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Plant-Derived Phytochemicals as Multi-Target Neuroprotective Strategies for Huntington's Disease: Molecular Mechanisms, Therapeutic Potential and Translational Challenges

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Abstract

Huntington's disease is an inherited progressive neurodegenerative disorder that is caused by expansion of the CAG trinucleotide in the HTT gene, leading to the production of the abnormal huntingtin (mHTT) protein that accumulates and causes the death of neurons. Although numerous efforts have been made for the symptomatic treatment, and new molecular therapies emerge, a disease-modifying treatment is not yet available. The medicinal plants and their bioactive phytochemicals may be useful for HD therapy, the promising therapeutic opportunities given their multi-target activities against key pathological mechanisms implicated in HD. In this review, the molecular basis of HD pathogenesis has been summarized and the neuroprotective potential of the plant-derived compounds namely curcumin, resveratrol, epigallocatechin-3-gallate (EGCG) withanolides, ginsenosides and quercetin has been critically evaluated. These phytochemicals have antioxidant, anti-inflammatory, mitochondrial protective, anti-apoptotic and autophagy-regulating activity, which involves the regulation of pathways like Nrf2/ARE, NFκB, SIRT1/PGC-1α,

AMPK/mTOR and protein clearance mechanisms. Experimental models suggest that these molecules have anti-oxidative, pro-mitocondrial, anti-neuro-inflammatory and pro-neuronal survival effects. However, poor bioavailability, limited penetration of the blood–brain barrier (BBB), variability of plant preparations and the lack of human studies are limiting the clinical translation. The therapeutic potential of plant derived compounds could be improved by future developments in the field of nanotechnology based drug delivery systems, artificial intelligence, computational drug discovery, precision medicine and standardized clinical evaluation. Medicinal phytochemicals are potential complementary candidates for multi-target approaches against HD, but need to be extensively validated in clinically relevant models and humans.

Introduction

Huntington's disease (HD) is a devastating inherited neurodegenerative disorder which is characterised by a progressive loss of motor function, cognitive ability and psychiatric health. It is due to the increase of the three trinucleotide cytosine-adenine-guanine (CAG) repeats in the 1st exon of the HTT gene on chromosome 4. This mutation causes production of the abnormal (mutant) huntingtin (mHTT) protein with an increased polyglutamine sequence that triggers a series of abnormalities in the cells which ultimately causes selective neuronal degeneration (Tabrizi et al., 2022; Afzal et al., 2025).

Symptoms of the disease usually first appear in adulthood and include abnormal movements, poor coordination, decreased mental function, depression, anxiety and behavioural changes. The disease is mainly confined to the medium spiny neurons of the striatum, with subsequent spread to the cortex. These neuronal populations have been shown to be selectively vulnerable because of their high metabolic demands, dependence on mitochondrial energy production and sensitivity to disturbance of calcium regulation and oxidative balance (Saudou, Humbert, 2016).

At the molecular level, the HD is a very complex disease including several intertwined pathogenic processes, and not a single disease pathway. The mutant huntingtin protein impacts on systems of transcriptional regulation, mitochondrial metabolism, intracellular transport, synaptic function and protein degradation. While the formation of mHTT aggregates is a major pathological hallmark of HD, there is growing evidence that soluble mHTT species can play significant roles in early neuronal functional dysfunction through disruption of normal cellular processes (Makeeva et al., 2023).

The current therapeutic strategies for HD are mainly aimed at symptom management and not at changing the course of the disease. Although drugs against motor symptoms, psychiatric issues and neurotransmitter imbalance are available that may make life better, they cannot halt passing away of neurons. With recent developments in gene-silencing techniques and molecular therapies, there is renewed hope for treatment, but challenges remain to be addressed, such as delivery issues, potential side effects and the complexity of the mechanisms of disease (Tabrizi et al., 2022).

There are no effective disease modifying therapies to date, which has propelled research into other therapeutic approaches, such as natural products from medicinal plants. There is a growing interest in plant-based compounds due to their multiple biological activities that could be able to intervene in various pathological pathways at the same time. Many phytochemicals have antioxidant, anti-inflammatory, mitochondrial protective and protein regulating properties which are relevant for multifactorial neurodegenerative diseases like HD, unlike conventional single-target drugs. In recent reviews, the protective effects of natural compounds studied in HD models have been identified to include decreasing oxidative damage, enhancing mitochondrial function, inhibiting apoptosis, suppressing inflammation, and regulating autophagy pathways (Lum et al., 2021).

Medicinal plants have been used for traditional health systems for neurological diseases historically due to their wide pharmacological activities. In the modern era of molecular investigations, a wide number of bioactive molecules responsible for the above mentioned effects have been identified, such as polyphenols, flavonoids, terpenoids, alkaloids and phenolic compounds. Of these, curcumin (Curcuma longa), resveratrol (Vitis vinifera), EGCG (Camellia sinensis), withanolides (Withania somnifera) and ginsenosides (Panax ginseng) have been extensively studied for their neuroprotective effects in experimental models (Salman et al. 2025).

There is recent evidence that compounds from plants can affect multiple pathways within molecular processes that are known to affect the progression of HD. The activation of the anti-oxidant pathway (Nrf2) increases cellular resistance to ROS and the inhibition of the NF-κB pathway decreases inflammatory responses. Likewise, the regulation of both SIRT1 and AMPK and mTOR pathways plays a role in maintaining mitochondria and the clearance of toxic protein aggregates through autophagy. The multitarget effects offer a scientific basis to explore medicinal plants as therapeutic agents for HD (Naqvi et al., 2023).

But, though encouraging experimental results are obtained, there are major restrictions. Most of the research on plant-derived compounds for HD has been conducted in cellular or animal models, and there is still some limited evidence from clinical trials in humans. Clinical translation is still hampered by issues of poor absorption, high metabolism, low penetration of the blood-brain barrier, instability of plant extracts, and absence of standardization of formulations.

The purpose of this review is to explore the therapeutic potential of traditional medicinal plants and plant derived phytochemicals based on their critical evaluation in case of the treatment of the disease-Huntingtons Disease. Special attention is given to the molecular mechanisms underlying neuroprotection, the experimental evidence from preclinical studies, recent advances in computational approaches, current translation problems, and future directions in developing plant-based therapeutic strategies.

Figure 1. Molecular Pathogenesis of Huntington's Disease and Therapeutic Intervention Targets of Phytochemicals

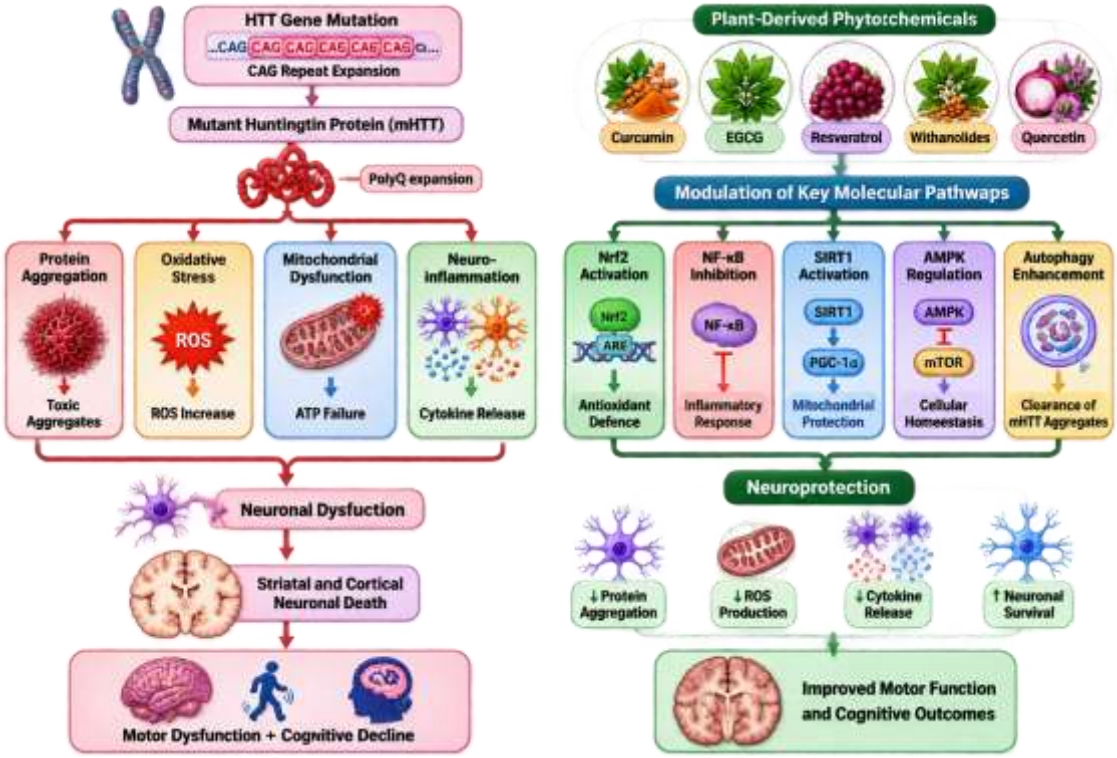

Figure 1. Integrated molecular mechanisms of plant-derived phytochemicals in Huntington's disease. Schematic illustration of mHTT-mediated pathogenic pathways and the neuroprotective actions of phytochemicals through antioxidant, anti-inflammatory, mitochondrial, and autophagy-regulating mechanisms.

Molecular Pathogenesis of Huntington's Disease

Mutant Huntingtin Protein and Polyglutamine Toxicity

HD is a disorder in which the basic molecular defect is the presence of mutant huntingtin protein with an extended polyglutamine tract. The size of the CAG expansion has been shown to be closely related to age of onset with larger expansions leading to earlier manifestation of the disease. The longer polyglutamine sequence causes changes in the protein folding characteristics, which make mHTT more likely to fold and interact with other important proteins in the cell (Jimenez-Sanchez et al., 2022).

There are several ways in which the mutant huntingtin interferes with normal neuronal function, such as by disrupting transcription, interfering with the transport of cargo down the axon, causing mitochondrial abnormalities or triggering faulty quality control of proteins. Inside the cell, mHTT binds to transcription factors and epigenetic modifiers, which leads to changes in the expression of genes involved in neuronal survival and metabolic control. These transcriptional abnormalities lead to progressive susceptibility and degeneration of neurons (Jimenez-Sanchez et al., 2022).

In addition, the build-up of misfolded mHTT is a great strain on protein clearance pathways in the cell. The ubiquitin–proteasome system and autophagic machinery become overwhelmed, resulting in accumulation of toxic protein species. While aggregate formation can be a cellular mechanism to sequester toxic proteins, their accumulation can eventually lead to disruption of neuronal communication and viability (Miguez et al., 2023).

Oxidative Stress and Redox Imbalance in Huntington's Disease

Generation of oxidative stress is one of the earliest and most chronic pathological events linked to the progression of the disease. Because of the high metabolic requirements of neurons, the central nervous system is especially sensitive to disruption of redox regulation. In HD, mutant huntingtin protein disrupts the respiration of mitochondria, leading to overproduction of reactive oxygen species (ROS), such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals. The accumulation of ROS is continuous and leads to oxidative modifications of proteins, lipids and nucleic acids which ultimately result in impaired neuronal function and cell death (Tabrizi et al., 2022).

Oxidative imbalance plays a major role and is linked to mitochondrial abnormalities related to mutant huntingtin. With ETC activity disrupted, there is greater leakage of electrons and a greater increase of ROS produced, and less antioxidant capacity is available to neutralise oxidative damage to neurons. Research in HD models has shown that there is a decrease in the activity of endogenous antioxidants such as superoxide dismutase (SOD), catalase and glutathione peroxidase which are involved in the progression of the disease (Cattaneo et al., 2020).

Nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway is one of the most crucial cellular pathways in the regulation of antioxidants. Nrf2 controls the expression of antioxidant response genes which maintain cellular redox balance under physiological conditions. In HD, however, oxidative stress is associated with a deregulation of the normal function of Nrf2, leading to decreased expression of protective antioxidant enzymes. Hence, the activation of Nrf2 pharmacologically is a promising therapeutic approach to prevent oxidative injury in neurodegenerative diseases (Saha et al., 2021).

Phytochemicals derived from plants have been extensively studied since many of them are potent antioxidants and play a role in the regulation of the endogenous defence systems instead of scavenging free radicals per se. Polyphenols like curcumin, resveratrol, epigallocatechin-3-gallate (EGCG) and quercetin have been noted to promote the antioxidant response via activation of Nrf2 signalling and improved mitochondrial function. These mechanisms can help lower the oxidative damage caused by mutant huntingtin toxicity and help maintain the survival of the neurons (Lum et al., 2021).

The major bioactive compound of Curcuma longa, curcumin, has been shown to have antioxidant properties by enhancing the transcription of antioxidant enzymes via the transcription factor Nrf2. Experimental studies indicate that curcumin decreases lipid peroxidation, increases mitochondrial activity and decreases oxidative stress mediated apoptosis. Yet, there are issues with absorption and limited brain access that obstruct its therapeutic use (Kunnumakkara et al., 2019).

Likewise, resveratrol has been a subject of many studies due to its ability to activate SIRT1, control mitochondrial biogenesis and increase cell resistance against the effects of oxidative damage. The activation of SIRT1 works to maintain the mitochondria by regulating PGC-1α signalling that is often compromised in Huntington's disease. Based on these results, it is possible that resveratrol can exert an opposite effect to that of the mHTT toxicity on mitochondrial and oxidative alterations (Fernández-Mar et al., 2021).

Mitochondrial Dysfunction and Energy Failure

A critical mechanism of selective neuronal vulnerability in HD is thought to be mitochondrial dysfunction. Neurons depend on continuous ATP production for maintaining membrane potential, release of neurotransmitter and synapse communication. Thus, even subtle defects in mitochondrial function can have severe impacts on the neurons. Mutant huntingtin directly binds to mitochondrial proteins and affects a number of mitochondrial functions related to energy metabolism. Experimental models have shown that there is decreased function of the respiratory complexes in the mitochondria, decreased ATP production, abnormal calcium regulation, and an increase in vulnerability to mitochondrial permeability transition (Saudou & Humbert, 2016).

Mitochondrial disturbances are especially detrimental to the striatum, the main region involved in HD, as the neurons of this region have high energetic demands and rely heavily on oxidative phosphorylation. Not only is there an energy deficiency, but defective mitochondrial function also leads to heightened ROS production and induction of apoptotic pathways. A key regulator affected in the course of HD progression is the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), which is involved in mitochondrial biogenesis and energy metabolism. Mutant huntingtin inhibits the expression of PGC-1α which results in decreased mitochondrial turnover and impaired adaptation of neurons to metabolic stress (McColgan & Tabrizi, 2018).

Thus, natural compounds that can restore mitochondrial function have become the focus as potential HD therapeutics. Resveratrol stimulates SIRT1-PGC-1α signalling for mitochondrial biogenesis and cell energy metabolism. Similarly, the ginsenosides of Panax ginseng have shown mitochondrial protective properties by regulating oxidative pathways and enhancing neuronal survival mechanisms (Lum et al., 2021). Recent reviews highlight that compounds derived from plants could have a role to play in neuroprotection in HD models by addressing multiple pathways simultaneously, such as mitochondrial dysfunction, oxidative stress, inflammation and apoptosis, which may be an advantage over targeting a single pathway with therapeutic drugs.

Neuroinflammation and Microglial Activation

Neuroinflammation has become an important factor in the pathology of HD. While activation of the immune system may be a protective mechanism at first, chronic inflammatory responses promote neuronal damage and hasten the progression of the disease. In the central nervous system, immune cells (microglia) are activated by the accumulation of mutant huntingtin and neuronal stress. Activated microglia produce inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1 beta and interleukin-6, which can lead to oxidative damage, synaptic dysfunction and neuronal degeneration.

One key pathway in the regulation of inflammatory responses is the nuclear factor kappa B (NF-κB) pathway. Overexpression of NFκB leads to increased transcription of inflammatory genes and increased production of cytokines. Thus, the ability to inhibit NF-κB signalling is a key point of how neuroprotective agents might be able to lower inflammation in HD (Glass et al., 2023). There are several compounds that have been found to be anti-inflammatory by regulating NF-κB signalling. Curcumin suppresses inflammatory gene expression, resveratrol down regulates the production of inflammatory cytokines and thymoquinone regulates inflammatory pathways related to oxidative damage. These findings suggest that medicinal plants may be useful as chronic neuroinflammation modulators in Huntington's disease (Lum et al., 2021).

Molecular mechanisms of plant-derived phytochemicals are neuroprotective for Huntington's disease.

The therapeutic possibilities of medicinal plants in the case of HD are partly due to their capacity to affect multiple interconnected molecular pathways relevant to the survival and degeneration of neurons. Many plant-derived compounds have pleiotropic effects, simultaneously affecting a variety of processes including oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, protein aggregation, and autophagic clearance. The activity has a multi-target nature and is of particular relevance to the pathological process of HD which involves a complex interaction between the toxicity of the mutant protein, huntingtin, and several abnormalities of cells downstream of this. It is important to note, however, that while these mechanisms offer strong biological rationale for further investigation, mechanisms seen in experimental models are not necessarily associated with disease modification in human patients with HD (Salman et al., 2025).

Regulation of Oxidative Stress Through the Nrf2/ARE Signalling Pathway

The oxidative imbalance is an integral part of the HD pathological process and a common mechanism that has been focused in the study of neuroprotective mechanisms of phytochemicals is the restoration of antioxidant defence mechanisms. Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a key pathway that regulates the antioxidant response of a cell. Normally, Nrf2 is constantly degraded by interaction with Kelch-like ECH-associated protein 1 (Keap1). In times of oxidative stress, however, Nrf2 will no longer be degraded, will be translocated to the nucleus, and will bind to antioxidant responsive elements (AREs) that will increase the expression of protective genes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), glutathione-related enzymes, and antioxidant proteins (Cuadrado et al., 2019).

Neurons are vulnerable to oxidative stress in HD as a result of increased production of reactive oxygen species (ROS) and decreased antioxidant capacity. Mutant huntingtin also contributes to mitochondrial dysfunction and oxidative damage, leading to a vicious cycle of increased oxidative stress promoting neuronal dysfunction. Thus, endogenous activation of the antioxidant pathways would be a more sustainable way of action than simply removing free radicals.

A number of compounds derived from plants have been shown to induce Nrf2 pathway activation. Curcumin has been extensively studied as a natural activator of Nrf2, and has been found to induce antioxidant enzyme expression in experimental models of neurodegeneration. In a similar manner, resveratrol, quercetin, naringin, and ginsenosides have shown a possible effect on the Nrf2-associated pathways, hinting that phytochemicals can possibly restore cellular redox balance via endogenous defence mechanisms (Farooqui et al., 2023).

Importantly, the evidence of enhanced antioxidant responses to reduce oxidative damage, preserve mitochondrial activity and promote neuronal survival supports the importance of Nrf2 regulation in HD. However, the exact links between activation of Nrf2 and the mHTT pathology are not fully understood. Future research will be required to know if the immediate effect of phytochemical-induced antioxidant activation is on mutant huntingtin aggregation and clearance or if it is a downstream effect that protects cells from stress.

Modulation of Neuroinflammation through NF-κB Signalling

Neuroinflammation has come to the fore as a major factor in the progression of HD. While inflammatory responses have a protective role at the onset, the continued activation of immune pathways can lead to neuronal damage, with excessive cytokine production, amplification of oxidative stress and disruption of synaptic communication being involved. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway is a major pathway controlling inflammatory responses. Activated NF-κB stimulates the expression of genes of inflammatory mediators, such as tumour necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). Immune dysregulation was accompanied by enhanced inflammatory signalling in HD patients and experimental models, which may play a role in the progression of the disease beyond just being a result of neuronal injury (Crotti & Glass, 2015).

Plant derived phytochemicals have significant anti-inflammatory activity which is due to the modulation of NF-κB activity. Curcumin acts by down-regulating the activation of NF-κB by acting on upstream inflammatory signaling molecules while resveratrol inhibits the production of inflammatory cytokines by its action on a number of regulatory pathways. Thymoquinone and flavonoids including quercetin have also been shown to have anti-inflammatory effect in neurological disease models. Phytochemicals' capacity to modulate both inflammatory and oxidative pathways is especially significant as these pathways are closely linked. ROS production by activated microglia will also promote inflammatory signalling as will oxidative stress itself. Thus, those compounds that can block this inflammatory-oxidative feedback loop may be more valuable than any compound targeting the individual pathways (Ransohoff, 2022).

But the majority of evidence for anti-inflammatory activity of phytochemicals comes from general models of neurodegeneration or toxin-induced models of HD. Future studies will be important to determine whether these compounds can affect immune responses in genetic HD models that express mutant huntingtin that are associated with disease.

Protection and recovery of energy metabolism at the mitochondria

Mitochondrial dysfunction is a large pathological feature of HD and is involved in the death of neurons, affecting ATP generation, oxidative stress, calcium homeostasis and activation of apoptosis pathways. Since mitochondria play a critical role in the functioning of neurons, mitochondria support is a major therapeutic goal. The disruption of mitochondrial biogenesis is caused by interfering with peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a very important factor in the regulation of the expression of mitochondrial genes by mutant huntingtin.

Loss of PGC-1α activity leads to defects in energy metabolism and to greater vulnerability of striatal neurons. In experimental studies, restoration of mitochondrial regulatory pathways leads to increase in neuronal resilience in HD models (McColgan & Tabrizi, 2018).

There are a number of phytochemicals that affect mitochondrial pathways. Sirtuins (SIRT1) are activated by Resveratrol leading to increased activity of PGC-1α and mitochondrial biogenesis. Curcumin increases the stability of mitochondrial membranes and decreases oxidative mitochondrial damage. Ginsenosides also have shown mitochondrial protective activity by regulating oxidative metabolism and the apoptotic signalling (Lum et al., 2021). Significantly, mitochondrial protection could be one of the most valuable characteristics of plant derived compounds as mitochondrial dysfunction is an upstream mechanism to a wide range of pathological processes. Phytochemicals may indirectly reduce ROS production, inflammatory activation, and apoptotic signalling by improving the efficiency of the mitochondria.

Regulation of Mutant Huntingtin Aggregation and Protein Homeostasis

The formation of aggregates of mutant huntingtin is a hallmark of the pathological process in HD. Formation of aggregates might be a cellular defence mechanism to sequester toxic proteins, but failure in protein clearance will eventually lead to neuronal dysfunction. The proper quality control of proteins relies on the concerted action of molecular chaperones, the ubiquitin-proteasome system and the autophagic machinery. Mutant huntingtin causes these systems to malfunction, which results in abnormal species of proteins being produced and in dysfunction of the neurons.

A number of natural compounds have been studied to determine their effects on protein homeostasis. EGCG has been the focus due to its interactions with abnormal protein aggregation processes with regard to neurodegenerative diseases. Resveratrol has the potential to affect protein clearance via SIRT1 related autophagic mechanisms, while Curcumin has been shown to have protein modulation effects in experimental models (Lum et al., 2021). However, direct evidence on the effects of phytochemicals on mutant huntingtin aggregation is still scarce. One hurdle is determining whether a compound actually increases mHTT clearance or just decreases the stress that cells are under.

Mechanisms of Cellular Clearance and Autophagy Regulation

Autophagy is a vital cellular process that is involved in the degradation of damaged proteins and organelles. The disease is characterized by an accumulation of toxic mutant huntingtin proteins, and the loss of neuronal maintenance, which is due to autophagic dysfunction. The initiation of autophagy may be still ongoing in HD, but the transport and recognition of cargo for autophagy may be impaired, thus limiting the efficiency of clearance of mutant proteins. Thus, the restoration of effective autophagic flux is seen to be a promising therapeutic approach.

There are some phytochemicals which act on pathways related to autophagy, including AMPK, mTOR, and SIRT1 signalling. AMPK activation leads to initiation of autophagy, while mTOR hyperactivity is associated with inhibition of autophagy. Resveratrol has been reported to increase autophagy via SIRT1-dependent mechanisms, and other polyphenols may have indirect effects on cellular clearance pathways via metabolic regulation (Menzies et al., 2017). The therapeutic relevance of autophagy modulation is related to its ability to target one of the core processes of HD pathology: that of toxic mutant protein accumulation. But a high level of autophagy can also have negative consequences, and it is important to control the action of the pathway instead of indiscriminately stimulating it.

Figure 2. Integrated Molecular Mechanisms of Plant-Derived Phytochemicals Against Huntington's Disease

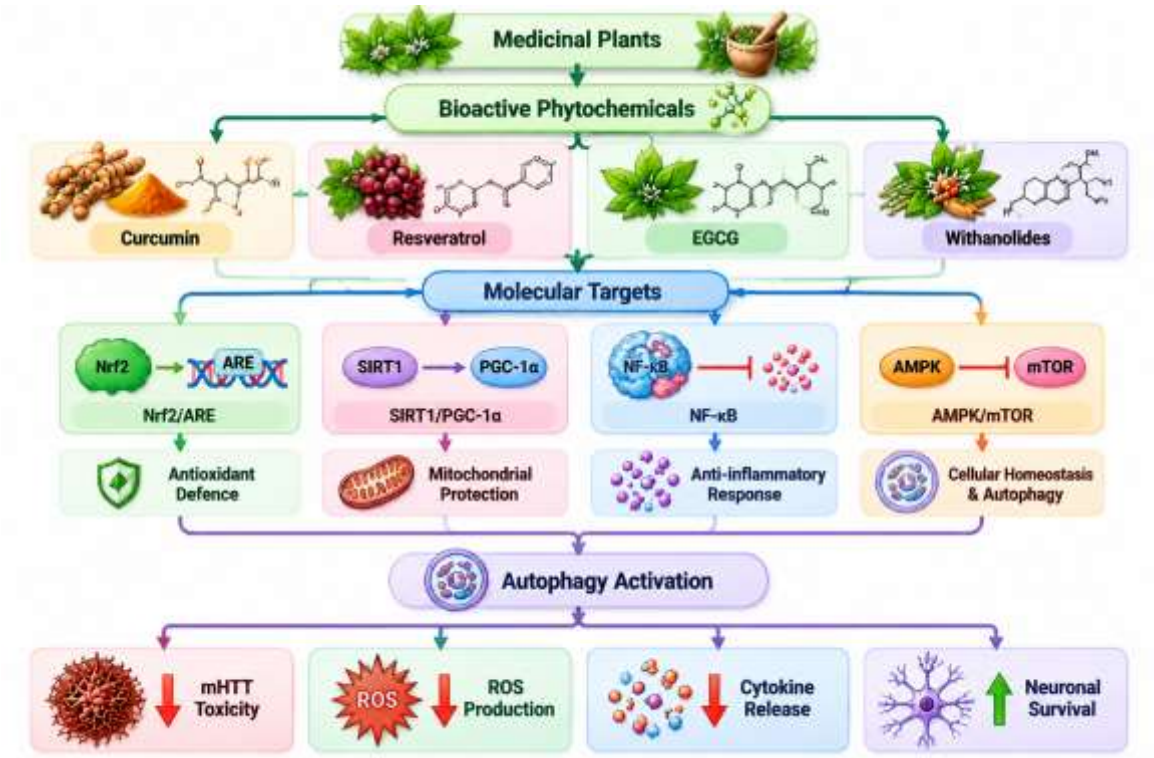

Figure 2. Molecular mechanisms underlying the neuroprotective effects of plant-derived phytochemicals in Huntington's disease. Schematic representation of medicinal plant bioactive compounds and their regulation of key pathways, including Nrf2/ARE, SIRT1/PGC-1α, NF-κB, and AMPK/mTOR signaling. These multi-target actions enhance antioxidant defense, mitochondrial function, autophagy, and neuronal survival while reducing mHTT toxicity, ROS production, and inflammatory responses

4. Translational Challenges in Developing Medicinal Plant-Based Therapies for Huntington's Disease

Despite the significant neuroprotective activity of medicinal plants and phytochemicals in experimental models of HD, there are significant challenges to be addressed before translating these results into the clinic. There are multiple biological, pharmacological, regulatory and clinical barriers to be crossed before translating promising laboratory observations to approved therapeutic interventions. Many naturally derived compounds have complex chemical structures, variable kinetic characteristics, and unknown mechanisms of action, which is different from the characteristics of conventional drugs that are developed by systematic optimization. This means that plant-derived compounds will need to be thoroughly tested before they are considered potential disease-modifying treatments for HD.

One of the significant limitations is that most of the evidence is from in vitro studies and animal models, and there is very little clinical evidence from human studies. Experimental models are useful for giving information about molecular mechanisms, but do not fully recapitulate the complexity of human HD, which is a disease of many decades arising as a result of inherited expression of the mutant HD gene. Many compounds that have been shown to have neuroprotective effects in toxin-induced models have not found similar clinical effects as a result of the differences in mechanism of disease, drug exposure level and biological complexity. Future studies should therefore focus on genetically correct HD-models, such as knock-in models and cellular systems derived from humans, like induced pluripotent stem cell (iPSC)-

derived neurons. These methods could make better predictions about therapeutic efficacy prior to human trials.

Poor Bioavailability and Pharmacokinetic Limitations

The major setback of the compounds from medicinal plants is related to poor pharmacokinetics. Numerous phytochemicals have been found to have high biological activity in vitro but have insufficient amounts in specific target tissues upon administration. Curcumin is a textbook case of this dilemma. Despite all the benefits it shows as antioxidant, anti-inflammatory and mitochondrial protective, its use is restricted due to its low water solubility, rapid metabolism and low systemic availability. There have been similar restrictions on the use of resveratrol, EGCG, and some flavonoids (Hewlings & Kalman, 2017).

Pharmacokinetic restrictions play an especially crucial role in the case of HD, as therapeutic molecules need to cross the blood–brain barrier (BBB) to access vulnerable neuronal populations in the striatum and cortex. If a compound exhibits antioxidant activity in peripheral tissues, but not sufficient levels in the CNS, there may be limited therapeutic use. Recent advances in drug delivery technologies provide possible solutions. Nanoformulations, liposomes, polymeric nanoparticles, and phytosome-based systems could be used to improve the absorption, stability, and delivery to the brain of poorly bioavailable phytochemicals. Nevertheless, further studies are needed to assess the safety, accumulation, immune responses, and feasibility of manufacturing for these approaches.

Blood–Brain Barrier Penetration

One of the biggest challenges in the development of treatments for neurodegenerative diseases is the blood–brain barrier (BBB). This extremely selective biological barrier shields the brain from toxic molecules, amongst which many therapeutic molecules as well. There are a number of plant derived compounds that have favourable biological activities and low permeability into the BBB. Access to the central nervous system is dependent on molecular size, polarity, lipophilicity, transport mechanisms and metabolism.

For instance, modified curcumin formulations show better brain availability than traditional formulations. The same can be done with resveratrol, flavonoids and other natural compounds to improve the therapeutic uses of these. However, safety must be maintained in the delivery of improved delivery as too many bioactive molecules may cause unexpected results in the brain. One of the difficulties in natural-product research is the variation of preparations made from plants. Medicinal plants are rich of bioactive and inactive components that constitute a mixture unlike the synthetic compounds which have defined chemical structures. Several factors can affect chemical composition, including geographical origin, cultivation conditions, harvesting time, extraction methods, and storage conditions.

Different preparations of Withania somnifera might have different concentrations of withanolides, and different turmeric extracts might have a significant difference in the amount of curcuminoids. This variability makes comparison between studies difficult and makes it hard to get regulatory approval. HPLC, LC-MS and metabolomic profiling can help to set up quality standards of the treatments based on medicinal plants.

Safety, Toxicological Evaluation, and Dose Optimization

Medicinal plants, due to their use in the tradition, are often considered to be safe, but biological activity does not necessarily mean clinical safety. At high concentrations, some phytochemicals may interact with the drug metabolizing enzymes, affect physiological pathways, or cause toxicity. Another big challenge is dose optimization. Concentrations are often used in experimental studies that cannot be translated

directly into therapeutic dose in humans. Careful evaluation of the pharmacokinetic and pharmacodynamic properties is important to develop clinically relevant dosing strategies.

Clinical Evidence and Human Translation

Although there has been a lot of experimental research, there is still not enough clinical evidence to prove that medicinal plants can be used to treat HD. The majority of the available studies show only biologic plausibility and not actually therapeutic efficacy. Disease-modifying drugs, as opposed to symptomatic drugs, must show evidence of slowing the neuronal degeneration or changing the disease itself. Long-term clinical studies will be necessary for demonstration of such effects, utilizing sensitive biomarkers and functional outcome measures.

Future clinical trial should be targeted to the development of well-chosen, standardized compounds that are well understood in terms of mechanism, have suitable pharmacokinetics, and have been shown to be safe.

Huntington's Disease Therapeutics:
Future Perspectives for Plant-Based Therapeutics

Combining traditional knowledge with recent molecular technologies will be essential to the future of medicinal plant based approaches to treating HD. In the future, research on phytochemicals should focus on them as complex regulators of disease associated biological networks, rather than simply as antioxidants. One of the promising directions is the development of multi-target therapeutic strategies. As HD pathogenesis is a combination of several interacting processes, drugs that can act on more than one of these processes at a time may be more beneficial than those that target only one.

Combination Therapy Approaches

Combination therapy is an important future approach due to the fact that no single molecular pathway fully explains the progression of HD. Another possibility is that phytochemicals could be combined with current symptomatic treatments or new molecular treatments, which could give a synergistic effect. Antioxidant compounds for example, could be used in conjunction with the gene-silencing strategies, and minimise the damage to cells that happens downstream of mutant huntingtin suppression. But one should be careful with combination therapies due to possible pharmacological interactions.

Precision Medicine and Patient-Specific Approaches

There is variation in the onset age, rate of progression and severity of symptoms in HD. Future therapies therefore may need to be tailored to each individual, based on: CAG repeat length, genetic background, molecular biomarkers and disease stage. The combination of genomics, transcriptomics and metabolomics might help identify the patients most likely to benefit from a particular therapeutic approach.

Artificial Intelligence and Systems Biology

As more and more plant-based therapeutics are discovered, artificial intelligence, systems biology and computational modelling will take on a greater role. These technologies are capable of analysing vast amounts of data to discover: novel phytochemical targets, synergistic compound combinations and patient-specific responses (Zahid et al., 2025; Fatima et al., 2026).

Optimized drug delivery strategies that result in optimized therapy.

This combination of AI and experimental validation could greatly speed up the process of developing natural-product-based therapies.

Nanotechnology and Advanced Drug Delivery

One of the most promising approaches to overcome limitations of plant-derived compounds is nanotechnology. Advanced delivery systems have the potential to enhance: BBB penetration, stability, controlled release and therapeutic concentration. Therefore, the future research direction should be on the safe, scalable and clinically acceptable nanocarriers specifically designed for neurological disorders.

Conclusion

Despite major advances, HD is still a fatal, neurodegenerative disorder with complex molecular mechanisms including mutant huntingtin toxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity, and protein clearance. Since none of the existing therapies was found to be effective in changing the course of the disease, it has been worth considering the use of medicinal plants and plant phytochemicals.

A growing body of experimental data has been pointing towards the neuroprotective properties of various compounds like curcumin, resveratrol, EGCG, ginsenosides, withanolides, quercetin and other phytochemicals. They are able to control multiple disease-associated mechanisms such as antioxidant defence, inflammatory signalling, mitochondrial maintenance, apoptosis regulation, and autophagic clearance. The existing evidence, however, is largely preclinical in nature. However, significant challenges such as bioavailability, restricted delivery to the brain, variability of extracts, and inadequate toxicity studies and lack of extensive clinical testing will need to be overcome before these compounds can become part of a treatment strategy for HD.

In the future, research on medicinal plants will need to be combined with molecular neuroscience, computational biology, nanotechnology, and precision medicine. Plant-derived compounds do not replace traditional strategies, but end up being complementary or synergistic parts of a multi-target therapeutic strategy that slows down the neurodegeneration process and improves function.

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