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 effected 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[2,4] along with modifications in the number of N-methyl-D-aspartate (NMDA) receptors.[5] 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.

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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

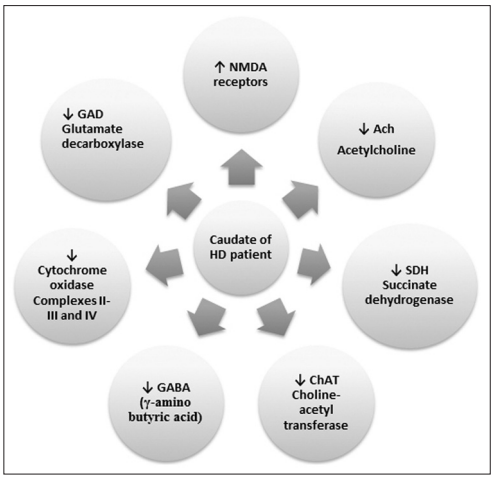

Figure 1: Various biochemical changes during Huntington's disease

movements and abnormal voluntary movements.[2,6] The involuntary movements usually follow a biphasic pattern, initially hyperkinetic that increase with time, followed by bradykinesia leading to severe hypokinesia and rigid-akinetic state.[13] Characteristic abnormal involuntary movements involve Chorea, or choreoathetosis, which consist of continuous and irregular jerky or writhing motions.[6,14]

Non-motor symptoms

Patients suffering from HD have particular and distinctive cognitive impairments.[2,6] 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.[6,13] 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.[6,10,13-15]

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.[16,17] 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.[18-21] 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.[22,23] OS also promotes mutant Huntingtin aggregation and mutant Huntingtin-dependent cell death by mimicking proteasomal malfunction.[24] Increased levels of free radicals impair mitochondrial functions, energy production, and metabolic inhibition predisposes to excitotoxic damage.[3,25] 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.[26,27]

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[28-30] and in HD post-mortem brain.[31] Further, there is an augmentation in the lactate levels in the CSF as well as in cerebral cortical tissue.[32,33] Deregulation of mitochondrial function by a mitochondrial toxin, 3-nitropropionic acid (3-NP), causes metabolic impairment due to energy impairment, oxidative stress, and excitotoxicity[34-37] leading to cytotoxicity mainly in the striatum despite the fact that metabolic impairment actually occurs throughout the entire body and brain.[37,38] 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 neurodegerative diseases.[39,40] 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.[41,42] It is used for the treatment of epilepsy, insomnia, anxiety, and as memory enhancer for centuries.[43,44]

The major chemical constituents present in the plant are dammarane type of tri-terpenoid saponins, Bacosides A and B [Figure 2].[41,45] Apart from these major constituents, it also contain various types of saponin including bacopasaponin A-G[46-49] along with pseudojujubogenin, jujubogenin,[50] bacopaside I-V, X, and N_1 and N_2.[51-53] The plant has also been reported to contain brahmine, herpestine, and monnierin.[54,55] Ample reports have shown memory enhancing effects of the plant.[44,56-58] Among various constituents, Bacoside A has shown to improve memory.[42,59] Various clinical trials have also shown beneficial effects of Brahmi in improving

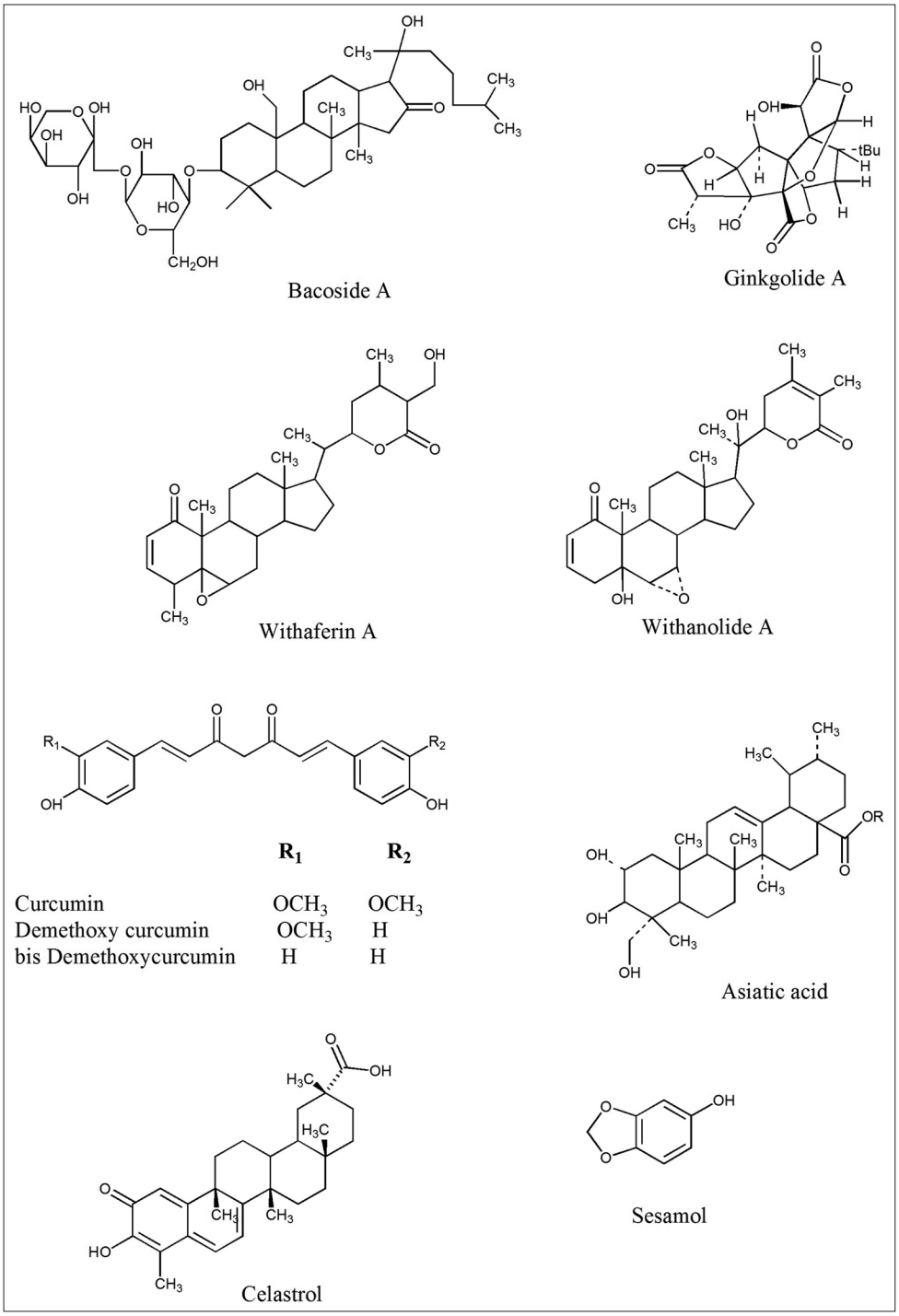

Figure 2: Various chemical constituents

memory.[60] The neuroprotective and memory enhancing effects of BM extracts have been reported due to several mechanisms such as chelation of metal ions,[61] scavenging of free radicals,[62] and enhanced antioxidative defense enzymes.[62,63] Besides this, it also displays antioxidant,[63] anti-stress,[64] antidepressant,[65] anxiolytic,[66] free radical scavenging capacity,[62] hepatoprotective,[67] and antiulcerogenic activity.[68]

3-NP inactivates the mitochondrial enzyme succinate dehydrogenase (SDH) and complex II-III of the electron transport chain.[2,69,70] It also increases the levels of ROS, MDA, and free fatty acids, suggesting the vital role of oxidative stress in the manifestation of neurotoxicity.[71] The dietary intake of BM leaf powder significantly decreased the basal levels of several oxidative markers, enhanced thiol-related antioxidant molecules and activities of antioxidant enzymes suggesting its antioxidant potential. One of the study has showed that dietary BM supplements leads to a significant protection against neurotoxicant-induced oxidative damage in brain.[43] The study further suggests that due to strong antioxidant effect and protective effect against stress-mediated neuronal dysfunctions BM can be useful in HD treatment.

Ginkgo biloba (maidenhair tree, family: Ginkgoaceae)

Ginkgo biloba L. was mentioned in Chinese Materia Medica 5,000 years ago.[72] Since ginkgo tree is known to be among the oldest living species on this planet, it is called a "living fossil".[73] The chemical constituents present in the leaf are the trilactonic diterpenes: Ginkgolide A-C, Ginkgolide J-M; a trilactonic sesquiterpene: Bilobalide; flavonoids including quercetin, kaempferol, isorhamnetins, and biflavonoids (amentoflavone, bilobetin, 5-methoxybilobetol, ginkgetin, isoginkgetin, and sciadopitysin); and proanthocyanidins [Figure 2].[73-75] 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.[76] These versatile activities of the Ginkgo leaf extract are due its antioxidant effect,[77] anti-platelet activating factor (Anti-PAF) activity (cardio and cerebral vascular diseases),[75] inhibition of beta amyloid peptide (Aβ) aggregation (prevent Alzheimer's progression),[78] decreased expression of peripheral benzodiazepine receptor (stress alleviation),[79] and stimulation of endothelium derived relaxing factor (improve blood circulation).[74] The *G. biloba* extract (100 mg/kg, i.p. for 15 days) improved the 3-NP induced neurobehavioral deficits[80] 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.[80]

Withania somnifera

Withania somnifera (WS), commonly known *Ashwagandha* (Fam: Solanaceae), has been used since ages in Ayurvedic medicine to increase longevity and vitality.[81] The plant has reported for its antioxidant,[82,83] anti-inflammatory,[84] immune-modulating,[85] anti-stress,[86] memory enhancing,[87] and anti-convulsant properties.[88] 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.[83,89-91] It acts as an anti-inflammatory agent through inhibition of complement, lymphocyte proliferation, and delayed-type hypersensitivity.[84] Various studies have shown that WS increase circulating cortisol, decrease fatigue, increase physical performance, and decrease refractory depression in stress.[92,93] It also modulates various neurotransmitter receptor systems in the CNS. Recently, WS has been found beneficial in 18 clinically diagnosed Parkinson's patients.[87,94]

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, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropane, choline, cuscohygrine, isopelletierine, anaferine, anahygrine, and anahydrine.[95-98]

Role of GABAergic in the pathogensis 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.[99,100] 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.[99,100]

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.[101] 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.[102]

CL contains yellow coloring matter, various curcuminiods, sesquiterpenes, essential oil, and starch. Most of the curcuminiods are diarylheptanoid, a derivative of which curcumin is the major bioactive component. The other two curcuminoids are desmethoxycurcumin, and bis-desmethoxycurcumin [Figure 2].[102,103] Curcumin has antioxidant,[104] anti-inflammatory,[105] antifungal, antibacterial, antiparasitic, choleretic, analgesic, hepatoprotective, free

radical scavenging, iron chelating, antiviral,[102,106] and anti-mutagenic activity.[107] Various mechanisms like direct scavenging activity of superoxide, hydroxyl radicals, metal chelating property[104,108,109] and ability to induce antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, and hemeoxygenase) have been responsible for the antioxidant potential of CL.[110] 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,[111,112] and is useful in the treatment of aging and memory dysfunctions.[113] 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.[114]

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.[115] Asian ginseng (*Panax ginseng C. A. Meyer*) and American ginseng (*Panax quinquefolium L.*) belonging to family Araliaceae are the most common ginseng species.[116] Ginseng contains a series of tetracyclic dammarane triterpenoid saponin glycosides called, ginsenosides, which are active constituents of the drug.[117] Ginsenosides, depending on their structural differences, are classified into three categories: the panaxadiols (e.g., Rb1-Rb3, Rc, Rd, Rg3, Rh2, and Rs1), panaxatriols (e.g., Re, Rf, Rg1-2, and Rh1) and oleanolic acid derivatives (e.g., Ro).[118] 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.[118,119] It also possesses antioxidant,[120] anti-apoptotic,[120] anti-inflammatory,[121] and immune-stimulatory activities.[119] It also reduces lipid peroxidation, inhibits excitotoxicity, and Ca^{2+} over-influx into neurons, maintains cellular ATP levels, preserves structural integrity of neurons, and increase cognitive performance.[119] Ginsenoside Rb1 and Rg3 have exhibited protective effects on cortical neurons against glutamate-induced cell death by blocking Ca^{2+} influx through glutamate receptors.[122] Saponins from ginseng also inhibit both NMDA and glutamate-induced increase Ca^{2+} levels in rat hippocampal neurons.[123] Ginsenosides Rb1, Rb3, and Rd have exhibited neuroprotective effect against 3-NP-induced striatal neuronal damage.[124,125] Ginsenoside Rb1, Rc, and Rg5 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 Ca^{2+} responses in cultured spinal neuronal cultures.[126] 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.[127] Studies have shown various neuropharmacological effects of CA which comprises of memory enhancement,[128,129] increased neurite elongation and acceleration of nerve regeneration.[130] It also possesses anti-oxidant property.[131,132] The most important chemical constituents from CA are triterpenoid saponins including asiaticoside, asiatic acid, madecassoside, and madecassic acid [Figure 2].[133,134] Other saponins present in minor quantities are brahmoside and brahminoside.[133,135] Various triterpene acids, betullic acid, brahmic, and isobrahmic acid are reported from the plant.[133,135] The essential oil from the leaves of the plant contains monoterpenes, including bornyl acetate, α-pinene, β-pinene, and γ-pinene.[136] 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.[137] 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.[137] 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).[138,139] Flavonoids exhibit several biological effects such as anti-inflammatory, anti-hepatotoxic, anti-ulcer, anti-allergic, and antiviral actions.[139-141] They are potent antioxidants and have free radical scavenging abilities by virtue of their aromatic hydroxyl groups.[142,143]

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.[144] They also exert protective action against peroxynitrite-induced oxidative damage.[145] Flavonoids inhibit nitric oxide synthase (involved in neurodegenerative process including HD),[146-148] cyclooxygenase expression,[147] protect against oxidative stress,[148] and modulate calcium homeostasis.[144] These polyphenols act by direct scavenging of various ROS and reactive nitrogen species.[144,149] Antioxidants have shown beneficial effects agains 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).[99,150,151] Various flavonoides such as naringin,[149] hesperidin,[149] kaempferol,[152] and epigallocatechin gallate (EGCG)[151,153] have been reported to provide beneficial effects against 3-NP-induced neurotoxicity.

Celastrol

Celastrol [Figure 2] is a triterpenoid quinone methide isolated from *Tripterygium wilfordi* (Thunder of God vine) and *Celastrus regelii* belonging to the Celastraceae family, exhibits antioxidant (15 times the potency of α-tocopherol),[154] anti-inflammatory,[155] anticancer,[156] and insecticidal[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.[158] It also protect from 3-NP-induced striatal damage by regulating heat shock protein (*hsp*) gene expression in dopaminergic neurons.[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.[160,161] Though it is not synthesized in mammals, still it has exhibited various beneficial effects in them.[160] Various reports have shown that it inhibits amyloid formation,[162] aggregation of β-amyloid,[163] polyglutamine (polyQ) [3]-mediated protein aggregation, and decreased Huntingtin 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.[164,165] It has also been reported that trehalose increase the autophagic activity against various aggregation proteins such as mutant Huntingtin, thereby, by providing neruoprotective activity against HD.[165] Hence, both properties of trehalose (inducer of autophagy and chemical chaperone) can be utilized in developing a new therapeutic agent for HD.[165]

Lycopene

It is a well-known carotenoids present in considerable amounts in tomatoes and tomato-based products.[166] Several studies have reported their therapeutic potential against oxidative stress and its related pathologies, including HD.[167,168] It has been reported to possess potent neuroprotective,[169] antioxidant,[170] antiproliferative, anticancer,[171] anti-inflammatory,[172] memory enhancing,[173] and hypocholesterolemic activities.[174] Lycopene is more powerful carotenoid quencher of singlet oxygen with respect to vitamin E and glutathione.[174] Lycopene treatment significantly attenuated various behavioral and biochemical changes-induced by 3-NP, suggesting its therapeutic potential against HD-like behavior.[175] The results of the study clearly indicated that lycopene exhibited its protected effect through its antioxidant property and nitric oxide pathway.[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.[176] Sesamol [Figure 2], one of the main constituents in sesame oil, is responsible for its antioxidant activity.[177] Sesamol has shown to control increased blood pressure, hyperlipidemia and lipid peroxidation (by increasing enzymatic and non-enzymatic antioxidants),[176] and a strong antitumor action.[178] It has been reported that sesamol exhibited its protective effect through nitric oxide mechanism (suppression of inducible nitric oxide synthase (iNOS) expression).[179] It also attenuated 3-NP-induced Huntington-like behavioral, biochemical, and cellular alterations in rodents.[180] It also protects against 3-NP-induced memory impairment,[150] oxidative stress, neuroinflammation in hippocampus neurons, and consequently improves synaptic plasticity and neurotransmission.[181] It also inhibits nitrite production and inducible NOS expression in the liver of septic rats.[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.

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