Investigating Holistic Natural Strategies for The Management of Huntington's Disease

Abstract. Huntington's Disease (HD) is an autosomal dominant neurodegenerative condition that is characterized by the degeneration of neurons in the brain. CAG (Cytosine-Adeine-Guanine) triplet expansions in the HTT gene lead to the production of a mutant Huntingtin protein (mHTT) that is toxic to the cells and leads to neurodegeneration. The major pathological finding is the presence of polyglutamine (polyQ) aggregates which cause neurotoxicity. The early symptoms and signs of HD include motor and cognitive impairments. In this manuscript, the authors will discuss the pathogenesis of HD, the importance of neuroprotective strategies, and the potential of natural compounds as therapeutic agents. The article will focus on a few phytoconstituents that are known to have a variety of neuroprotective intervention. Nevertheless, certain naturally occurring compounds have exhibited promising outcomes in preclinical investigations. This article focuses on a few phytoconstituents that are known to have a variety of neuroprotective intervention.

1 Introduction

The enlarged CAG triplet repeats that code for a PolyQ expansion in the corresponding proteins are the root cause of the polyQ illnesses. Nine polyQ disorders have been identified till date which include “Spinocerebellar ataxia type 3 (SCA3), Huntington's disease (HD), Dentatorubralpallidoluysian atrophy (DRPLA), and spinocerebellar-associated disorders (SCA).” A major hallmark of polyQ disorders is the pathological involvement of the striatum, which affects the voluntary movements, trouble in decision making and understanding new concepts are some of the early symptoms of HD. It is brought on by the autosomal dominant mutation that is inherited in the HTT protein, which in normal state is necessary for proper brain function. The HTT gene which is situated on the short p arm of chromosome 4, has a CAG repeat number ranging from 8 to 35, but when there is a CAG expansion greater than 36 it results in HD. The HTT protein which has 36 glutamine residues is a central mediator in many of the polyQ disorders. The polyQ expansion strongly inversely corresponds with the age of disease onset. The HTT protein is mostly in possession of 36 or more CAG repeats. The HTT gene which is situated on the short p arm of chromosome 4, was discovered in 1993 and encodes for the large huntingtin protein. The protein's polyQ domain in HD is enlarged past a limit of 36 glutamine residues. It may assume one of the two following forms since the length of the mutant protein determines the pathological consequences. A large proportion of the research focuses on the role of huntingtin in the pathogenesis of HD. This protein is recognized as a causative agent in HD and its polyQ expansion is the root cause of neurodegeneration that impairs behavior and physical function. It mediates the release of metals like iron, copper, and zinc which leads to the formation of reactive oxygen species (ROS) and further neurodegeneration. Huntington's Disease is a neurodegenerative illness that worsens with time and is hereditary. Patients with HD experience motor, cognitive, and behavioral impairments starting at a mean age of 35 years old. It is brought on by the autosomal dominant mutation that is inherited in the HTT protein, which in normal state is necessary for proper brain function.
capacity for thought processing. Following the onset of symptoms, patients typically survive for about 15 to 20 years.

The juvenile form of this disease begins in childhood or adolescence. This less prominent form involves issues with mobility as well as mental and emotional disturbances. Hence, academic performance and athletic endeavors of the afflicted individual suffers. Seizures come about in 30-50 percent of impacted individuals. Juvenile HD evolves more swiftly than the adult-onset variant since individuals afflicted by this form of HD often survive for 10 to 15 years following the onset of symptoms. Juvenile HD accounts for 5-10% of all HD cases. Adult HD onset is caused by 40-50 CAG repeats, whereas HD with a juvenile onset is caused by 50-120 CAG repeats. Environmental variables and an individual's genetic makeup contribute for 30% of the range in age of onset, whereas polyQ length assists for 70% of that variation.[5]

All human populations carry the HD mutation, although the prevalence of HD varies greatly depending on ancestry, with populations of European heritage having the highest prevalence. Since Caucasians account for the bulk of HD cases worldwide, global European migration is thought to have had a greater historical influence on overall prevalence than any other factor. According to reports, there are between 1.6 to 12.3 HD instances per 100,000 people in the United Kingdom[6]. Fewer than 5,000 cases of this illness are thought to exist in the US. Other populations, such as those who are Indian, Japanese, Chinese, or African, seem to experience the disease at a lower rate.

2 Role of free radicals in progression of HD

The primary threat factor for the majority of neurodegenerative illnesses is thought to be the overproduction of ROS in neural tissues[7]. Examples of these oxygen containing reactive species include singlet oxygen (\(1O_2\)), hydrogen peroxide (H\(_2\)O\(_2\)), superoxide (O\(_2^\cdot\)), and hydroxyl (OH).[8] Although a small amount of ROS is beneficial for cellular functions, too much ROS production causes oxidative stress which ultimately lead to neurodegeneration and other diseases. Increased ROS production, decreased antioxidant activity, or both can contribute to the situation known as oxidative stress in a biological system. While overt oxidative stress typically results in cell death, moderate oxidative stress may produce cell malfunction and altered behaviour.[9]

No matter how these are produced in the body, ROS interact with diverse cellular macromolecules found in different cell organelles and may result in cellular malfunction (Fig. 1). In worst cases, these interact with DNA and change it in response to oxidative stress. Additionally, they trigger the activation of a number of transcription factors that control the expression of genes linked to cell death[10,11]. These can also cause lysosomal malfunction, which results from changes to the vesicular recycling process autophagy, which causes cell death[12]. These species harm DNA, lipids, and proteins in the mitochondria[13,14]. Cell death is eventually brought on by the ER(Endoplasmic Reticulum) stress caused by build-up of misfolded proteins[15,16].

3 Protective effects of herbs and phytoconstituents in HD

The anti-inflammatory and antioxidant benefits of the natural products as well as the chemicals derived from them have received a lot of attention over the past 20 years. These properties are frequently characterised by high efficacy and low side effects. With HD pathogenesis, numerous molecular pathways are involved. As a result, a medicine is required that should inhibit disease-causing pathways through a variety of mechanisms[17]. This article focuses on a few phytoconstituents (Fig. 2) with a wide range of biological activities that are known to have a variety of neuroprotective effects that can be the lead for the treatment of HD.
3.1 Astaxanthin (AST)

3.1.1 Antioxidant Activity

Its great antioxidant capacity is determined by its structure. Its special structure, which includes both hydroxyl and keto groups, is crucial in neutralising ROS. The molecule scavenges dangerous singlet oxygen, transforms hydroxyl and peroxyl radicals into more stable molecules, stops the generation of free radicals, and blocks the chain process of autoxidation.

3.1.2 Anti-inflamatory Activity

Inflammation that is excessive or out of control is bad for the host and could injure its cells and tissues. AST inhibits the activation of the NF-κB and mitogen-activated protein kinase pathways along with activating Nrf2-induced antioxidant system activation [22, 23]. ROS levels eventually decrease as a result of the antioxidant enzyme's activity becoming more active. Additionally, mitophagy, mitochondrial biogenesis, and mitochondrial dynamics, all of which are crucial for maintaining cellular and mitochondrial metabolism are controlled and regulated by AST [24, 25].

3.1.3 Anti-apoptotic Activity

Apoptosis is a prevalent process in biological systems which when happens in excess can disrupt homeostasis and lead to a numerous disease, yet it is necessary as the growth of tissues, the preservation of homeostasis, and protection against a range of external and intracellular insults and mutations all rely on this. The Bcl-2 family, which includes the pro-apoptotic cytokines Bad (Bcl-2-associated death promoter) and Bax (Bcl-2-associated X protein) and the anti-apoptotic cytokines Bcl-2 (B cell lymphoma 2) and Bcl-xL (B cell lymphoma-extra large), modulates the process of this programmed cell death. Bad and Bax encourage the release of cytochrome c (Cyt c) when apoptosis is stimulated. Additionally, research has shown that AST is crucial in initiating PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) signaling pathway.

Fig. 2. Structure of the phytoconstituents directly associated with HD treatment

Fig. 3. Pathogenesis of the HD involves a number of processes, including oxidative stress, inflammation, and apoptosis.
B) signalling pathway, facilitating the phosphorylation of Bad and diminishing the initiation of Cyt c and caspase-3 signalling pathways [26].

**Fig3**

**Mechanism describing the neuroprotective activities of Astaxanthin.** Firstly, it scavenges free radicals. Secondly, it suppresses inflammatory cytokine expression by inhibiting the NF-κB pathway. Also, it activates PI3K/Akt signalling pathway which helps suppress apoptosis.

### 3.2 Berberine (BBR)

An isoquinoline alkaloid with a molecular weight of 336.4 g/mol is extensively found in many different therapeutic herbs, particularly those belonging to the genus *Berberis*. This tiny molecule is derived from the roots and barks of several species of *Berberis* as well as *Coptischinenses*. *Berberis* has been utilized in Chinese medicine for over six decades as an OTC(over-the-counter) remedy for bacterial gastroenteritis [27]. BBR demonstrates a wide variety of pharmacological effects, including immunomodulation, neurotransmitter, enzyme, and oxidative action [28]. This is thought to function as a double-edged sword since it functions as an antioxidant in healthy ones and conversely acts as a pro-oxidant in malignant cells. Besides fostering apoptosis, it causes oxidative stress in cancerous cells and inhibits apoptosis in healthy cells. Due to its significant antioxidant activity, BBR is likely to be a candidate to prevent neurodegeneration in a variety of circumstances. BBR has also been widely explored for its therapeutic usefulness against neurodegeneration [29].

There is evidence that BBR offers therapeutic promise for treating many neurodegenerative illnesses like Alzheimer's disease, Parkinson's disease, and Huntington's disease. It is an appealing drug candidate to evaluate its potentially beneficial impact on chronic neurological illnesses since it has been reported to be safe for prolonged use, is promptly absorbed into the bloodstream within two hours after ingestion, and most importantly, can readily penetrate the Blood-Brain Barrier (BBB). The high tolerance for oral doses (LD50>5g/kg), rapid availability in the bloodstream two hours after oral intake, and freedom to cross the BBB makes it a potential molecule for the treatment of neurodegenerative diseases. Given that both HD and AD are brought on by the buildup of misfolded proteins, it is encouraging to think that treatment with BBR may be able to minimize amyloid aggregation and accumulation in HD patients.

BBR is known to activate Nrf2, help phosphorylate Akt and CREB protein (cAMP responsive element binding protein), down-regulate NF-κB, and enhance the expression of PI3K i [30-41].

Demethyleneberberine, a metabolite of berberine, has been found to affect a number of the molecular processes involved in HD ([Fig. 4](#fig4)) [42].
Berberine induced neuroprotection by triggering Nrf2 pathway and P13K pathway

3.3 Curcumin (CCR)

Curcumin is a popular spice known for its numerous medicinal properties since ages. Owing to the various therapeutic benefits, this has received a lot of interest as a nutraceutical. The botanical source of this phytoconstituent is *Curcuma longa* which belongs to the Zingiberaceae family and is widely used in South Asia [43]. This can also be obtained from other sources like *C. phaeocaulis*, *C. aromatic*, *C. caesia* and *C. zedoaria* [44-46]. It has scientific name as diferuloylmethane also known as 1,7-bis (4-hydroxy, 3-methoxyphenyl) 1,6-heptadiene-3,5-dione, and belongs to polyphenolic class of phytoconstituents. It was isolated and purified for the first time in 1815 from the rhizomes of the plant, however the structure was confirmed in 1910 [47, 48]. It is used in food colouring because of the unique bright yellow colour due to two curcuminoids, desmethoxycurcumin and bis-desmethoxycurcumin [49].

CCR was originally used in the treatment of human ailments in 1937 [50]. It has an impact on many molecular pathways including NF-κB, STAT3 (signal transducer and activator of transcription 3), Nrf2, and COX2 (cyclooxygenase2), making it a potential therapeutic option for a variety of disorders (Fig. 5) [51].

Because of its wide array of therapeutic activities, it has a significant potential for cessation of neural degeneration process in HD by focusing on numerous mechanisms like 1) By ROS scavenging thus reducing oxidative stress, 2) Decreasing the expression of inflammatory mediators leading to reduced inflammatory stress, 3) Metal ion chelation and transcriptional alterations which halts protein aggregation, 4) Increasing the activity of HSPs which causes the reversal of misfolded proteins, 5) Reversing the polyQ-induced apoptosis and neuronal dysfunction in motor areas of HD patients [52-69].
Fig 5. Effects of curcumin at the cellular level where Curcumin leads to metal chelation and reduction in oxidative stress which are indeed one of the key mechanisms for the prevention or the treatment of neurodegenerative disorders including HD. The presence of one active methylene (CH$_2$) group and two phenolic (OH) groups in curcumin makes it an excellent ligand to chelate heavy metals. Also, it causes the upregulation of HSPs which helps in prevention of HD.

3.5 Naringin (NRG)

Naringin, also known as 4′,5,7-trihydroxy-3′-rhamnoglucoside, is a naturally occurring flavanone glycoside. Naringenin is the aglycone component while neohesperidose is the glycone component of NRG. This is abundant in grapes and in various citrus fruits and has an astringent taste. Both NRG and its aglycone moiety naringenin are reported to possess antioxidant activity, but, naringin is less active as the sugar moiety causes steric hindrance [70,71].

NRG is one of the potential candidates whose neuroprotective function against 3-nitropropionic acid (3-NP) induced neurotoxicity was investigated in experimental mice by modulating intrinsic apoptotic processes. NRG at a dose of 80 mg/kg body weight, increased the levels of antioxidant markers and decreased ATPase activity in the striatum. Furthermore, in a 3-NP-induced neurotoxicity model, NRG decreases cyt-c release from mitochondria and causes caspase-3 activation which leads to inhibition of multiple apoptotic phenomenon. Also, the expression of pro-apoptotic indicators (like Bad and Bax) was inhibited by this compound [72]. The same author also reported that NRG elevated the expression of matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2), and hence, improved the motor impairments [73].

Furthermore, another mechanism implicated in NRG neuroprotection was by causing decreased oxidative stress and inflammatory response by raising the expressions of phase II and antioxidant genes via Nrf2 activation [74]. NRG administration enhanced mobility, grooming, rearing, footprint analysis, grip strength, and neurological score in a quinolinic acid (QA) induced neurotoxicity model by modulating neuroinflammatory response, apoptotic indicators, oxidonoitrosative stress, and mitochondrial complex activity [75].

Recent investigations on aglycone moiety of NRG, i.e., naringenin, which has remarkable antioxidant properties, has been published in the literature. According to the findings, it significantly raised the levels of antioxidant enzymes such as SOD (superoxide dismutase) and GSH (glutathione), at doses of 20, 40, and 80 M. This was followed by a drop in MDA (Malondialdehyde) and ROS levels. Furthermore, adenylate levels (ATP, ADP, and AMP) as well as adenine nucleotide translocase (ANT) transport activity was significantly increased implying that it contributes to ATP production and cellular function. Additionally this impacted the expression levels of apoptotic markers (like Bax, Bcl-2, Cyt-c, and caspase-3) in rat neurons. Surprisingly, naringenin-induced oxidative stress and mitochondrial dysfunction are mostly caused by activation of the Nrf2/ARE (antioxidant responsive element) signalling pathway in neurons [76].

Despite the fact that the above-mentioned molecular mechanisms for neuroprotection have been proposed due to its antioxidant capacity, at doses of 50 mg/kg it has lead to increased 5-HT levels and MAO (monoamine oxidase) activity, hence, ameliorating 3-NP-induced neurotoxicity in rats. Additionally, this downregulated GFAP (Glial Fibrillary acidic protein) in striatal neurons which prevented neuronal cell death (Fig 6) [77]. In nutshell, all these findings suggest the use of naringin and its aglycone moiety naringenin as powerful nutraceutical agents in HD treatment.
Fig 6. Naringin treatment significantly enhances the level of antioxidant enzymes such as superoxide dismutase and catalase, followed by potent free radical scavenging activity, leading to a reduction in the level of oxidative stress and inflammation. ATPase activity can indirectly contribute to the reduction of inflammation through its role in maintaining ion balance and energy supply in cells. It exhibits an apoptotic effect by suppressing the release of cyt c from mitochondria and reduces the activation of Bax, thereby inhibiting its proapoptotic effect and helping protect the cell from apoptosis. By inhibiting COX-2 activity, Naringin reduces the production of pro-inflammatory prostaglandins, thereby dampening the inflammatory response. Reduction of caspase 3 activation in the presence of 3-nitropropionic acid (3NP) can lead to a decrease in proapoptotic proteins (Bax, Bad). NF-κB is known for its anti-apoptotic properties; when activated, it promotes cell survival and prevents apoptosis by upregulating the expression of anti-apoptotic genes and downregulating proapoptotic genes.

3.6 Sulforaphane (SFN)

Sulforaphane is a popular dietary isothiocyanate, chemically known as 1-isothiocyanato-4-(methylsulfonyl)-butane. Present in plants as glucoraphanin (GR) (inactive form), this compound is known for its chemopreventive activity and is abundant in cruciferous vegetables such as cauliflower, broccoli, and brussel sprouts [78]. Myrosinase, a plant thioglucosidase or bacterial thioglucosidase, present in the colon, hydrolyzes GR to the equivalent isothiocyanate SFN by mincing or masticating [79]. This may protect against mental diseases by decreasing oxidative stress, neuronal inflammation, and neuronal cell death [80, 81].

By stimulating the Nrf2 pathway and blocking NF-κB, SFN stimulates the antioxidant and anti-inflammatory responses. It also exerts an epigenetic effect via suppressing HDAC (Histone deacetylases) and DNA methyltransferases, as well as altering mitochondrial dynamics. Furthermore, by activating the proteasome, SFN maintains proteome homeostasis (proteostasis), which has been proven to increase cellular lifetime and prevent neurodegeneration [82]. The isothiocyanate group gives sulforaphane electrophile characteristics that allow it to easily interact with nucleophiles, particularly cysteine residues in proteins. Sulforaphane's lipophilic properties and small molecular size allow for passive absorption by cells [83]. SFN accumulates in the central nervous system, including ventral midbrain and striatum, since it can easily move across the BBB (blood-brain barrier) [84].

The activation of Nrf2 is one of the primary mechanisms of SFN. Under normal physiological settings, Nrf2 forms a cytoplasmic complex with a redox-sensitive E3 ubiquitin ligase substrate adaptor Keap1 (kelch-like ECH-associated protein 1) that reduces its impact while also promoting its ubiquitination and destruction via the UPS (Ubiquitin-proteasome system) [85]. SFN chemically interacts with Keap1’s reactive cysteine residues on entering the cell, eventually diverting Nrf2 from the inactive Keap1 [86]. Also, the SFN forms a heterodimer with MafG (musculoaponeurotic fibrosarcoma oncogene homolog G), MafK (musculoaponeurotic fibrosarcoma oncogene homolog K), and MafF (musculoaponeurotic fibrosarcoma oncogene homolog F) (the tiny Maf proteins) after translocation into the nucleus, giving it DNA binding abilities and enabling it to stick to its consensus sequence, the ARE of phase 2 genes, and ultimately activating their transcription [87, 88]. Besides, interacting with Keap1, this phytoconstituent increases Nrf2 activity via inhibiting GSK-3 (glycogen synthase kinase-3), thereby reducing the methylation of the Nrf2 promoter's first 15 CpGs [89, 90]; besides modifying Nrf2's translocation and stability [91, 92]. When Nrf2 activates ARE, its downstream products, like NAD(P)H quinone dehydrogenase 1, haem oxygenase 1 (HO-1) [95] and glutamate cysteine ligase, are upregulated, protecting neural cell lineages from numerous oxidative damages [96-99].

SFN controls the inflammatory response by a mechanism linked to NF-κB. Inhibitors of NF-κB (IB) family members sequester NF-κB in the cytoplasm as an inactive state [100-104]. The IB proteins are ubiquitinated and degraded when
an infection factor activates certain immunological signalling pathways, which causes NFκB to be translocated to the nucleus where NFκB attaches to DNA and triggers the production of proinflammatory cytokines like TNF(tumour necrosis factor), IL1(interleukin 1), and IL6 (interleukin 6) as well as PGE2(prostaglandin E2), iNOS(inducible nitric oxide synthase), COX2 and others[103,104]. Hence, SFN exerts anti-inflammatory properties by decreasing NFκB expression, its nuclear translocation, and hence preventing DNA-binding [105,106]. Besides using the NFκB pathway, SFN suppresses neuroinflammation by regulating MAPKs(mitogen-activated protein kinases) such as p38, JNK(Jun N-terminal kinase) and ERK(extracellular signal-regulated kinase) [107,108], as well as by promoting microglia polarisation from proinflammatory M1 to anti-inflammatory M2 [109,110].

Fig7 Sulforaphane controls the inflammatory response by a mechanism linked to NFκB inhibition for the prevention of neurodegeneration in HD

4 Conclusion

From this review, it can be concluded that several major phytoconstituents significantly contribute in the pathophysiology of HD, thus, streamlining the contemporary epidemiological trend of utilizing botanicals with protective effects on nervous system. Based on documented clinical research, the review examined the effectiveness of phytoconstituents for their possible neuroprotective effects. Only a few numbers of phytoconstituents exhibit in vitro and in vivo activity and fewer are under human trials from among the enormous number of phytoconstituents that have been assessed for HD.

The findings show that natural phytochemicals have the potential to function as important signaling molecules, but it is yet unclear if they may also function as neuroprotective agents. These natural compounds act through various pathways and combinatorial methods have demonstrated positive additive and/or synergistic effects in the treatment of the disease. Nevertheless, despite an increase in investigations, the findings are still largely speculative. Few phytochemicals have successfully undergone well-designed clinical trials to demonstrate their value. Preclinical research is crucial because it will serve as the foundation for the design and synthesis of novel lead molecules with improved pharmacological and biological properties in the future. The use of nanomaterial-linked targeting has improved the efficacy of phytochemicals. However, the primary issue of nanoparticles’ toxicity prevents their usage for oral intake. ‘Green’ nanoparticles, which are biodegradable and environmentally friendly and are quickly taking over as the preferred nanoparticle for treating various diseases, can help to overcome this. Due to the variety of molecular structures, many natural substances have complex characteristics. In order to promote the specific targeting of diseases, it is crucial to introduce the idea of precision nutrition. More research into phytochemicals will reveal not only their advantageous benefits but also their harmful effects, thereby optimizing the dosage and target of phytochemicals.

5 References


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pharmacology and antioxidative and anti-inflammatory properties, suggesting its potential as a preventive and therapeutic agent. It reactivates cellular antioxidant defense by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress.

Sulforaphane is a bioactive isothiocyanate found in cruciferous vegetables and is recognized for its role in neurodegenerative diseases. Nong Zhang and Hui Li, in their study, showed that sulforaphane attenuation of experimental diabetic nephropathy involves GSK-3β inhibition and activates Nrf2 signaling cascade against neurological disorders. Rahman, Bijo Mathew, Mohamed M. Abdel-Wahab, Jason Santín, Daniel Aguilar, A., López, V. M., A., and others further explored its neuroprotective effect in Huntington’s disease.

Naringenin, a flavone glycoside found in grapefruit, orange peel, and many medicinal plants, also shows neuroprotective effects. This compound reduces oxidative stress and improves mitochondrial dysfunction via activation of the Nrf2/ARE pathway. Magesh, Sadagopan, Yu Chen, and Longqin Hu, in their recent study, demonstrated its role in neuroprotection.

In another line of research, Zhao, Fangfang, Jianlei Zhang, and Na Chang investigated the effect of sulforaphane on Nrf2's epigenetic modification, which increases its efficiency in cellular processes. They found that sulforaphane increases the efficiency of photovoltaic cells and the activity of PPAR γ, Bax/Bcl-2, and caspase 3, indicating its role in apoptosis and inflammation in a cellular model of Alzheimer’s disease.
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