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THERAPEUTIC POTENTIAL OF VARIOUS HERBAL PLANTS AND PHYTOCHEMICALS IN THE MANAGEMENT OF HUNTINGTON'S DISEASE

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ABSTRACT

Huntington's disease (HD) is a neurodegenerative disease that affects people of all ages. Chorea and dystonia, as well as mental illness, memory loss, and weight loss, are all symptoms of accelerating motor disorder. Spiny striatum and cortex neurons in the medium size range in HD, they are predominantly carried out. Different assumptions, including molecular genetics, oxidative stress, excitotoxicity, metabolic stress and mitochondrial dysfunction are the reason for neuron dysfunction and destruction of cells. While no cure is possible to entirely avoid the progression of the disease, there are medications available to prevent the disease from developing. Assist in managing the Chorea. The present analysis focuses on brief disease pathophysiology, plants and phytochemicals those are explored in the management of HD.

Keywords: Huntington's disease (HD), phytochemicals, pathophysiology, Chorea and dystonia

INTRODUCTION

Huntington's chorea, also known as Huntington's disease, was first recorded by George Huntington, an Ohio physician (HD). Chorea and dystonia are symptoms of this neurodegenerative autosomal genetic conditionwhich also includes psychological problems, mental problem and reduce in weight **[1]**. The striatum's medium spiny neurons (MSNs) and the lower portion of the cortex are affected by

pathological alteration. Further damage to γ-amino butyric acid (GABA),enkephalin neurons of basal ganglia in HD disease **[2]**. There is also change in number of N-Methyl-D-aspartate (NMDA) receptors **[3]**. One of the reasons for HD is increase in the Repeats of cytosine, adenine, and guanine (CAG) contribute to the development of polyglutamine stretch, an irregular protein. The death usually happens after the first appearance of symptoms **[4]**. Many biochemical modifications shown in which is seen in HD pateints includes, decrease in GABA as well as ACH levels further more decrease in the enzymes which synthesise these like glutamate decarboxylase (GAD) and choline-acetyl transferase (CAT). The amount of these peptides found only in middle-sized small neurons is also decreasing **[5]**. HD is now observed in a variety of countries and various cultural groups all over the world **[6]**.

CLINICAL SYMPTOMS

Motor symptoms: Involuntary movements and abnormal voluntary movements are linked to movement difficulties. Involuntary movements normally follow a biphasic pattern, in beginning hyperkinetic and increasing over time, then decreasing. rigid-akineticbradykinesia leading to extreme hypokinesia situation. Chorea, or choreoathetosis, is a type of an usual spontaneous movement that consists of jerky or writhing movements that occur on a daily basis **[7]**. Non-motor symptoms: person sufeering of HD have distinct and unique neurological impairments also called as "subcortical dementia". Bradyphrenia, faulty memory, weakening of complex intellectual functions, difficulty performing functions, and other cognitive symptoms are common as well as personality shifts. HD is also characterized by depression, anxiety, irritability, anger, impulsivity, and a proclivity for suicide **[8]**.

PATHOLOGICAL FEATURES

Oxidative stress: The pathology of neurodegenerative diseases is characterized by oxidative stress (OS). High levels of reactive oxygen species (ROS) production and reduced anti-oxidant activity are linked to neurodegenerative diseases which leads to the destruction of neuronal cells **[9 10]**. Lipid peroxidation, protein degradation, and deoxyribonucleic acid (DNA) mutation are all due to oxidative stress, further oxidation injury lipids, proteins, and harm to nerve cell. The levels of8-hydroxydeoxyguanosine have increased significantly in a number of ways. (an oxidized DNA marker). Malondialdehyde (MDA), a lipid peroxidation marker, 3-nitrotyrosine, and heme-oxygenase levels have also been found to be elevated in HD patients' brain **[11]**. By simulating proteasomal dysfunction, oxidative stress leads to mutant Huntingtin aggregation and finaly causes mutant Huntingtin-dependent

cell death **[12]**. Rise in free radical volume disrupt mitochondrial working, energy production, and metabolic hindrance, multiply the risk of excitotoxic damage **[13]**. Despite the fact that the studies mentioned above explicitly show that the Os plays an important role in the pathogenesis of HD, there is no direct link between these two.

Excitotoxicity: It's one of the theories proposed to understand why the striatum's spiny projection neurons degenerate in HD. According to this theory, glutamate receptors are overactive, resulting in reduced glutamate absorption because of hypersensitivity of post-synaptic glutamate receptors in the projection neurons of the striatum. As a result of these metabolic improvements, as well as downstream of glutamate receptor activation and mitochondrial malfunction, abnormal signaling and neuronal impairment **[13]**.

Metabolic dysfunction and mitochondrial impairment: The cell's powerhouse, mitochondria here oxidative phosphorylation and cellular respiration happen, resulting in the production of adenosine triphosphate (ATP). It also helps in regulating low calcium level along with cytosol. Mitochondrial defect, resulting in lower mitochondrial oxygen uptake, glucose metabolism, and cyclic adenosine amount cAMP (cyclic adenosine monophosphate) in the cerebrospinal fluid (csf) it was noticed **[13]**. Deregulation of mitochondrial activity by a mitochondrial toxin, 3-nitropropionic acid (3-NP), results in metabolic dysfunction due to energy deficiency, oxidative stress, and other factors Excitotoxicity and stress **[14]**. Despite the fact, that metabolic dysfunction exists in the body and brain, this causes cytotoxicity primarily in the striatum. Both of these modifications, which are triggered by mitochondrial dysfunction in HD, expose striatal neurons to excitotoxicity.

Preventive function of herbs and secondary metabolites

Nature is the world's biggest combinatorial scientist, and has the answers to all of humanity's ailments. The majority of the world's thousands of people are affected by the pharmacological effects of plant.natural elements that revealsanti-oxidant, decrease in inflamation, calcium antagonization, control apoptosis, and improves neuron activity **[15]**. Many of the important plants and phytochemicals have been discovered acting against 3-NP-induced neuronal impairment in mice, a commonly used animal model for HD.

Herbal plants and Phytochemicals

***Bacopa monnieri*:** also known as *Herpes tismonniera* also known as Brahmi belongs to family *Scrophulariaceae* and it is easily found in all over India. It is called as medhyarasayana in Ayurveda **[4]**.

Chemical components resent in the herb are: tri-terpenoidsaponins, Bacosides A and Bbacopasaponin A-G further with pseudojujubogenin, jujubogeninbacopaside **[16]**. Bacoside A, it has been observed in improving memory **[17]**. Brahmi has also been shown to improve memory in a number of clinical trials.BM extracts helps in guarding neurons as well as improves memorythrough a variety of mechanisms, including metal ion chelation, free radical scavenging., **[13]** and enhanced antioxidative guarding enzymes **[18]** further it has antioxidant, reduce stress, antidepressant, anxiolytic, free radical scavenging, prevent damage to liver and antiulcerogenic properties as well **[19]**. 3-NP deactivates the mitochondrial enzyme succinate dehydrogenase (SDH) as well as complex II-III of the electron transport chain **[20]**. According to one review, dietary BM supplements provide important defense against neurotoxicant-induced oxidative damage in the brain **[21]**.

Ginkgo biloba: The ginkgo tree is considered a "living fossil" since it is one of the world's oldest living animals. **chemical constituents:** trilactonic diterpenes: Ginkgolide A-C, Ginkgolide J-Mtrilactonic sesquiterpene: Bilobalide flavonoids: quercetin, kaempferol, isorhamnetins, and bioflavonoids.

its leaf extract has been shown to protect against dementia (Alzheimer's disease), cardiovascular disease, stress, other complication like vertigo, age-related problems and schizophrenia **[22]**. Its leaf extract has a wide range of protective activities due to its antioxidant and its ability to stimulate anti platelet activity **[23]** restrain of beta amyloid peptide acculamation that helps in stopping of alzimer disease growth **[24]** decrease in the benzodiazepine receptor which is responsible for increasing stress, **[25]** and Relaxing factor produced by the endothelium is encouraged which provides better circulation of blood inside the body. The 3-NP-induced neurobehavioral deficiencies is strengthened by G. biloba extract (100 mg/kg, i.p. for 15 days) **[26]**.

***Withania somnifer*:** *Withania somnifera* (W S) commonly known as **Ashwagandha** family *Solanaceae* it has been used since ages in Ayurvedic medicine.

Chemical constituents: It's all made up of steroidal lactones. Withanolides and alkaloids are the names given to a group of compounds. Withaferin A, withanolide A, and withanolide B are the most common withanolides isolated from plants. withanolide D-P, withanone, sitoindoside VII-X **(Figure 1)**. Withanine (major alkaloid), somniferine, somnine, and somniferinine are only a few more alkaloids **[13]**.

Antioxidant, prevent inflamation, immune-stimulating, anti-stress, improvement in

memory and anti-convulsant compounds are all present in the herb. The GABAergic mechanism has been implicated in the action of WS. In 3-NP treated animals, WS root extract pretreatment increased cognitive capacity and restored acetyl cholinesterase enzyme activity and glutathione enzyme levels.

***Curcuma longa*:** *Curcuma longa* (CL), also known as Haldi or turmeric, is a plant native to India. It is included in family *Zingiberaceae* rhizomes have been utelisein India's, China's, Japan's, and other South Asian countries'as conventional medicinal systems **[27, 28]**. It's been seen as a seasoning and a natural anti-inflammatory, skin disorders, and wounds, as well as have antiseptic property **[28]** yellow coloring is due tom presence of, various curcuminiods, sesquiterpenes, essential oil, and starch. Curcumin exhibit antioxidant, prevent inflamtion **[29]** fungicidal, bactericidal, protect liver, free radical rumage, antiviral. It works through processes such as direct scavenging activity of superoxide, hydroxyl radicals, metal chelating activity also its ability to stimulate the production of antioxidant enzymes its capability to stimulate the production of antioxidant enzymes likesuperoxide dismutase, catalase, glutathione it is the main reason for antioxidant potential of CL as they inhibit effects on xanthine dehydrogenase/xanthine oxidase **[30]**.

Curcumin and the manganese complex of curcumin have antioxidant properties that protect against vascular dementia. The curcumin manganese complexes (AcylCpCpx and CpCpx) also gave the highest inhibitory activity to H2O2-induced cell damage (oxidative stress) at 0.1 microg/ml (< 0.2 microM) in NG108-15 cells, which were more potent than curcumin and related compounds. these complexes significantly improved the learning and memory **[31]**.

Ginsenosides: Ginseng root is a well-known herbal remedy that has been used as a representative tonic in far eastern countries such as China, Japan, and Korea for over 2,000 years. It belongs to family *Araliaceae*.

Chemical constituent's: Ginsenosides are a group of tetracyclic dammarane, triterpenoid, saponin, glycosides that are active constituents of the compound **[32]**. Ginseng has been shown to have beneficial effects in a variety of pathological conditions, including cardiovascular disease. diseases, central nervous system disorders, cancer, immune deficiency, and hepatotoxicity.

Its main ingredients have anti-aging and anti-neurodegenerative properties **[33]**. In addition, it decreases lipid peroxidation as well as prevents excitotoxicity and Ca2+ over-influx into neurons, retains neuronal ATP levels, and maintains the structural

integrity of neurons. Andincrease cognitive performance thus prevents HD. Ginseng also help in reducing nitric oxide (NO), scavenging of free radicals **[34]**. By blocking Ca2+ influx by glutamate receptors, ginsenoside has been shown to shield cortical neurons from glutamate-induced cell death **[35]**. In rat hippocampal neurons, saponins from ginseng inhibit both NMDA and glutamate-induced increases in Ca2+ levels **[36]**.

It has been proven that these ginsenosides' neuroprotective effect is attributed to their ability to inhibit Ca2+ responses caused by glutamate HD is prevented in cultured spinal neuronal communities.

Centella asiatica: *Centella asiatica* (CA), also known as Gotu kola, Indian Pennywort, and Jalbrahmi, is a plant native to Asia. It is member of family Umbelliferae. Because of its potential to enhance memory and age-related brain diseases, it was published as Rasayanas in Ayurveda.

Chemical constituents: triterpenoid saponins which contains asiaticoside, asiatic acid, madecassic acid. Also contaions brahmoside. triterpene acids, betullic acid and isobrahmic acid are reported from the plant.

Aqueous extract of whole plant (200 mg/kg for 14 days) showed an improvement in learning and memory in both shuttle box and step through paradigms. The aqueous extract tested on rats, oxidative stress parameters only 200 and 300 mg/kg showed a significant decrease in the brain levels of malondialdehyde (MDA) with simultaneous significant increase in levels of glutathione.Neuropharmacological effects of CA which includes memory improvement, **[37]** rise in neurite elongation and speeding of nerve regeneration the Male Sprague-Dawley rats given Centella ethanolic extract in their drinking water (300-330 mg kg-1 daily) demonstrated more rapid functional recovery and increased axonal regeneration it indicates that components in Centella ethanolic extract may be useful for accelerating repair of damaged neurons.

CA attenuated the 3-NPA Nitropropionic acid-induced GSH, gross thiols, and endogenous antioxidants are both depleted in the striatum and other brain areas. It also showed resistance to 3-NP-induced mitochondrial dysfunctions, such as decreased SDH activity, electron transport chain enzymes, and mitochondrial viability **[38]**.

Flavonoids:

Flavonoids are a class of polyphenolic compounds found in plants all over the world. They all have the same phenylbenzopyrone structure. Flavonoids exhibit various prevent inflammation, prevent liver and antiviral **[39]**.

Neurodegeneration (especially in the elderly), cognitive dysfunction, mood loss, and oxidative pathologies are all prevented or delayed by flavonoids as Oxidative and nitrosative stress is increasingly associated with the pathology of neurodegeneration and aging. The molecular mechanisms underlying oxidative stress appear to involve a mode of death in which mitogen-activated protein kinase (MAPK) signaling pathways and constituent's present in flavonoids act as potent modulators of intracellular signal transduction **[40]**.

cyclooxygenase (COX) inhibitors has shown neuron protection in the therapy of severals neurological disorders in rat model show, selective COX-2 inhibitor (5 and 10 mg/kg p.o.) substantial reduction in 3-NP-induced oxidative stress. Cyclooxygenase inhibitors also remarkbely re-establishthe reduced SDH activity.

Various flavonoides such as naringin, hesperidin. Hesperidin [flavonoids] dose (50 mg/kg)In the 3-NP treated population, pretreatment greatly reduced behavioral changes, oxidative stress, and mitochondrial enzymes complex dysfunction.It shows therapeutic potential of hesperidin and naringin against Huntington's disease **[41]**.

3-NP model is a helpful method for developing appropriate therapeutic agents for Huntington's disease treatment. The effects of EGCG (10, 20, and 40 mg/kg) on memory and glutathione system activity were important. By involving nitric oxide receptors, EGCG could be used to treat 3-NP-induced behavioral and biochemical changes **[42]**.

Celastrol: It is a triterpenoid quinone it prevents inflammation and kills inscets **[43]**. Celastrol was reported to stop proinflammatory cytokines, inducible nitric oxide synthase, and lipid peroxidation. Celastrol reduced dopaminergic nerve damage and dopamine deficiency in MPTP mice. testedrodents Celastrol treatment remarkably decrease the reduction in dopamine concentration induced by MPTP.

Celastrol inhibited the neurotoxin 3-nitropropionic acid from causing striatal lesions in rat model.It also protects dopaminergic neurons from striatal injury caused by 3-NP by regulating heat shock protein gene expression. **[44]**. The research presented above demonstrates celastrol importance as neuroprotective agent against HD.

Trehalose: It's a non-reducing disaccharide found in a variety of organisms, including bacteria, yeast, fungi, insects, invertebrates, and plants **[45]**. It is also effective in inhibiting aggregation of Abeta and reducing its cytotoxicity, although it shows differential effects toward Abeta40 and Abeta42. When co-incubated with Abeta40, trehalose inhibits formation of both fibrillar and oligomeric morphologies **[46]**.

Trehalose has been shown to improveAutophagic action against aggregation proteins including mutant Huntingtin, resulting in neruoprotective activity against HD **[47]**.

Lycopene: It is also known as carotenoids and present in small amounts in tomatoes and tomato-based products. It is said to provide protection to neurons, antioxidant, prevents inflamation, improves memory, and properties. Rats which received lycopene at a dosage of 4 mg/kg, showed significant infarct size reductions in brain **[48]**. Lycopene therapy greatly reduced the behavioural and biochemical improvements caused by 3-NP, implying that it could be used to treat HD-like behavior **[41]**.

Sesamol: *Sesamum indicum* Linn. Belongs to family *Pedaliaceae,* Sesame, or sesame seed, In India and other East Asian nations, it's been used as a healthy foodstuff for centuries by rise in enzymatic and non-enzymatic antioxidants, it aids in the regulation of high blood pressure, hyperlipidemia, and lipid peroxidation. It protects by suppressing inducible nitric oxide synthase (iNOS) expression via a nitric oxide mechanism. **[50]**. In rodents, it also reduced 3-NP-induced Huntington-like behavioral, biochemical, and cellular changes. Male rats were treated with 14-day regimen of 3-NP (10 mg/kg). Group treated with sesamol shows remarkable improvement like better locomotor action and lesser oxidative injury in various areas of rat brain. Besides these, SML treatment also remarkably revamp mitochondrial enzymes in all areas of the brain as compare to test. And futher provides protection to neurons from getting inflammation and repeatedly improves synaptic plasticity and neurotransmission **[41]**. Sesamol reduced lipid peroxidation, hydroxyl radical, superoxide anion formation, and xanthine oxidase activity in iron-intoxicated mice. It also lowers aspartate aminotransferase and alanine levels in the blood **[50]**.

CONCLUSION

The information presented above explicitly shows that the pathophysiology of HD is complicated by oxidative stress. In both in vivo and in vitro studies, plants with well-known antioxidant and neuroprotective properties were shown to be effective against the symptoms of HD. The above listed plants and chemical compounds can be used for treatment of this disease but more research need to be done for better result. In addition, a variety of other plants with important antioxidant and neuroprotective properties may be investigated for their ability to treat HD.

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