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Huntington's disease: Pathophysiology and therapeutic intervention

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Abstract

Huntington's disease [HD] is a progressive neurodegenerative condition characterized by movement disorder, cognitive impairment, and behavioral symptoms. It is inherited as an autosomal-dominant trait and normally manifests in mid-adulthood. HD is common in India and parts of Central Asia, with a prevalence rate of 4–8 per 100 000 in most European populations. Juvenile onset affects around 5–10% of cases, with signs appearing before the age of 20. Patients may show more parkinsonian symptoms such as bradykinesia, dystonia, tremors and a cognitive deficit in place of chorea. There is no therapy that can completely stop the condition from progressing. There are medications that can help to regulate chorea, dystonia, mental, and psychiatric disturbances. The study covers the disease's pathophysiology, as well as plants and phytochemicals that have been shown to be beneficial.

Keywords: Huntington's disease; Neurotransmission; Etiology; Pathophysiology; Treatment

1. Introduction

Huntington's disease (HD) is a progressive neurodegenerative condition characterized by movement disorder, cognitive impairment, and behavioral symptoms. It is inherited as an autosomal-dominant trait and normally manifests in mid-adulthood [1, 2]. Since CAG codes for the amino acid glutamine, the expansion results in an abnormally long glutamine tract inside the huntingtin protein's N-terminus (Htt) [3]. HD is common in India and parts of Central Asia, with a prevalence rate of 4–8 per 100, 000 in most European populations. This prevalence rate has been verified in more recent studies in other European countries. While HD is uncommon in Finland and Japan, data for Eastern Asia and Africa is lacking. Wide populations of patients with HD are also well-known in Scotland and the Lake Maracaibo area of Venezuela. In the Black American population, the disease may be underestimated. Since the widespread availability of genetic testing, no large-scale epidemiological studies of HD have been conducted in the United States, but it is estimated that approximately 25, 000–30, 000 people have manifest HD and another 150, 000–250, 000 are at risk. Men and women are also affected, and symptoms usually appear in the third and fourth decades [4]. The expansion of the Cytosine-Adenine-Guanine (CAG) trinucleotide repeat in the huntingtin protein on chromosome 4p16.3 causes HD. When the disease progresses, the mutant huntingtin accumulates within brain cells, causing cell toxicity and neuron damage in the brain. Although neuropathological changes can be seen all over the brain, the striatum and cerebral cortex are the primary sites of atrophy. The choreiform movements seen in HD are thought to be caused by substantial loss of striatal medium-sized spiny neurons, which results in distinct striatal atrophy [5].

Men and women are also affected, and symptoms usually appear in the third and fourth decades. HD symptoms may appear at any age, from 1 to 90 years old. Juvenile onset affects around 5–10% of cases, with signs appearing before the

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age of 20. The vast majority of juvenile cases are inherited paternally, and patients may show more parkinsonian symptoms such as bradykinesia, dystonia, tremors, and a cognitive deficit in place of chorea. The Westphal version of HD is diagnosed when patients have more hypokinetic symptoms [6]. Motor disorders, cognitive impairment, and psychological symptoms are all symptoms of the disorder. Chorea, which is marked by involuntary muscle contractions that progress over time and interfere with everyday activities, is one of the most well-known motor signs in HD [7].

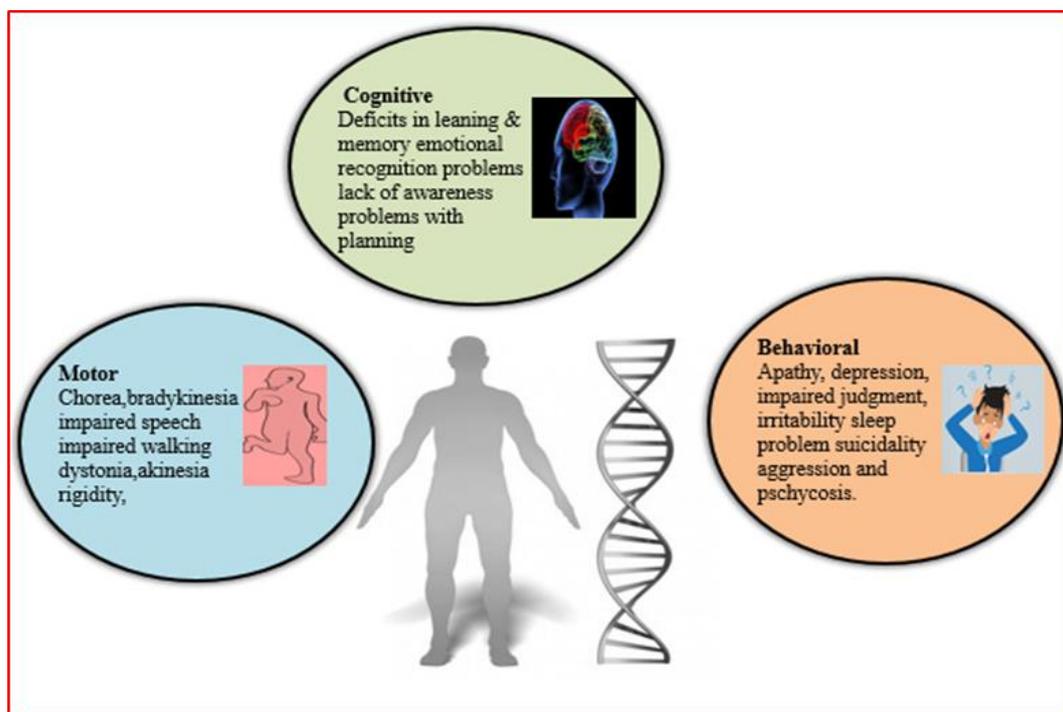


Figure 1 Different symptoms involved in HD [6, 7].

2. Huntington's disease

2.1. Neurotransmission affected in HD

The striatum contains up to 95% of medium spiny neurons in a healthy human brain. These projection neurons are active in the involuntary movement suppression feedback loop. The striatum's atrophy is the disease's pathological hallmark, and medium spiny neurons are the most damaged cells [8, 9]. The loss of medium spiny neurons leads to irregular neurotransmission of the dopamine, glutamate, and gamma-aminobutyric acid (GABA) systems, which is why pharmacotherapy for HD is based on them [10]. Dopamine is a neurotransmitter involved in movement control, perception, motivation, reward processing, and emotion regulation, among other things [11, 12]. Dopamine activates specific dopamine receptors on pre- and post-synaptic neurons, which are commonly expressed in the central nervous system. The high affinity dopamine transporter will transport free, unbound dopamine to the presynaptic terminal (DAT). The vesicular monoamine transporter type 2 (VMAT2) repackages it into vesicles, or enzymes like monoamine oxidase break it down into inactive metabolites [12]. Postsynaptic dopaminergic dysfunction of dopaminergic type 1 (D1) and type 2 (D2) receptors in the striatum is primarily caused by neurodegenerative processes in HD [12-14]. Premanifest and manifest HD both have dopaminergic dysfunction, with manifest patients having a greater loss of striatal D1 and D2 receptor binding [15, 16]. This decline in dopamine receptor binding has been linked to clinical motor evaluation (UHDRS-TMS), functional ability ratings, and evaluations of executive dysfunction in PET studies [17]. Pharmacological agents that alter the function of the dopaminergic system have been of particular interest because choreiform movements in HD are thought to be due to overstimulation of dopamine receptors. However, the glutamate neurotransmitter system is still compromised in early stages of the disorder, and it is thought that increased glutamatergic neurotransmission in the thalamocortical pathways leads to hyperkinetic movements [8]. Modulation of peripheral manifestations of the disorder, such as signs of the muscular, circulatory, metabolic, and digestive systems, can also provide new therapeutic approaches and have a beneficial impact on motor symptoms, according to the researcher [18].

2.1.1. Genetics

HD is caused by autosomal dominant inheritance of an extended CAG trinucleotide repeat within the Huntingtin (HTT) gene on chromosome 4; it is a single-gene disease. Genetic tests may be used to determine this [19]. The HTT gene produces the protein huntingtin, which is needed for normal neural development but whose functions are unknown [20, 21]. The expanded HTT gene in HD codes for a mutant type of huntingtin protein, which induces or contributes to the onset of symptoms through a variety of pathogenic mechanisms [22]. There are fewer than [36] repeats in a "normal" Huntington gene. If a gene has [36] or more repeats, it is uncommon or extended, and CAG repeats of 40 or more will often cause HD. CAG repeat lengths of [36 to 39] have lower penetrance, meaning that some people with these lengths will grow HD and others will not. Those that do get sick are more likely to get sick later in life [23]. HD is not caused by intermediate repeat lengths of [29 to 35], although they may extend into the pathogenic range in future generations. When repeats are present in the pathogenic spectrum, children inherit repeat expansion, which causes "genetic anticipation," or disease onset that is earlier than in the parent. This is most common when fathers pass the mutant gene on to their children, which may be due to the fact that spermatogenesis is characterized by repeat instability. In the middle stages of the illness, in addition to progressive cognitive disturbances, a movement disorder with repeated repetitive twitching and writhing motions of the face, trunk, and extremities known as chorea becomes more common [3].

2.1.2. Mutation of the genome

In the exon 1 of the HTT gene, a pathological increase in the number of copies (expansion) of the glutamine encoding CAG repeats causes HD [19]. Since this mutation causes elongation of the polyglutamine tract within the gene product known as "huntingtin," HD is classified as a polyglutamine disease [3]. Both gametogenesis (especially spermatogenesis) and somatic tissues are characterized by genetic instability in the pathologically elongated CAG tract; the size of the enlarged HTT allele determines polymorphism of the HD clinical features to a large extent [24, 25]. The number of CAG repeats in the mutant allele is inversely related to the age of onset of disease and the age at death. We were the first to demonstrate that the number of CAG repeats is directly related to the rate of HD progression, a finding that was later verified by other researchers. However, the mutation is responsible for approximately 66% of the variability in the course of HD, emphasizing the importance of various modifying factors in this condition [26].

2.1.3. Inherited property

Huntington's disease (HD) is a neurodegenerative disorder that is inherited as an autosomal dominant trait [2]. This means that an affected person inherits one copy of the gene with an expanded trinucleotide repeat (the mutant allele) from a parent who is also affected. Children of HD gene carriers have a 50% chance of inheriting the gene in this type of inheritance pattern, and because penetrance is full, those who inherit the gene will eventually develop the disease [27]. As a result of the mutant allele, they are affected by the disorder. The size of the expanded HTT allele to a large extent determines polymorphism of the HD clinical features; the elongated CAG tract is characterized by genetic instability both in gametogenesis (especially in spermatogenesis) and in somatic tissues; the size of the expanded HTT allele to a large extent determines polymorphism of the HD clinical features. The number of CAG repeats in the mutant allele is inversely proportional to the age at which the disease manifests and the age at which the patient dies [18].

2.2. Pathophysiology

The degeneration of neurons in the putamen, caudate, and cerebral cortex is the most prominent feature. Chorea is caused by the preferential degeneration of enkephalin-containing medium spiny neurons in the basal ganglia via the indirect pathway. Dystonia and akinesia develop as a result of the further loss of substance-P-containing medium spiny neurons in the direct pathway. The phenotypic variability could be explained by a region-specific pattern of neuron loss in the cortex and basal ganglia in the affected patients. Multiple theories exist regarding the pathogenesis of HD, and multiple processes can occur at the same time:

- Neuronal aggregates are a type of neuronal grouping that occurs when neurons the proteolytic pathway in HD is comprised of intracytoplasmic and intra-nuclear inclusions containing the mutant HTT.
- The ubiquitin-proteasome pathway could be harmed by the accumulation of these mutant protein aggregates.
- Excitotoxicity is the term used to describe the toxic effects of excitation. This is due to increased glutamate and glutamate agonist release from cortical afferents working together.
- Mitochondrial dysfunction and a change in energy metabolism are two symptoms of mitochondrial dysfunction. Synaptic dysfunction and changes in axonal transport [28].

2.3. Pathogenesis

In terms of pathology, HD is linked to a diffuse loss of neurons, particularly in the cortex and striatum. The primary neurons targeted in HD are medium spiny neurons in the striatum, which contain GABA and enkephalin and are affected early in the disease. The lateral globus pallidus is where these neurons typically project. The remaining basal ganglia, including the cortex and substantia nigra, are then affected, with subsequent dissemination. The aggregate HTT contains both intranuclear and cytoplasmic inclusions. In neurons, huntingtin is cross-linked with other soluble HTT to form inclusion bodies. It is unknown whether the accumulation of the HTT conglomerate causes cell death or whether the soluble form of the protein is toxic. Although dopamine, glutamate, and GABA are thought to be the neurotransmitters that are most affected in HD and are targeted for treatment, multiple neurotransmitters and their receptors are involved in various parts of the HD brain [29, 30, 4].

2.4. Mechanisms

2.4.1. The function of huntingtin

Physiological HTT is a cytoplasmic protein with a polyglutamine chain at the NH₂-terminus that is expressed throughout the body. HTT is found in all mammalian cells, with the highest levels of expression in the brain. It is involved in neurogenesis and neuronal functions, transcription, cell trafficking, and axonal transport, as well as upregulating the expression of neurotrophic factors like BDNF and NGF [31, 32].

HTT is normally found in high concentrations in the brain, and a lack of this important protein could explain some of the clinical features of HD, as BDNF deficiency is associated with memory loss and motor dysfunction, both of which are seen in HD. HTT has been shown to play a significant role in the development of the embryonic brain, as HTT knockout mice show severe neurogenesis impairment [33].

The polyglutamine chain (polyQ) in mHTT has been lengthened to more than 40 CAG repeats. Because misfolding of this protein causes neurotoxicity, mHTT plays a role in the pathogenesis of HD. The ubiquitin-proteosomal and lysosomal systems do not degrade mHTT, but its toxic protofibrils and fibrils are neutralized in aggregates and inclusions. In the cytoplasm and nucleus of neurons, these aggregates build up [34, 35]. The striatum nuclei of the brain have been reported to have the highest expression of pathological HTT [36].

The exact mechanism by which mHTT causes neuronal degeneration and dysfunction is unknown. Nonetheless, abnormal protein-protein interaction, impaired ubiquitin-proteasome activity, defective autophagy-lysosomal function, transcriptional dysregulation, oxidative stress, apoptosis, mitochondrial and metabolic dysfunction, neuroinflammation, and oxidative stress are all thought to play a role in the pathogenesis of HD [35, 37, and 38] are three numbers that can be used to make a number of different combinations.

2.4.2. Changes in the cells

The formation of cytoplasmic aggregates and nuclear inclusions throughout the brain is one of the most striking hallmarks of HD, and mutant huntingtin (mHTT) is particularly prone to aggregation. Polyglutamine inclusions contain highly ordered amyloid fibres with a high β -sheet content and low detergent solubility; they also sequester a variety of other proteins, including transcription factors and protein quality control factors, implying that their presence is detrimental to cellular function and contributes to a complex loss-of-function phenotype [39].

2.4.3. Macroscopic changes

HD is characterized by brain shrinkage and striatum degeneration (caudate nucleus and putamen), as well as the loss of efferent medium spiny neurons (MSNs) [8]. Despite the fact that the striatum appears to be the brain's most affected region, patients with HD have a regionally specific thinning of the cortical ribbon. Cortical mass loss occurs early in the pathology of HD and progresses from the posterior to the anterior cortical regions as the disease progresses [40].

2.4.4. Dysregulation of the transcriptome

The mechanisms that cause transcriptional dysregulation in HD are numerous. The toxic N-terminal fragments of mHTT can modulate the transcriptional process by interacting abnormally with the transcriptional machinery, either by modifying chromatin or by directly interacting with genomic DNA. The polyQ stretch at mHTT's N terminus provides an appropriate motif for its interaction with glutamine-rich activation domains of various transcription factors, including cAMP response element-binding protein (CREB), Sp1, and the transcriptional coactivator, CREB binding protein (CBP). PolyQ repeats of mHTT were previously thought to form insoluble aggregates, according to previous

models. In both *in vitro* and *in vivo* models of HD, the expression of CREB target genes has been reported to be down regulated. In HD mice and postmortem brains of patients with HD, expression of one of these CREB target genes [peroxisome proliferator-activated receptor (PPAR) gamma coactivator (PGC)-1], which plays a critical role in mitochondrial biogenesis, is reduced [41].

2.5. Factors that may play a role in the development of HD Pathogenesis is the process by which disease develops

2.5.1. Oxidative stress

Oxidative stress is caused by an imbalance in the production of Reactive Oxygen Species (ROS) and the inability of the biological system to detoxify those species and repair the damage that results. Increased levels of oxidative damage products such as malondialdehyde, 8-hydroxydeoxyguanosine, 3-nitrotyrosine, and hemeoxygenase in areas of degeneration in the HD brain, as well as increased free radical production in animal models, suggest that oxidative stress is involved in the disease, either as a causative event or as a secondary component of the cell death cascade. Numerous studies have shown that oxidative damage plays a significant role in the pathogenesis of neurodegenerative diseases such as HD [42-44].

2.5.2. Mitochondrial dysfunction

Mitochondrial function is impaired in HD, and this occurs early in the disease process. Mitochondrial dysfunction is likely fundamental to the pathogenesis of HD. In early studies, functional abnormalities in mitochondria were also discovered. A defect in succinate dehydrogenase, a component of both the Krebs cycle and the electron transport chain's complex II, was discovered in the caudate and to a lesser extent in the cortex of postmortem HD brains in 1974. Following studies found a significant decrease in complex II activity in the caudate nucleus of HD brains (approximately 50% reduction) when compared to levels in matched control brains. In addition to decreases in complex II activity, there have been decreases in complex III activity in the caudate and putamen, as well as complex IV activity in the putamen. However, because the majority of these patients had advanced neuropathy, including severe striatal atrophy (pathological grades 3 and 4 of HD), alterations in the mitochondria's source (i.e., glial, neuronal, etc.) are likely to have been affected [45].

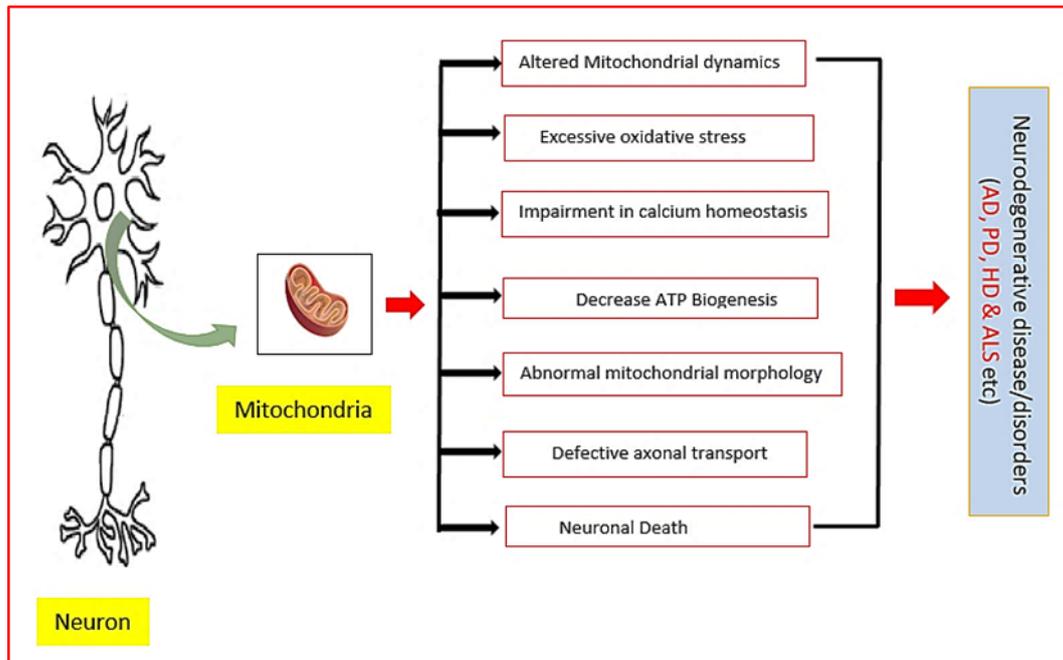


Figure 2 Mitochondrial dysfunction associated with neurological disorders/disease[97].

2.5.3. Excitotoxicity

Excitotoxic neuronal death is caused by excessive glutamate neurotransmission, which is accompanied by persistent increases in intracellular calcium levels [46]. Excitatory amino acids over activate NMDA receptors, resulting in the production of free radicals and the opening of the mitochondrial permeability transition pore, both of which are fatal. Since the direct injection of acids such as QA and kainic acid into the striatum nuclei causes neurodegeneration of GABAergic MSN as seen in HD, the role of excitotoxicity has been recognized as important [38].

2.5.4. Neuroinflammation

The inflammatory process is a protective mechanism that protects our bodies from harm and disease by releasing cell mediators that combat foreign substances and aid in infection prevention. Although inflammatory processes have been clearly demonstrated in the pathophysiology of HD, there is no direct link between neuroinflammation and the progression of the disease. In degenerating neurons in HD, post-mortem studies have revealed high levels of activated microglia and macrophages. IL-6, IL-1, and TNF- levels have been found to be upregulated in the striatum and plasma of HD patients, as well as in animal models of the disease. Microglial cells may recognize the pathogenic mHTT aggregates as foreign substances, resulting in neuroinflammation [47-49, 38].

2.5.5. Apoptosis

Apoptosis is a pathogenic mechanism underlying chronic neurodegenerative diseases, including HD [50]. Caspases are cysteine-dependent, aspartate-specific proteases that play a key role in the initiation and execution of programmed cell death. In HD patients and various animal models of HD, transcriptional upregulation and increased expression of caspase-1, caspase-3, and caspase-9 have been reported [51]. The ability of mHTT to cause apoptosis has been demonstrated [52, 38].

Other than above factors gut microbiota impairment associated with the neurological disorders such as depression, Autism spectrum disorder, Alzheimer's, Parkinson's disease and Huntington disease (HD) [98, 99].

2.6. Prognosis

Genetic testing confirms the presence of the expanded trinucleotide repeat that causes HD in about 99 percent of HD diagnoses based on the typical symptoms and a family history of the disease. Diagnostic testing to confirm or rule out disease, presymptomatic testing to determine the carrier status of a person at genetic risk of inheriting the disease, and prenatal testing to determine the carrier status of a foetus are the three forms of HD genetic testing available. These three test scenarios necessitate various types of information being provided to the person taking the test. The HD genetic test is widely available, and it can be ordered as a clinical diagnostic procedure by submitting a blood sample to one of the numerous DNA diagnostic laboratories. Recent research suggests that the incidence of new HD mutations could be much higher than previously thought. As a result, in the absence of a family background, HD testing is beneficial [53].

2.7. Biomarkers are biological markers that can be used to identify people

Because of the heterogeneity of motor/psychiatric and cognitive disorders in HD, as well as the normal difference in rates of development, evaluating the effects of any possible therapy can be challenging. As a result, biomarkers are needed to represent disease status objectively and accurately. Furthermore, genetic testing helps us to classify presymptomatic HD patients, in which the aim will be to implement medication to postpone or even avoid neurodegeneration; biomarkers are critical in determining the timing of such treatments once they become available.

We now have a much better understanding of the natural progression of HD from premanifest via manifest disease thanks to large-scale longitudinal studies like TRACK-HD [54-57] and PREDICT-HD [58-60]. Even in those reported to be more than 15 years from estimated disease onset, structural magnetic resonance imaging revealed substantially faster rates of striatal volume decline in premanifest and manifest individuals relative to age-matched controls [61]. In this case, Diffusion tensor imaging, which has shown anomalies in neuronal fibre orientation and integrity in white matter and subcortical gray-matter structures in both premanifest and manifest HD, functional magnetic resonance imaging techniques, and 18F-fluorodeoxyglucose positron emission tomography are other imaging modalities that can serve as possible biomarkers of disease [62].

Performance on the speeded tapping task and degradation of emotion recognition have both been found to monitor clinical decline in premanifest individuals; performance on the Stroop test and indirect circle tracing have both been found to track clinical decline in those with early HD [57]. The researchers created an ultrasensitive single-molecule counting mHTT immunoassay that can detect very low levels of mHTT in the cerebrospinal fluid (in the femtomolar

range). The amount of mHTT detected was linked to disease onset and decreased cognitive and motor function, and it is a promising biomarker that is currently being tested in clinical trials [63]. Tau levels in the cerebrospinal fluid have also shown promise as a biomarker for Alzheimer's disease [64]. In Huntington's disease, the amount of neurofilament light protein (NfL) in plasma, which can be measured with a simple blood test, has recently shown promise as a prognostic blood biomarker of disease initiation and progression [65, 66].

2.8. Treatment

2.8.1. Plants that have medicinal properties

Plants and natural compounds including *Bacopa monnieri*, *Withania somnifera* (ashwagandha), *Ginkgo biloba*, *Centella asiatica*, Ginseng, and curcumin have been used to prevent or mitigate neurological disorders and relieve neurological symptoms *in vivo* and in clinical trials.

2.8.2. *Bacopa monnieri*

Bacopa monnieri (BM) or *Herpestis monniera*, commonly known as Brahmi (Family: Scrophulariaceae), is a medhyarasayana in Ayurveda and is found in the Indian subcontinent [67, 68]. BM extracts have been shown to have neuroprotective and memory-enhancing properties through a variety of mechanisms, including metal ion chelation, free radical scavenging, and increased antioxidative protection enzymes. Apart from that, it has antioxidant, anti-stress, anti-depressant, anxiolytic, and free radical scavenging properties. BM may be useful in the treatment of HD because of its strong antioxidant activity and defensive effect against stress-mediated neuronal dysfunctions [69].

2.8.3. *Withania somnifera*

Withania somnifera, also known as Ashwagandha, is an Ayurvedic medication that has been used for centuries for its anti-inflammatory, anti-oxidant, anti-stress, neuroprotection, immune boosting, and memory capacity enhancing properties, as well as its function in neuronal axon and dendrite regeneration [70]. Ashwagandha and its active constituents (sitoindosides VIIX and withaferin A) serve as antioxidants, increasing endogenous superoxide dismutase, catalase, and ascorbic acid levels while lowering lipid peroxidation [71]. Complement, lymphocyte proliferation, and delayed form of hypersensitivity are all inhibited by it, making it an anti-inflammatory agent [72]. The role of the GABAergic system in the pathogenesis of HD has been well known, and WS has been reported to function via the GABAergic system. In 3NP treated animals, *Withania somnifera* root extract pretreatment significantly improved cognitive function and restored acetyl cholinesterase enzyme activity and glutathione enzyme level system. Because of its GABAergic and antioxidant properties, the root extract of WS showed a potential neuroprotective impact in rats against a3NP-induced neurotoxicity, making it a promising lead in the treatment of HD [73, 74, 69].

2.8.4. *Ginkgo biloba*

Ginkgo biloba L. was first described 5, 000 years ago in Chinese Materia Medica [75]. The ginkgo tree is considered a "living fossil" since it is one of the oldest living organisms on the earth [76]. It is a fact that Ginkgo leaf extract has been shown to protect against neurodegenerative diseases such as dementia (Alzheimer's disease), cardiovascular diseases, cancer, stress, tinnitus, and geriatric complaints such as vertigo and age-related macular degeneration, as well as psychiatric disorders such as schizophrenia [77].

2.8.5. *Centella Asiatica*

Centella asiatica (CA), also known as Gotu kola, Indian Pennywort, and Jal brahmi, is a member of the Umbelliferae family of plants. Because of its ability to enhance memory and age-related brain problems, it has been classified as Rasayanas in Ayurveda [78]. In the striatum and other brain regions, CA reduced the depletion of GSH, total thiols, and endogenous antioxidants caused by 3NP. It also showed resistance to 3NP-induced mitochondrial dysfunctions, such as decreased SDH activity, electron transport chain enzymes, and mitochondrial viability. The findings of this study show that CA's protective effect against neuronal damage caused by OS and mitochondrial dysfunctions, as well as its memory enhancing activity, can be useful in managing HD-related impairment [79]. Ginsenosides are a type of amino acid that can be found in plants.

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 [80]. The most common ginseng species are Asian ginseng (*Panax ginseng* C. A. Meyer) and American ginseng (*Panax quinquefolium* L.), both of which are members of the Araliaceae family [81]. In genetically engineered mice, the ginsenosides Rb1, Rc, and Rg5 have been shown to protect medium spiny neurons from glutamate-induced apoptosis. The capacity of these ginsenosides to suppress glutamate-induced Ca²⁺

responses in cultured spinal neuronal cultures has been proposed as a possible explanation for their neuroprotective effects [82]. These findings strongly suggest that ginseng and ginsenosides can be used to create new therapeutics for the treatment of HD and other neurodegenerative diseases.

2.8.6. Flavonoids

Flavonoids are a class of polyphenolic compounds found in plants all over the world. They have the form of a common phenylbenzopyrone (C₆C₃C₆)[83 and 84]. Flavonoids have been shown to prevent and delay neurodegeneration (especially in the elderly), cognitive impairment, mood deterioration, and oxidative pathologies in recent preclinical and clinical studies [85]. They also defend the body from oxidative damage caused by peroxynitrite [86]. If you want to be more formal, Flavonoids block the enzyme nitric oxide synthase, which is involved in neurodegenerative diseases such as Alzheimer's and Parkinson's [87, 88].

2.9. Method of treatment

The new therapeutics are only symptomatic and have little effect on the disease's progression. In 2008, the US Food and Drug Administration (FDA) approved tetrabenazine (TBZ; Xenazine™) for the treatment of chorea in HD. Deutetrabenazine (AUSTEDOT™), a deuterated form of TBZ, has a better pharmacokinetic profile and was recently approved by the FDA for the treatment of chorea associated with HD as well as tardive dyskinesia [89].

2.10. Chorea

Tetrabenazine TBZ blocks the dopamine pathway by inhibiting Vesicular Monoamine Transporter (VMAT) type 2, lowering available dopamine in the synapse and reducing interactions with postsynaptic dopamine receptors. As a result, TBZ has antichoreic properties. TBZ improved chorea and other motor symptoms in mice models, as well as reducing the loss of striatal neuronal cells. The FDA has approved TBZ for the treatment of chorea in people with HD [90].

2.11. Deutetrabenazine (aka SD809)

One disadvantage of TBZ is that it has a variable metabolism and must be taken three times a day due to its short half-life. Any of the side effects, such as anxiety, nausea, and akathisia, may be attributed to the drug's pK profile, which includes a short half-life and failure to achieve steady state. Deuterium is a nontoxic, heavier type of hydrogen that forms a stronger bond with carbon and thus requires more energy to break. As a result, it is more difficult to metabolize, resulting in a longer half-life and the ability to administer lower doses and less regularly (i.e., twice a day). Deutetrabenazine was examined in ninety patients with manifest HD in a recent study [91]. Treatment resulted in a significant improvement in chorea, similar to that seen with TBZ. There was also an increase in total motor scores and dystonia, which TBZ did not display. Depression and Parkinsonism side effects were not observed in this deutetrabenazine study. Given that VMAT inhibition depletes dopamine, this is critical. Depression is a side effect of TBZ, and considering the high suicide rate among HD patients, this is a serious concern [92]. The lack of depression may be attributed to the benefits of deutetrabenazine being administered at a lower dosage, but this needs to be repeated over a longer period of time, since this study was only 12 weeks long. Deutetrabenazine was approved by the Food and Drug Administration in 2017 for the treatment of chorea caused by HD [93].

2.12. Disturbance of Behaviour and Psychiatry

Aggression, irritability, impulsivity, depression, anxiety, apathy, mania, drug abuse, sexual addiction, and psychosis are only a few of the behavioural and psychological disorders that could be present in HD. Where appropriate, management options other than pharmacotherapy, such as environmental improvements, should be considered [9]. While citalopram is widely used in HD for depression, anxiety, obsessive-compulsive disorder symptoms, and apathy, depression also responds well to non-stimulating selective serotonin reuptake inhibitors (SSRIs) including citalopram. SSRIs that are stimulating, like fluoxetine, can intensify anxiety at first, so use caution when starting this medication. Mirtazapine, a sedating antidepressant, can be used if insomnia is an issue as well. For properly chosen patients, cognitive behavioural therapy may be beneficial. Anxiety, irritability, anger, obsessive-compulsive behaviours, and psychosis are among the psychological symptoms that can lead to treatment in both traditional and atypical neuroleptics [94].

Parkinson's disease is a neurological condition that affects people. Antiparkinsonian drugs, such as levodopa, dopamine agonists, and amantadine, can be helpful for patients with the akinetic type of HD (Westphal variant)[95, 96]. Botulinum toxin injections may be used to treat focal dystonia caused by HD, both in the standard and Westphal variants. Even in patients with chorea, there may be underlying dystonia and/or bradykinesia that needs to be treated [9].

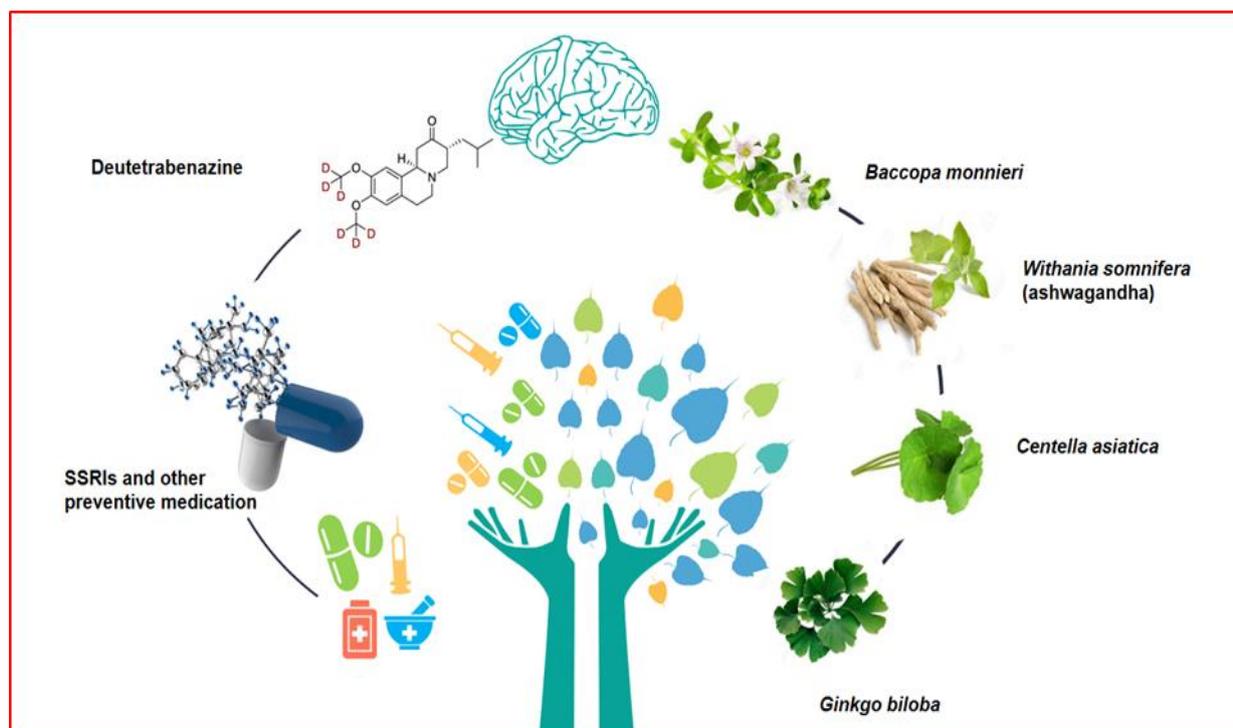


Figure 3 Various therapeutic intervention for HD [69, 70, 75, 78, 88, 90, 93].

3. Conclusion

HD is an inherited neurodegenerative disease with no known treatment that affects motor and cognitive functions by targeting striatal MSNs. The mHTT protein, which has a polyQ tract expansion, is toxic to neurons and is the cause of HD. Genetic testing is widely available, but genetic counselling prior to testing is critical since both positive and negative test outcomes have a significant effect on both the child and the family. Chorea, mental and psychiatric disturbances, and parkinsonism-like symptoms are currently treated with symptomatic treatments. The information presented above clearly shows that oxidative stress plays an important role in the pathophysiology of HD. Furthermore, in both *in vivo* and *in vitro* studies, plants with well-established antioxidant and neuroprotective effects have shown beneficial effects against the symptoms of HD. These numerous clinical trials suggest that therapies that may improve the quality of life for HD patients in the future will be discovered.

Compliance with ethical standards

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Disclosure of conflict of interest

There was no conflict of interest in this study.

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