beneficial effects against this neurodegenerative disorder. Evidences used are mostly details from researches on animal models or on bioactive principles.

CLINICAL CHARACTERISTICS

The whole course of HD progression has been divided into three major stages based on the severity of the disease: Early, middle, and late. HD is usually associated with the triad of motor, cognitive, and emotional disturbances.

Motor symptoms
The movement difficulties are associated with involuntary...
movements and abnormal voluntary movements. The involuntary movements usually follow a biphasic pattern, initially hyperkinetic that increase with time, followed by bradykinesia leading to severe hypokinesia and rigid-kinetic state. Characteristic abnormal involuntary movements involve Chorea, or choreathetosis, which consist of continuous and irregular jerky or writhing motions.

**Non-motor symptoms**
Patients suffering from HD have particular and distinctive cognitive impairments. The nature of the progressive cognitive disorder is “frontal-subcortical”, and is also called as subcortical dementia. Common cognitive features include bradyphrenia, defective recall, deterioration of complex intellectual functions, difficulty in executing functions, and personality changes. Apart from various cognitive abnormalities, various other psychiatric disturbances such as depression, anxiety, irritability, aggression, impulsivity, and tendency to suicide are also the key features of HD.

**PATHOLOGICAL FEATURES OF HD**

**Oxidative stress in HD**
Oxidative stress (OS) is a mainstay of the pathology of neurodegenerative disorders. In neurodegenerative diseases, high levels of reactive oxygen species (ROS) generation and decreased activity of anti-oxidant mechanisms leads to neuronal cell death. Oxidative stress leads to lipid peroxidation, protein oxidation, deoxyribonucleic acid (DNA) mutation, and oxidation causing damage to nerve cells. Various studies have shown a significant increase in levels of 8-hydroxydeoxyguanosine (an oxidized DNA marker) in the caudate, mitochondrial DNA (mtDNA) of the parietal cortex of HD patients, and in forebrain tissue and striatum of rodents. Elevated levels of malondialdehyde (MDA), a marker of lipid peroxidation, 3-nitrotyrosine, and heme-oxygenase have also been observed in the brain of HD patients and rodents. OS also promotes mutant Huntingtin aggregation and mutant Huntingtin-dependent cell death by mimicking proteosomal malfunction. Increased levels of free radicals impair mitochondrial functions, energy production, and metabolic inhibition predisposes to excitotoxic damage. The studies mentioned above clearly indicate the OS plays an important role in pathogenesis of HD but a direct association between OS and HD has not been reported.

**Excitotoxicity**
It is one of the suppositions that have been set forth to explain the degeneration of spiny projection neurons of the striatum in HD. According to this hypothesis, there is excessive activation of glutamate receptors and decreased uptake of glutamate by glia or hypersensitivity of post-synaptic glutamate receptors on striatal projection neurons. These biochemical changes, along with pathological signaling downstream of glutamate receptor activation (due to altered intracellular calcium homeostasis) and mitochondrial dysfunction, results in neuronal dysfunction and death of striatal MSNs.

**Metabolic dysfunction and mitochondrial impairment in HD**
Mitochondria, the power source of the cell, are the sites of oxidative phosphorylation and cellular respiration leading to generation of adenosine triphosphate (ATP). They also play a significant role in the maintenance of a low concentration of calcium within the cytosol. Mitochondrial dysfunction, leading to decreased mitochondrial oxygen consumption, glucose metabolism, and levels of cyclic adenosine monophosphate (cAMP) in the cerebrospinal fluid (CSF), has been reported in individuals affected from HD and in HD post-mortem brain. Further, there is an augmentation in the lactate levels in the CSF as well as in cerebral cortical tissue. Deregulation of mitochondrial function by a mitochondrial toxin, 3-nitropropionic acid (3-NP), causes metabolic impairment due to energy impairment, oxidative stress, and excitotoxicity leading to cytotoxicity mainly in the striatum despite the fact that metabolic impairment actually occurs throughout the entire body and brain. All these changes due to mitochondrial dysfunction also make striatal neurons sensitive to excitotoxicity in HD.

**Protective effects of herbs and secondary metabolites in HD**
Nature is the best combinatorial chemist and possibly has answers to all diseases of mankind. Many of the thousands of plant species growing throughout the world have a direct pharmacological action on the body. Natural compounds with the effects of anti-oxidant, anti-inflammation, calcium antagonization, anti-apoptosis, and neurofunctional regulation exhibit preventive or therapeutic effects on various neurodegenerative diseases. Some of the plants and phytochemicals that have shown efficacy against 3-NP-induced neuronal impairment, a widely used animal model for HD, are discussed below:
Bacopa monnieri

Bacopa monnieri (BM) or Herpestis monniera, commonly known as Brahmi (Fam: Scrophulariaceae), is found throughout the Indian subcontinent and is classified as a medhyarasayana in Ayurveda. It is used for the treatment of epilepsy, insomnia, anxiety, and as memory enhancer for centuries.

The major chemical constituents present in the plant are dammarane type of tri-terpenoid saponins, Bacosides A and B. Apart from these major constituents, it also contains various types of saponin including bacopasaponin A-G along with pseudojujubogenin, jujubogenin. The plant has also been reported to contain brahmine, herpestine, and monnierin. Ample reports have shown memory enhancing effects of the plant. Among various constituents, Bacoside A has shown to improve memory. Various clinical trials have also shown beneficial effects of Brahmi in improving

![Various chemical constituents](image-url)
memory. The neuroprotective and memory enhancing effects of BM extracts have been reported due to several mechanisms such as chelation of metal ions, scavenging of free radicals and enhanced antioxidative defense enzymes. Besides this, it also displays antioxidant, anti-inflammatory, anti-stress, anxiolytic, free radical scavenging capacity, hepatoprotective, and antiulcerogenic activity.

3-NP inactivates the mitochondrial enzyme succinate dehydrogenase (SDH) and complex II-III of the electron transport chain. It also increases the levels of ROS, MDA, and free fatty acids, suggesting the vital role of oxidative stress in the manifestation of neurotoxicity. The dietary intake of BM leaf powder significantly decreased the basal levels of several oxidative markers, enhanced thiol levels (dehydrogenase and isopelletierine), and upregulated striatal glyceraldehyde-3-phosphate dehydrogenase activity.

**Ginkgo biloba (maidenhair tree, family: Ginkgoaceae)**

*Ginkgo biloba* L. was mentioned in Chinese Materia Medica 5,000 years ago. Since ginkgo tree is known to be among the oldest living species on this planet, it is called a “living fossil”. The chemical constituents present in the leaf are the tritaconic diterpenes: Ginkgolide A-C, Ginkgolide J-M; a tritaconic sesquiterpene: Bilobalide; flavonoids including quercetin, kaempferol,isorhamnetins, and biflavonoids (amentoflavone, bilobetin, 5-methoxybilobetol, ginkgetin, isoginkgetin, and sciadopitysin); and proanthocyanidins. Ginkgo leaf extract has exhibited protective effects against neurodegenerative diseases like dementia (Alzheimer’s disease), cardiovascular diseases, cancer, stress, tinnitus, geriatric complaints like vertigo, age-related macular degeneration, and psychiatric disorders like schizophrenia. These versatile activities of the Ginkgo leaf extract are due its antioxidant effect, anti-platelet activating factor (Anti-PAF) activity (cardio and cerebral vascular diseases), inhibition of beta amyloid peptide (Aβ) aggregation (prevent Alzheimer’s progression), decreased expression of peripheral benzodiazepine receptor (stress alleviation), and stimulation of endothelium derived relaxing factor (improve blood circulation). The *G. biloba* extract (100 mg/kg, i.p. for 15 days) improved the 3-NP induced neurobehavioral deficit and also decreased the level of striatal MDA. Standardized *G. biloba* extract (EGB 761) also caused down- and up-regulation of striatal glyceraldehyde-3-phosphate dehydrogenase and Bcl-xl expression levels, respectively. These biochemical results, supported by the histopathological studies suggested neuroprotective role of EGB 761 in HD.

**Ashwagandha (Fam: Solanaceae),** has been used since ages in Ayurvedic medicine to increase longevity and vitality. The plant has reported for its antioxidant, anti-inflammatory, immune-modulating, anti-stress, memory enhancing, and anti-convulsant properties. As an antioxidant, WS and its active constituents (sitoindosides VII-X and withaferin A) increase the levels of endogenous superoxide dismutase, catalase, and ascorbic acid, and decrease lipid peroxidation. It acts as an anti-inflammatory agent through inhibition of complement, lymphocyte proliferation, and delayed-type hypersensitivity. Various studies have shown that WS increase circulating cortisol, decrease fatigue, increase physical performance, and decrease refractory depression in stress. It also modulates various neurotransmitter receptor systems in the CNS. Recently, WS has been found beneficial in 18 clinically diagnosed Parkinson’s patients.

Chemical analysis of *Ashwagandha* shows that it mainly contains steroidal lactones (collectively known as withanolides) and alkaloids. The important withanolides isolated from plant are withaferin A, withanolide A, withanolide D-P, withanone, sitoindoside VII-X [Figure 2]. Various alkaloids that have been reported from WP are withanine (major alkaloid), somniferine, somnine, somniferinine, withanamine, pseudo-withanine, tropine, pseudo-tropine, 3-glyoxyloxytropane, choline, cuscohygrine, isopelletierine, afanerine, anahydrine, and anahydrine.

Role of GABAergic in the pathogenesis of HD has been well documented and WS has been well reported to act by GABAergic system. WS root extract pretreatment significantly improved cognitive function, restored acetyl cholinesterase enzyme activity and glutathione enzyme level system in 3-NP treated animals. The root extract of WS exhibited possible neuroprotective effect against a 3-NP-induced neurotoxicity in rats due to its GABAergic and antioxidant action and make it a suitable lead in the treatment of HD.

**Curcuma longa**

*Curcuma longa* (CL), commonly known as *Haldi* or turmeric, is a perennial herb of family Zingiberaceae. Its rhizomes have been used since ages in the traditional medicinal system of India, China, Japan, and other South Asian countries. It has a long history of use as a spice and a household remedy for the treatment of inflammation, skin diseases, wounds, and as an antibacterial and antiseptic.

CL contains yellow coloring matter, various curcuminoids, sesquiterpenes, essential oil, and starch. Most of the curcuminoids are diarylheptanoid, a derivative of which curcumin is the major bioactive component. The other two curcuminoids are desmethoxycurcumin, and bis-desmethoxycurcumin [Figure 2]. Curcumin has antioxidant, anti-inflammatory, antifungal, antibacterial, antiparasitic, choleretic, analgesic, hepatoprotective, free
radical scavenging, iron chelating, antiviral, and anti-mutagenic activity. Various mechanisms like direct scavenging activity of superoxide, hydroxyl radicals, metal chelating property and ability to induce antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, and heme-oxygenase) have been responsible for the antioxidant potential of CL. Its anti-inflammatory property may be related to its ability to inhibit upregulation of cyclooxygenase (COX)-2. Furthermore, it showed neuroprotective action in various neurological disorders. Curcumin and manganese complex of curcumin offer protective action against vascular dementia by virtue of its antioxidant activity, and is useful in the treatment of aging and memory dysfunctions. Chronic administration of curcumin consistently improved body weight, reversed motor deficits, and increase SDH activity in 3-NP treated rats. The improved 3-NP-induced motor and cognitive impairment along with a strong antioxidant property indicates that curcumin could be useful and can act as a lead molecule in the treatment of HD.

Ginsenosides

Ginseng root is a well-known herbal medicine and has been used as a representative tonic for over 2,000 years in the far eastern countries like China, Japan, and Korea. Asian ginseng (Panax ginseng C. A. Meyer) and American ginseng (Panax quinquefolium L.) belonging to family Araliaceae are the most common ginseng species. Ginseng contains a series of tetracyclic dammarane triterpenoid saponin glycosides called, ginsenosides, which are active constituents of the drug. Ginsenosides, depending on their structural differences, are classified into three categories: the panaxadions (e.g., Rb1-Rb3, Rc, Rd, Rg3, Rh2, and Rg1), panaxatriols (e.g., Re, Rf, Rg1-2, and Rh1) and oleanolic acid derivatives (e.g., Ro). Ginseng has been used primarily as a tonic to revitalize weak bodies and help the restoration of proper metabolism in the body. Various studies (in vitro and in vivo) have exhibited beneficial effects of ginseng in several pathological conditions such as cardiovascular diseases, CNS disorders, cancer, immune deficiency, and hepatotoxicity. It has also been reported that ginseng and some of its active constituents also exert beneficial effects on aging and neurodegenerative diseases. It also possesses antioxidant, anti-apoptotic, anti-inflammatory, and immune-stimulatory activities. It also reduces lipid peroxidation, inhibits excitotoxicity, and Ca²⁺ over-influx into neurons, maintains cellular ATP levels, preserves structural integrity of neurons, and increase cognitive performance. Ginsenoside Rb1 and Rg3 have exhibited protective effects on cortical neurons against glutamate-induced cell death by blocking Ca²⁺ influx through glutamate receptors. Saponins from ginseng also inhibit both NMDA and glutamate-induced increase Ca²⁺ levels in rat hippocampal neurons. Ginsenosides Rb1, Rb3, and Rd have exhibited neuroprotective effect against 3-NP-induced striatal neuronal damage. Ginsenoside Rb1, Rc, and Rg3 have shown to protect medium spiny neurons from glutamate-induced apoptosis in genetically modified rodents. It has been hypothesized that neuroprotective effect of these ginsenosides could be due to their ability to inhibit glutamate-induced Ca²⁺ responses in cultured spinal neuronal cultures. Such reports strongly support that potential of ginseng and ginsenosides can be exploited in developing new therapeutics for the treatment of HD and other neurodegenerative disorders.

Centella asiatica (syn. Hydrocotyle asiatica)

Centella asiatica (CA), commonly known as Gotu kola, Indian Pennywort and Jal brahmi, belongs to family Umbelliferae. It has been categorized as Rasayanas in Ayurveda due to its ability to improve memory and age related brain disorders. Studies have shown various neuropharmacological effects of CA which comprises of memory enhancement, increased neurite elongation and acceleration of nerve regeneration. It also possesses anti-oxidant property. The most important chemical constituents from CA are triterpenoid saponins including asiaticoside, asiatic acid, madecassoside, and madecassic acid [Figure 2]. Other saponins present in minor quantities are brahmoside and brahminoside. Various triterpene acids, betullic acid, brahmic, and isobrahmic acid are reported from the plant. The essential oil from the leaves of the plant contains monoterpens, including bornyl acetate, α-pinene, β-pinene, and γ-pinene. Apart from these constituents flavones, sterols, and lipids have also been reported from CA.

CA attenuated the 3-NP-induced depletion of GSH levels, total thiols, and endogenous antioxidants in striatum and other brain regions. It also exhibited protection against 3-NP-induced mitochondrial dysfunctions viz., reduction in the activity of SDH, electron transport chain enzymes, and decreased mitochondrial viability. The results of this study clearly indicate that the protective effect of CA against neuronal damage induced by OS and mitochondrial dysfunctions along with its memory enhancing activity can be helpful in controlling HD-related impairments.

Flavonoids

Flavonoids are a group of polyphenolic compounds, distributed throughout the plant kingdom. They possess a common phenylbenzopyrone structure (C6-C3-C6). Flavonoids exhibit several biological effects such as anti-inflammatory, anti-hepatotoxic, anti-ulcer, anti-allergic, and antiviral actions. They are potent antioxidants and have free radical scavenging abilities by virtue of their aromatic hydroxyl groups.

Recent studies, both pre-clinical and clinical, suggested that flavonoids prevent and delay neurodegeneration (especially in aged-population), cognitive dysfunction, mood decline, and
oxidative pathologies.\textsuperscript{[144]} They also exert protective action against peroxynitrite-induced oxidative damage.\textsuperscript{[145]} Flavonoids inhibit nitric oxide synthase (involved in neurodegenerative process including HD),\textsuperscript{[146-148]} cyclooxygenase expression,\textsuperscript{[147]} protect against oxidative stress,\textsuperscript{[148]} and modulate calcium homeostasis.\textsuperscript{[144]} These polyphenols act by direct scavenging of various ROS and reactive nitrogen species.\textsuperscript{[144,149]} Antioxidants have shown beneficial effects against 3-NP induced toxicity possibly by free radical scavenging activity (decreases MDA and nitrite concentration) and increased endogenous antioxidant defense (increased levels of superoxide, catalase, and glutathione).\textsuperscript{[99,150,151]} Various flavonoids such as naringin,\textsuperscript{[149]} hesperidin,\textsuperscript{[149]} kaempferol,\textsuperscript{[152]} and epigallocatechin gallate (EGCG)\textsuperscript{[153,153]} have been reported to provide beneficial effects against 3-NP-induced neurotoxicity.

**Celastrol**

Celastrol [Figure 2] is a triterpenoid quinone methide isolated from *Tripterygium wilfordii* (Thunder of God vine) and *Celastrus regelii* belonging to the Celastraceae family, exhibits antioxidant (15 times the potency of α-tocopherol),\textsuperscript{[154]} anti-inflammatory,\textsuperscript{[155]} anticancer,\textsuperscript{[156]} and insecticidal\textsuperscript{[157]} activities. It is known to prevent the production of pro-inflammatory cytokines, inducible nitric oxide synthase, and lipid peroxidation. Celastrol attenuated the loss of dopaminergic neurons and dopamine depletion in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated rodents.\textsuperscript{[158]} It also protect from 3-NP-induced striatal damage by regulating heat shock protein (hsp) gene expression in dopaminergic neurons.\textsuperscript{[158,159]} The above reports indicate celastrol to be a promising neuroprotective agent against Parkinson’s disease and HD.

**Trehalose**

It is a non-reducing disaccharide found in many organisms, including bacteria, yeast, fungi, insects, invertebrates, and plants. It is a natural hemolymph sugar of invertebrates and protects the integrity of cells by preventing protein denaturation due to various environmental stresses.\textsuperscript{[160,161]} Though it is not synthesized in mammals, still it has exhibited various beneficial effects in them.\textsuperscript{[162]} Various reports have shown that it inhibits amyloid formation,\textsuperscript{[162]} aggregation of β-amyloid,\textsuperscript{[163]} polyglutamine (polyQ)\textsuperscript{3}-mediated protein aggregation, and decreased Huntington aggregates-induced toxicity. It also alleviated polyQ-induced pathology in the R6/2 mouse model of Huntington disease by stabilizing the partially unfolded mutant protein.\textsuperscript{[164,165]} It has also been reported that trehalose increase the autophagic activity against various aggregation proteins such as mutant Huntingtonin, thereby, by providing nueroprotective activity against HD.\textsuperscript{[165]} Hence, both properties of trehalose (inducer of autophagy and chemical chaperone) can be utilized in developing a new therapeutic agent for HD.\textsuperscript{[165]}

**Lycopene**

It is a well-known carotenoids present in considerable amounts in tomatoes and tomato-based products.\textsuperscript{[166]} Several studies have reported their therapeutic potential against oxidative stress and its related pathologies, including HD.\textsuperscript{[167,168]} It has been reported to possess potent neuroprotective,\textsuperscript{[169]} antioxidant,\textsuperscript{[170]} antiproliferative, anticancer,\textsuperscript{[171]} anti-inflammatory,\textsuperscript{[172]} memory enhancing,\textsuperscript{[173]} and hypocholesterolemic activities.\textsuperscript{[174]} Lycopene is more powerful carotenoid quencher of singlet oxygen with respect to vitamin E and glutathione.\textsuperscript{[172]} Lycopene treatment significantly attenuated various behavioral and biochemical changes-induced by 3-NP, suggesting its therapeutic potential against HD-like behavior.\textsuperscript{[175]} The results of the study clearly indicated that lycopene exhibited its protected effect through its antioxidant property and nitric oxide pathway.\textsuperscript{[151,175]}

**Sesamol**

*Sesamum indicum* Linn. (Pedaliaceae), commonly known as sesame, has been used as a health food in India and other East Asian countries.\textsuperscript{[176]} Sesamol [Figure 2], one of the main constituents in sesame oil, is responsible for its antioxidant activity.\textsuperscript{[177]} Sesamol has shown to control increased blood pressure, hyperlipidemia and lipid peroxidation (by increasing enzymatic and non-enzymatic antioxidants),\textsuperscript{[176]} and a strong antitumor action.\textsuperscript{[178]} It has been reported that sesamol exhibited its protective effect through nitric oxide mechanism (suppression of inducible nitric oxide synthase (iNOS) expression).\textsuperscript{[179]} It also attenuated 3-NP-induced Huntington-like behavioral, biochemical, and cellular alterations in rodents.\textsuperscript{[180]} It also protects against 3-NP-induced memory impairment,\textsuperscript{[152]} oxidative stress, neuroinflammation in hippocampus neurons, and consequently improves synaptic plasticity and neurotransmission.\textsuperscript{[181]} It also inhibits nitrite production and inducible NOS expression in the liver of septic rats.\textsuperscript{[182]} Protective effect of sesamol against 3-NP induced HD like symptoms can make it a lead molecule against HD. Detailed and mechanistic based studies are still warranted.

**Conclusion**

The above data clearly indicates that the oxidative stress plays a significant role in the pathophysiology of HD. Further, the plants having well established antioxidant and neuroprotective effects have shown beneficial effects against the symptoms of HD in both *in vivo* and *in vitro* studies. Still ample work is required to fully elucidate the mechanism of these plants and phytochemicals against HD. Furthermore, lot of other plants with significant antioxidant and neuroprotective potential can be explored for their protective effect against HD.
REFERENCES

1. Krobitsch S, Kazantsev AG. Huntington’s disease: From molecular basis to therapeutic advances. Int J Biochem Cell Biol 2011;43:20-4.
2. Kumar P, Kalonia H, Kumar A. Huntington’s disease: Pathogenesis to animal models. Pharmacol Rep 2010;62:1-14.
3. Sawa A, Tomoda T, Bae BI. Mechanisms of neuronal cell death in Huntington’s disease. Cytogenet Genome Res 2003;100:287-95.
4. Zadori D, Geisz A, Vamos E, Vecsei L, Klivenyi P. Valproate ameliorates the survival and the motor performance in a transgenic mouse model of Huntington’s disease. Pharmacol Biochem Behav 2009;94:148-53.
5. Ellerby LM. Hunting for excitement: NMDA receptors in Huntington’s disease. Neuron 2002;33:841-2.
6. Ross CA, Margolis RL. Huntington disease. American College of Neuropsychopharmacol; 2002.
7. Perez-De La Cruz V, Santamaria A. Integrative hypothesis for huntington’s disease: A brief review of experimental evidence. Physiol Res 2007;56:513-26.
8. Shoulson I. Huntington’s disease. A decade of progress. Neurol Clin 1984;2:515-26.
9. Kent A. Huntington’s disease. Nurs Stand 2004;21:45-51.
10. Kumar P, Naidu PS, Padi SS, Kumar A. Huntington’s disease: A review. Indian J Pharm Edu Res 2007;41:287-94.
11. Harper PS. The epidemiology of Huntington’s disease. Hum Gen 1992;89:365-76.
12. Jha S, Patel R. Some observations on the spectrum of dementia. Neurol India 2004;52:213-4.
13. Strurock A, Leavitt BR. The clinical and genetic features of Huntington disease. J Geriatr Psychiatry Neurol 2010;23:243-59.
14. Purdon SE, Mohr E, Ilivitsky V, Jones BD. Huntington’s disease: Pathogenesis, diagnosis and treatment. J Psychiatry Neurosci 1994;19:359-67.
15. Phillips W, Shannon KW, Barker RA. The current clinical management of Huntington’s disease. Mov Disord 2001;17:1491-504.
16. Farooqui T, Farooqui AA. Aging: An important factor for the pathogenesis of neurodegenerative diseases. Mech Aging Dev 2009;130:203-15.
17. Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol Sin 2009;30:379-87.
18. Bogdanov MB, Andreassen OA, Dedeoglu A, Ferrante RJ, Beal MF. Increased oxidative damage to DNA in a transgenic mouse model of Huntington’s disease. J Neurochem 2001;79:1246-9.
19. Tabrizi SJ, Workman J, Hart PE, Mangiarini L, Mahal A, Bates G, et al. Mitochondrial dysfunction and free radical death in the Huntington R6/2 transgenic mouse. Ann Neurol 2000;47:80-6.
20. Polidori MC, Mecacci P, Browne SE, Senin U, Beal MF. Oxidative damage to mitochondrial DNA in Huntington’s disease parietal cortex. Neurosci Lett 1999;272:53-6.
21. Browne SE, Bowling AC, MacGarvey U, Baik MJ, Berger SC, Muqit MM, et al. Oxidative damage and metabolic dysfunction in Huntington’s disease: Selective vulnerability of the basal ganglia. Ann Neurol 1997;41:646-53.
22. Chen CM. Mitochondrial dysfunction, metabolic deficits, and increased oxidative stress in Huntington’s disease. Chang Gung Med J 2011;34:135-52.
23. Browne SE, Ferrante RJ, Beal MF. Oxidative stress in Huntington’s disease. Brain Pathol 1999;9:147-63.
24. Goswami A, Dikshit P, Mishra A, Mulherkar S, Nukina N, Jana NR. Oxidative stress promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death by mimicking proteasomal malfunction. Biochem Biophys Res Commun 2006;342:184-90.
25. Túnez I, Tasset I, Pérez-De La Cruz V, Santamaria A. 3-Nitropropionic acid as a tool to study the mechanisms involved in Huntington’s disease: Past, Present and Future. Molecules 2010;15:878-916.
26. Raymond LA, Andre VM, Cepeda C, Gladding CM, Milnerwood AJ, Levine MS. Pathophysiology of Huntington’s disease: Time-dependent alterations in synaptic and receptor function. Neuroscience 2011;198:252-73.
27. DiFiglia M. Excitotoxic injury of the neostriatum: A model for Huntington’s disease. Trends Neurosci 1990;13:286-9.
28. Leenders KL, Frackowiak RS, Quinn N, Marsden CD. Brain energy metabolism and dopaminergic function in Huntington’s disease measured in vivo using positron emission tomography. Mov Disord 1986;1:69-77.
29. Stahl WL, Swanson PD. Biochemical abnormalities in Huntington’s chorea brains. Neurology 1974;24:813-9.
30. Cramer H, Warter JM, Renaud B. Analysis of neurotransmitter metabolites and adenosine 3’,5’-monophosphate in the CSF of patients with extrapyramidal motor disorders. Adv Neurol 1984;40:431-5.
31. Gines S, Seong IS, Fossale E, Ivanova E, Trettel F, Gusella JF, et al. Specific progressive cAMP reduction implicates energy deficit in presymptomatic Huntington’s disease knock-in mice. Hum Mol Genet 2003;12:497-508.
32. Koroshetz WJ, Jenkins BG, Rosen BR, Beal MF. Energy metabolism defects in Huntington’s disease and effects of coenzyme Q10. Ann Neurol 1997;41:160-5.
33. Jenkins BG, Koroshetz WJ, Beal MF, Rosen BR. Evidence for impairment of energy metabolism in vivo in Huntington’s disease using localized 1H NMR spectroscopy. Neurology 1993;43:2689-95.
34. Fatokun AA, Smith RA, Stone TW. Resistance to kynurenic acid of the NMDA receptor-dependent toxicity of 3-nitropropionic acid and cyanide in cerebellar granule neurons. Brain Res 2008;1215:200-7.
35. Huang QY, Yu L, Ferrante RJ, Chen JF. Mutant SOD1G93A in bone marrow-derived cells exacerbates 3-nitropropionic acid induced striatal damage in mice. Neurosci Lett 2007;418:175-80.
36. Alexi T, Borlongan CV, Faull RL, Williams CE, Clark RG, Gluckman PD, et al. Neuroprotective strategies for basal ganglia degeneration: Parkinson’s and Huntington’s diseases. Prog Neurobiol 2000;60:409-70.
37. Alexi T, Hughes PE, Faull RL, Williams CE. 3-Nitropropionic acid’s lethal triplet: Cooperative pathways of neurodegeneration. Neuroreport 1998;9:R57-64.
38. Fontaine MA, Geddes JW, Banks A, Butterfield DA. Effect of exogenous and endogenous antioxidants on 3-nitropropionic acid-induced in vivo oxidative stress and striatal lesions: Insights into Huntington’s disease. J Neurochem 2000;75:1709-15.
39. Wu PF, Zhang Z, Wang F, Chen JG. Natural compounds from traditional medicinal herbs in the treatment of cerebral ischemia/ reperfusion injury. Acta Pharmacol Sin 2010;31:1523-31.
40. Sandhya S, Vinod KR, Kumar S. Herbs used for brain disorders. Hygia J Drugs Med 2010;2:38-45.
41. Gohill KJ, Patel JA. A review on Bacopa monniera: Current research and future prospects. Int J Green Pharm 2010;4:1-9.
42. Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant: An overview. Phytotherapy Research 2005;19:305-17.
43. Shinomol GK, Muralidhara. Bacopa monnieri modulates endogenous cytoplasmic and mitochondrial oxidative markers in prepubertal mouse brain. Phytomedicine 2011;18:317-26.

44. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: A randomized, double-blind, placebo-controlled trial. J Altern Complement Med 2008;14:707-13.

45. Bammidi SR, Volluri SS, Chippada SC, Avangadda S, Vangalapati M. A review on pharmacological studies of Bacopa monniera. J Chem Biol Phys Sci 2011;1:250-9.

46. Hou CC, Lin SJ, Cheng JT, Hsu FL. Bacopasides III, bacopasaponin G, and bacopaside A, B and C from Bacopa monniera. J Nat Prod 2002;65:1759-63.

47. Mahato BS, Garai S, Chakravarty AK. Bacopasaponins E and F: Two jujubogenin bisdesmosides from Bacopa monniera. Phytochemistry 2000;53:711-4.

48. Garai S, Mahato BS, Ohtani K, Yamasaki K. Dammarane-type triterpenoid saponins from Bacopa monniera. Phytochemistry 1996;42:815-20.

49. Garai S, Mahato BS, Ohtani K, Yamasaki K. Bacopasaponin D: A pseudojujubogenin glycoside from Bacopa monniera. Phytochemistry 1996;43:447-9.

50. Kawai KI, Shibata S. Pseudojujubogenin: A new sapogenin from Bacopa monniera. Phytochemistry 1978;17:287-9.

51. Murthy RB, Raju VR, Ramakrisana T, Charavarty MS, Kumar KV, Kannababu S, et al. Estimation of twelve Bacopa saponins in Bacopa monniera extracts and formulations high-performance liquid chromatography. Chem Pharm Bull (Tokyo) 2006;54:907-11.

52. Chakravarty AK, Garai S, Masuda K, Nakane T, Kawahara N. Bacopasides III-V: Three new triterpenoid glucosides from Bacopa monniera. Chem Pharm Bull (Tokyo) 2003;51:215-7.

53. Chakravarty AK, Sarkar T, Masuda K, Shiqijma K, Nakane T, Kawahara N. Bacopasides I and II: Two pseudojujubogenin glycosides from Bacopa monniera. Phytochemistry 2001;58:553-6.

54. Kapoor R, Srivastava S, Kakkar P. Bacopa monnieri modulated antioxidant responses in brain and kidney of diabetic rats. Environ Toxicol Pharmacol 2009;27:62-9.

55. Deepak M, Amit A. The need for establishing the identities of 'bacoside A and B', the putative major bioactive saponins of Indian medicinal plant Bacopa monnieri. Phytomedicine 2004;11:264-8.

56. Volla VR, Upadhyea S, Nayak S. Learning and memory-enhancing effect of Bacopa monniera in neonatal rats. Bratist Lek Listy 2011;112:663-9.

57. Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J. Chronic effects of brahmi (Bacopa monnieri) on human memory. Neuropsychopharmacology 2002;27:279-81.

58. Singh HK, Dhawan BD. Neuropsychopharmacological effects of the Ayurvedic nootropic Bacopa monniera. (Brahmi). Indian J Pharmacol 1997;29:359-65.

59. Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by Bacopa monniera, a reputed Indian nootropic plant. J Ethnopharmacol 2000;71:383-90.

60. Stough C, Lloyd J, Clarke J, Downey LA, Hutchison CW, Rodgers T, et al. The chronic effects of an extract of Bacopa monniera (Brahmi) on cognitive function in healthy human subjects. Psychopharmacology (Berl) 2001;156:481-4.

61. Tripathi YB, Chaurasia S, Tripathi E, Upadhyay A, Dubey GP. Bacopa monnieri Linn. as an antioxidant: Mechanism of action. Indian J Exp Biol 1996;34:523-6.

62. Russo A, Izzo AA, Borrelli F, Renis M, Vanella A. Free radical scavenging capacity and protective effect of Bacopa monnieri L. on DNA damage. Phytother Res 2003;17:870-5.

63. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of Bacopa monniera in rat frontal cortex, striatum and hippocampus. Phytother Res 2000;14:174-9.

64. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Antistress effect of bacosides of Bacopa monniera: Modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res 2002;16:639-45.

65. Sairam K, Dorababu M, Goel RK, Bhattacharya SK. Antidepressant activity of standardized extract of Bacopa monnieri in experimental models of depression in rats. Phytochemistry 2002;9:207-11.

66. Shanker G, Singh HK. Anxiolytic profile of standardized Brahmi extract. Indian J Pharmacol 2000;32:152.

67. Sumathy T, Subramanian S, Govindaswamy S, Balakrishna K, Veluchamy G. Protective role of Bacopa monnieri on morphine induced hepatotoxicity in rats. Phytother Res 2001;15:643-5.

68. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of Bacopa monniera in gastric ulcer models. Phytochemistry 2001;8:423-30.

69. Andreassen OA, Ferrante RJ, Hughes DB, Klivenyi P, Dedeeoglu A, Ona VO, et al. Malonate and 3-nitropropionic acid neurotoxicity are reduced in transgenic mice expressing a caspase-1 dominant-negative mutant. J Neurochem 2000;75:847-52.

70. Coles CJ, Edmondson DE, Singer TP. Inactivation of succinate dehydrogenase by 3-nitropropionate. J Biol Chem 1979;254:5161-7.

71. Kim GW, Copin JC, Kawase M, Chen SF, Sato S, Bobbelt G, et al. Excitotoxicity is required for induction of oxidative stress and apoptosis in mouse striatum by the mitochondrial toxin, 3-Nitropropionic acid. J Cereb Blood Flow Metab 2000;20:119-29.

72. Nakanishi K. Terpene triactones from Ginkgo biloba: From ancient times to 21st century. Bioorg Med Chem 2005;13:4987-5000.

73. McKenna DJ, Jones K, Hughes K. Efficacy, safety, and use of Ginkgo biloba in clinical and preclinical applications. Altern Ther Health Med 2001;7:70-86, 88-90.

74. Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol 2004;64:465-72.

75. DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: Basic studies and clinical applications. Curr Drug Targets 2000;1:25-58.

76. Ramassamy C, Longpre F, Christen Y. Ginkgo biloba extract (EGb 761) in Alzheimer’s disease: Is there any evidence? Curr Alzheimer Res 2007;4:253-62.

77. Pietri V, Maurelli E, Drieu K, Culsaci M. Cardioprotective and anti-oxidant effects of the terpenoid constituents of Ginkgo biloba extract (EGb 761). J Mol Cell Cardiol 1997;29:733-42.

78. Mahadevan S, Park Y. Multifaceted therapeutic benefits of Ginkgo biloba L.: Chemistry, efficacy, safety, and uses. J Food Sci 2008;73:R14-9.

79. Amri H, Ogwuegbu SO, Boujard N, Drieu K, Papadopoulos V. In vivo regulation of peripheral-type benzodiazepine receptor and glucocorticoid synthesis by Ginkgo biloba extract EGb 761 and isolated ginkgolides. Endocrinology 1996;137:5707-18.

80. Winters M. Ancient medicine, modern use: Withania somnifera (Shami) and glucocorticoid synthesis by Ginkgo biloba extract EGb 761 and isolated ginkgolides. Endocrinology 1996;137:5707-18.

81. Winters M. Ancient medicine, modern use: Withania somnifera and its potential role in integrative oncology. Altern Med Rev 2006;11:269-77.

82. Yadava SA, Hakkim L, Sathishkumar F, Sathishkumar R. Antioxidant activity of Withania somnifera (L.) dual by different solvent extraction methods. J Pharm Res. 2011;4:1428-30.
83. Bhattacharyya SK, Satyan KS, Ghosal S. Antioxidant activity of glycowithanolides from Withania somnifera. Indian J Exp Biol 1997;35:236-9.

84. Davis L, Kuttan G. Effect of Withania somnifera on cell mediated immune response in mice. J Exp Clin Cancer Res 2002;21:585-90.

85. Davis L, Kuttan G. Immunomodulatory activity of Withania somnifera. J Ethnopharmacol 2000;71:193-200.

86. Bhattacharyya SK, Goel RK, Kaur R, Ghosal S. Anti-stress activity of sitosterolides VII and VIII, new acetylglucosides from Withania somnifera. Phytother Res 1987;1:32-7.

87. Kulkarni SK, Verma A. Ashwagandha and Bramhi: Nootropic and de-addiction profile of psychotropic indigenous plants. Drugs Today 1993;29:257-63.

88. Kulkarni SK, Akula KK, Dhir A. Effect of Withania somnifera Dunal root extract against pentylentetrazol seizure threshold in mice: Possible involvement of GABAergic system. Indian J Exp Biol 2008;46:465-9.

89. Bhatnagar M, Sisodia SS, Bhatnagar R. Antilucre and antioxidant activity of Asparagus racemosus Willd and Withania somnifera Dunal in rats. Ann N Y Acad Sci 2003;1056:261-78.

90. Gupta SK, Dua A, Vohra BP. Withania somnifera (Ashwagandha) attenuates antioxidant defense in aged spinal cord and inhibits copper induced lipid peroxidation and protein oxidative modifications. Drug Metabol Drug Interact 2003:19:211-22.

91. Bhattacharyya SK, Bhattacharya D, Sairam K, Ghosal S. Effect of Withania somnifera glycowithanolides on a rat model of tardive dyskinesia. Phytomedicine 2002;9:167-70.

92. Singh B, Chandan BK, Gupta DK. Adapogenic activity of a novel withanolide-free aqueous fraction from the roots of Withania somnifera Dun. (Part II). Phytother Res 2003;17:531-6.

93. Singh B, Saxena AK, Chandan BK, Gupta DK, Bhatuni KK, Anand KK. Adapogenic activity of a novel, withanolide-free aqueous fraction from the roots of Withania somnifera Dun. Phytother Res 2001;15:311-8.

94. Naidu PS, Singh A, Kulkarni SK. Effect of Withania somnifera root extract on reserpine-induced orofacial dyskinesia and cognitive dysfunction. Phytother Res 2006;20:140-6.

95. Singh G, Sharma PK, Dudhe R, Singh S. Biological activities of Withania somnifera. Ann Biol Res 2010;1:56-63.

96. Mirjallili MH, Moyano E, Bonfill M, Cusido RM, Palazón J. Steroidal lactones from Withania somnifera, an ancient plant for novel medicine. Molecules 2009;14:2373-93.

97. Kapoor LD. Handbook of Ayurvedic Medicinal Plants. London, UK: CRC Press; 2001.

98. Kirtikar KR, Basu BD. Indian Medicinal Plants. Dehradun, India: Shiva Publishers; 1991.

99. Kumar P, Kumar A. Possible neuroprotective effect of Withania somnifera root extract against 3-Nitroporopic acid induced behavioral, biochemical, and mitochondrial dysfunction in an animal model of Huntington's disease. J Med Food 2009;12:591-600.

100. Kumar P, Kumar A. Effects of root extract of Withania somnifera in 3-Nitroporopic acid-induced cognitive dysfunction and oxidative damage in rats. Int J Health Res 2008;1:139-49.

101. Jain S, Shrivastava S, Nayak S, Sumbhate S. Recent trends in Curcuma longa Linn. Pharmacog Rev 2007;1:119-28.

102. Joe B, Vijaykumar M, Lokesh BR. Biological properties of curcumin-cellular and molecular mechanisms of action. Crit Rev Food Sci Nutr 2004;44:97-111.

103. Akram M, Shahab-uddin, Ahmed A, Usmanghani K, Hananan A, Mohiuddin E, et al. Curcuma longa and curcumin: A review. Rom J Biol-Plant Biol 2010;55:65-70.

104. Kunchandy F, Rao MN. Oxygen radical scavenging activity of curcumin. Int J Pharm 1990;58:237-40.

105. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: A component of turmeric (Curcuma longa). J Altern Complement Med 2003;9:161-8.

106. Chattopadhyay I, Biswas K, Bandypadhyay U, Banerjee RK. Turmeric and curcumin: Biological actions and medicinal applications. Curr Sci 2004;87:44-53.

107. Simon A, Allais DP, Duroux JL, Baely JP, Durand-Fontanier S, Delage C. Inhibitory effect of curcuminoinds on MCF-7 cell proliferation and structure-activity relationships. Cancer Lett 1998:129:111-6.

108. Sreejayan, Rao MN. Nitric oxide scavenging by curcuminoinds. J Pharm Pharmacol 1997;49:105-7.

109. Daniel S, Limson JL, Dairam A, Watkins GM, Daya S. Through metal binding, curcumin protects against lead- and cadmium-induced lipid peroxidation in rat brain homogenates and against lead-induced tissue damage in rat brain. J Inorg Biochem 2004;98:266-75.

110. Ghoneim AI, Abdel-Naim AB, Khalifa AE, El-Denshary ES. Protective effects of curcumin against ischaemia/reperfusion insult in rat forebrain. Pharmacol Res 2002;46:273-9.

111. Vajragupta O, Boonchoong P, Watanabe H, Tohda M, Kumasud N, Sumanont Y. Manganese complexes of curcumin and its derivatives: Evaluation for the radical scavenging ability and neuroprotective activity. Free Radic Biol Med 2003:35:1632-44.

112. Thiyagarajan M, Sharma SS. Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats. Life Sci 2004;74:969-85.

113. Frautschy SA, Hu W, Kim P, Miller SA, Chu T, Harris-White ME, et al. Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol Aging 2001;22:993-1005.

114. Kumar P, Padi SS, Naidu PS, Kumar A. Possible neuroprotective mechanisms of curcumin in attenuating 3-nitroporopic acid-induced neurotoxicity. Methods Find Exp Clin Pharmacol 2007;29:19-25.

115. Nah SY, Kim DH, Rhim H. Ginsenosides: Are any of them candidates for drugs acting on central nervous system. CNS Drug Rev 2007;13:381-404.

116. Lu JM, Yao Q, Chen C. Ginseng compounds: An update on their molecular mechanisms and medical applications. Curr Vasc Pharmacol 2009;7:293-302.

117. Liu CX, Xiao PG. Recent advances on ginseng research in China. J Ethnopharmacol 1992;36:27-38.

118. Rausch WD, Liu S, Gille G, Radad K. Neuroprotective effects of ginsenosides. Acta Neurobiol Exp (Wars) 2006;66:369-75.

119. Radad K, Gille G, Liu L, Rausch WD. Use of ginseng in medicine with emphasis on neurodegenerative disorders. J Pharmaco Sci 2006;100:175-86.

120. Keum YS, Park KK, Lee JM, Chun KS, Park JH, Lee SK, et al. Antioxidant and anti-tumor promoting activities of the methanol extract of heat-processed ginseng. Cancer Lett 2000;13:41-8.

121. Li X, Li SH. Effect of total saponins of Sanchi (Panax pseudoginseng notoginseng) on TNF, NO and its mechanisms. Zhong Cao Yao 1999;30:514-7.

122. Kim YC, Kim SR, Markelonis GJ, Oh TH. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res 1998;53:426-32.

123. Kim S, Ahn K, Oh TH, Nah SY, Rhim H. Inhibitory effect of ginsenosides on NMDA receptor-mediated signals in rat hippocampal neurons. Biochem Biophys Res Commun 2002;296:247-54.

124. Lian XY, Zhang Z, Stringer JL. Protective effects of ginseng components in a rodent model of neurodegeneration. Ann Neurol 2005;57:642-8.
125. Kim JH, Kim S, Yoon IS, Lee JH, Jang BJ, Jeong SM, et al. Protective effects of ginseng saponins on 3-nitropropionic acid-induced striatal degeneration in rats. Neuropharmacology 2005;48:743-56.

126. Wu J, Jeong HK, Bulin SE, Kwon SW, Park JH, Bezprozvanniy I. Ginsenosides protect striatal neurons in cellular model of Huntington’s disease. J Neurosci Res 2009;87:1904-12.

127. Handa SS, Rasayana Drugs Part-I. Pharm Times 1993;25:9-15.

128. Veerendra Kumar MH, Gupta YK. Effect of different extracts of Centella asiatica on cognition and markers of oxidative stress in rats. J Ethnopharmacol 2002;79:253-60.

129. Wijeweera P, Amason JT, Koszycki D, Merali Z. Evaluation of anxiolytic properties of Gotukola—(Centella asiatica) extracts and rat behavioral models. Phytomedicine 2006;13:668-76.

130. Soumyanath A, Zhong YP, Gold SA, Yu X, Koop DR, Boudrette D, et al. Centella asiatica accelerates nerve regeneration upon oral administration and contains multiple active fractions increasing neurite elongation in vitro. J Pharm Pharmacol 2005;57:1221-9.

131. Zainol MK, Abdul-Hamid A, Yusof S, Muse R. Antioxidative activity and total polyphenolic contents of leaf, root and petiole of four accessions of Centella asiatica (L.) urban. Food Chem 2003;81:575-81.

132. Hussin M, Hamid AA, Mohamad S, Saari N, Ismail M, Hair Bejo M. Protective effect of Centella asiatica extract and powder on oxidative stress in rats. Food Chem 2007;100:535-41.

133. Singh B, Rastogi RP. A reinvestigation of the triterpenes of Centella asiatica. Phytochemistry 1969;8:917-21.

134. Randriamampionona D, Diallo B, Rakotonirianar F, Rabemanantsoa C, Cheuk K, Corbisier AM, et al. Comparative analysis of active constituents in Centella asiatica samples from Madagascar: Application for ex situ conservation and clonal propagation. Fitoterapia 2007;78:482-9.

135. Singh B, Rastogi RP. Chemical examination of Centella asiatica Linn.-Ill. Phytochemistry 1968;7:1385-93.

136. Asakawa Y, Mastuda R, Takemoto T. Monoterpenoids and sesquiterpenoids from Hydrocotyle and Centella species. Phytochemistry 1982;21:2590-2.

137. Shinomol GK, Muralidhara. Prophylactic neuroprotective property of Centella asiatica against 3-nitropropionic acid induced oxidative stress and mitochondrial dysfunctions in brain regions of prepupetal mice. Neurotoxicology 2008;29:948-57.

138. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavanoids: Promising anticancer agents. Med Res Rev 2003;23:519-34.

139. Narayana KR, Reddy MS, Chaluvadi MR, Krishna DR. Bioflavonoids classification, pharmacological, biochemical effects and therapeutic potential. Indian J Pharmacol 2001;33:2-16.

140. Bors W, Heller W, Michel C, Saran M. Flavonoids as antioxidiants: Determination of radical-scavenging efficiencies. Methods Enzymol 1990;186:343-55.

141. Coleridge Smith PD, Thomas P, Scarr JH, Dormandy JA. Causes of various ulceration: A new hypothesis. Br Med J (Clin Res Ed) 1988;296:1726-7.

142. Prior RL, Cao G, Prior RL, Cao G. Analysis of botanicals and dietary supplements for antioxidant capacity: A review. J AOAC Int 2000;83:950-8.

143. Renugadevi J, Prabu SM. Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. Toxicology 2009;256:128-34.

144. Schroeter H, Boyd C, Spencer JP, Williams RJ, Cadenas E, Rice-Evans C. MAPK signaling in neurodegeneration: Influences of flavonoids and of nitric oxide. Neurobiol Aging 2001;23:861-80.

145. Lopez-Lopez G, Moreno L, Cogolludo A, Galisteo M, Ibarra M, Duarte J, et al. Nitric oxide (NO) scavenging and NO protecting effects of quercetin and their biological significance in vascular smooth muscle. Mol Pharmacol 2004;65:851-9.

146. Kumar P, Padi SS, Naidu PS, Kumar A. Cyclooxygenase inhibition attenuates 3-nitropropionic acid-induced neurotoxicity in rats: Possible antioxidant mechanisms. Fundam Clin Pharmacol 2007;21:297-306.

147. Raso GM, Meil R, Di Carlo G, Pacilio M, Di Carlo R. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. Life Sci 2001;68:921-31.

148. Ishige K, Schubert D, Sagara Y. Flavanoids protect neuronal cells from oxidative stress by three distinct mechanisms. Free Radic Biol Med 2001;30:433-46.

149. Kumar P, Kumar A. Protective effect of hesperidin and naringin against 3-nitropropionic acid induced Huntington’slike symptoms in rats: Possible role of nitric oxide. Behav Brain Res 2010;206:38-46.

150. Kumar P, Kalonia H, Kumar A. Protective effect of sesamol against 3-nitropropionic acid-induced cognitive dysfunction and altered glutathione redox balance in rats. Basic Clin Pharmacol Toxicol 2010;107:577-82.

151. Kumar P, Kumar A. Effect of lycopene and epigallocatechin-3-gallate against 3-nitropropionic acid induced cognitive dysfunction and glutathione depletion in rat: A novel nitric oxide mechanism. Food Chem Toxicol 2009;47:2522-30.

152. Lagoa R, Lopez-Sanchez C, Samhan-Arias AK, Ganam CN, Garcia-Martinez V, Gutierrez-Merino C. Kaempferol protects against rat striatal degeneration induced by 3-nitropropionic acid. J Neurochem 2009;111:473-87.

153. Kumar P, Kumar A. Protective effects of epigallocatechin gallate following 3-nitropropionic acid-induced brain damage: Possible nitric oxide mechanisms. Psychopharmacology (Berl) 2009;207:257-70.

154. Allison AC, Cabacelos R, Lombardi VR, Alvarez XA, Vigo C. Celastrol, a potent antioxidant and anti-inflammatory drug, as a possible treatment for Alzheimer’s disease. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:1341-57.

155. Kim DH, Shin EK, Kim YH, Lee BW, Jun JG, Park JH, et al. Suppression of inflammatory responses by celastrol, a quinone methide triterpenoid isolated from Celastrus regelii. Eur J Pharm Sci 2009;39:819-27.

156. Lee JH, Choi KJ, Seo WD, Jung SY, Kim M, Lee BW, et al. Enhancement of radiation sensitivity in lung cancer cells by celastrol is mediated by inhibition of Hsp90. Int J Mol Med 2011;27:441-6.

157. Avilla J, Teixido A, Velazquez C, Alvarenga N, Ferro E, Canelas R. Insecticidal activity of Maytenus species (Celastraceae) nortriterpene quinone methides against codling moth, Cydia pomonella (L.) (Lepidoptera: tortricidae). J Agric Food Chem 2000;48:88-92.

158. Cleren C, Calingasan NY, Chen J, Beal MF. Celastrol protects against MPTP- and 3-nitropropionic acid-induced neurotoxicity. J Neurochem 2005;94:995-1004.

159. Zhang YQ, Sarge X, Chen W, Jun SY, Beal MF. Celastrol inhibits polyglutamine aggregation and toxicity though induction of the heat shock response. J Mol Med (Berl) 2007;85:1421-8.

160. Chen Q, Haddad GG. Role of trehalose phosphate synthase and trehalose during hypoxia: From flies to mammals. J Exp Biol 2004;207:3125-9.

161. Kandror O, Bretschneider N, Kreydin E, Cavaleri D, Goldberg AL. Yeast adaptation to near-freezing temperatures by STRE/Msn2,4-dependent induction of trehalose synthesis and certain molecular chaperones. Mol Cell 2004;13:771-81.
162. Arora A, Ha C, Park CB. Inhibition of insulin amyloid formation by small stress molecules. FEBS Lett 2004;564:121-5.
163. Liu R, Barkhordarian H, Emadi S, Park CB, Sierks MR. Trehalose differentially inhibits aggregation and neurotoxicity of beta-amyloid 40 and 42. Neurobiol Dis 2005;20:74-81.
164. Tanaka M, Machida Y, Niu S, Ikeda T, Jana NR, Doi H, et al. Trehalose alleviates polyglutamine-mediated pathology in a mouse model of Huntington disease. Nat Med 2004;10:148-54.
165. Sarkar S, Davies JE, Huang Z, Tunncliffe A, Rubinsztejn DC. Trehalose, a novel mTOR-independent autophagy enhancer, accelerates the clearance of mutant huntingtin and alpha-synuclein. J Biol Chem 2007;282:5641-52.
166. Visioli F, Riso P, Grande S, Galli C, Porrini M. Protective activity of tomato products on in vivo markers of lipid oxidation. Eur J Nutr 2003;42:201-6.
167. Karahan I, Atessahin A, Yilmaz S, Ceribasi AO, Sakin F. Protective effect of lycopene on gentamicin-induced oxidative stress and nephrotoxicity in rats. Toxicology 2005;215:198-204.
168. Tapiero H, Townsend DM, Tew KD. The role of carotenoids in the prevention of human pathologies. Biomed Pharmacother 2004;58:100-10.
169. Hsiao G, Fong TH, Tzu NH, Lin KH, Chou DS, Sheu JR. A potent antioxidant, lycopene, affords neuroprotection against microglia activation and focal cerebral ischemia in rats. In Vivo 2004;18:351-6.
170. Rafi MM, Yadav PN, Reyes M. Lycopene inhibits LPS-induced proinflammatory mediator inducible nitric oxide synthase in mouse macrophage cells. J Food Sci 2007;72:S069-74.
171. Gunasekera RS, Sewgobind K, Desai S, Dunn L, Black HS, McKeehan WL, et al. Lycopene and lutein inhibit proliferation in rat prostate carcinoma cells. Nutr Cancer 2007;58:171-7.
172. Kuhad A, Sethi R, Chopra K. Lycopene attenuates diabetes-associated cognitive decline in rats. Life Sci 2008;83:128-34.
173. Akbaraly NT, Faure H, Gourlet V, Favier A, Berr C. Plasma carotenoid levels and cognitive performance in an elderly population: Results of the EVA Study. J Gerontol A Biol Sci Med Sci 2007;62:308-16.
174. Atessahin A, Yilmaz S, Karahan I, Ceribasi AO, Karaoğlu A. Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. Toxicology 2005;212:116-23.
175. Kumar P, Kalonia H, Kumar A. Lycopene modulates nitric oxide pathways against 3-nitropropionic acid-induced neurotoxicity. Life Sci 2009;85:711-8.
176. Sankar D, Sambandam G, Ramakrishna Rao M, Pugalendi KV. Modulation of blood pressure, lipid profiles and redox status in hypertensive patients taking different edible oils. Clin Chim Acta 2005;355:97-104.
177. Baba NH, Antoniades K, Habbal Z. Effects of dietary canola, olive, and linolenic acid enriched olive oils on plasma lipids, lipid peroxidation and lipoprotein lipase activity in rats. Nutr Res 1998;19:41-5.
178. Kapadia GJ, Azuine MA, Tokuda H, Takesaki M, Mukainaka T, Konoshima T, et al. Chemopreventive effect of resveratrol, sesamol, sesame oil and sunflower oil in the Epstein-Barr virus early antigen activation assay and the mouse skin two-stage carcinogenesis. Pharmacol Res 2002;45:499-505.
179. Hsu DZ, Chen KT, Li YH, Chuang YC, Liu MY. Sesamol delays mortality and attenuates hepatic injury after cecal ligation and puncture in rats: Role of oxidative stress. Shock 2006;25:528-32.
180. Kumar P, Kalonia H, Kumar A. Sesamol attenuate 3-nitropropionic acid-induced Huntington-like behavioral, biochemical, and cellular alterations in rats. J Asian Nat Prod Res 2009;11:439-50.
181. Hsu DZ, Wan CH, Hsu HF, Lin YM, Liu MY. The prophylactic protective effect of sesamol against ferric-nitritotriacetate-induced acute renal injury in mice. Food Chem Toxicol 2008;46:2736-41.
182. Hsu DZ, Chien SP, Chen KT, Liu MY. The effect of sesamol on systemic oxidative stress and hepatic dysfunction in acutely iron-intoxicated mice. Shock 2007;28:596-601.