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

Pragati Silakari[1*] Aditi Yadav[1], Aneesha Arora[1], Anushka Arora[1], Gulsheen[1], Paranjeet Kaur[1], Sanjeev Kumar Sahu[2]
[1]Chitkara College of Pharmacy, Chitkara University, Punjab, India
[2]Lovely School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India
*Corresponding author: pragati.silakari@chitkara.edu.in : p.silakari@gmail.com

Abstract. Huntington's disease (HD), a multifaceted neurological disorder, presents a complex clinical scenario. An autosomal dominant neurodegenerative ailment called Huntington's disease is brought on by increase in number of CAG (Cytosine-Adenine-Guanine) repeats, which causes the creation of a mutant Huntingtin protein (mHTT) resulting in neuronal death and mental disabilities in human beings. End signs and symptoms can include significant weight loss, difficulty swallowing or breathing, recurrent aspiration pneumonia, declined health and uncontrolled pain. The excessive production of ROS (Reactive Oxygen Species) in nervous tissues is considered a significant risk factor in most of the neurological diseases including HD. Transcriptional regulation, immunological system, and mitochondrial function are all disrupted by mHTT. Although natural products have shown promise in ameliorating symptoms, it is important to note that no singular "phytoconstituent" has been definitively linked to its therapeutic 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 effects through a wide range of biological activities. By stimulating the Nrf2 (Nuclear factor erythroid 2-related factor) pathway and suppressing NF-κB (Nuclear Factor Kappa-light-chain-enhancer of activated B cells), astaxanthin, berberine, and sulfarophane increase the antioxidant and anti-inflammatory activity, resulting in neuroprotection. Curcumin leads to metal chelating effect and decline in reactive oxygen species which are certainly one among the vital processes to impede and manage the disorders causing neurodegeneration including HD. This affects the upregulation of HSPs (Heat Shock Proteins) which helps in HD management. Naringin reduces level of oxidative stress and inflammation by free radical scavenging, NF-κB stimulates cell survival and prevents apoptosis by upregulating anti-apoptotic genes expression and downregulating proapoptotic genes.

1 Introduction

Diseases associated with polyglutamine (PolyQ) are dominant, late-onset genetic illnesses that appear as progressive neurodegeneration that impairs behavior and physical function. Depression, poor coordination, irritability, small voluntary movements, trouble in decision making and understanding new concepts are some of the early symptoms of this disease. 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 ataxias (SCA), MJD(Machado-Joseth Disease)/SCA3, HD, Dentatorubralpallidoluysian atrophy (DRPLA), and spinal and bulbar muscular atrophy, X-linked 1 (SMAX1/SBMA)”. A major hallmark of polyQ disorders is the pathological CAG expansion redevelopment in the translated section of discrete genes. Specific neuronal subpopulations become dysfunctional and degenerate as a result of the translated polyQ aggregating in the degenerating neurons[1]. In this article we will focus on HD and various phytoconstituents which can be used to treat the disease.

HD 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 [2]. 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 [3]. Majority of people are not at risk for HD since they have lower than 27 CAG triplet repeats in their genes. Those with 27 to 35 CAG repeats are unlikely to be impacted, however, they can transmit it to their descendants. HD patients are 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[4]. 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 polyQ expansion strongly inversely corresponds with the age of disease onset. The adult-onset HD which is the mainstream form of this disorder, frequently manifests in a person's third or fourth decades. Emotional Instability, despair, minor involuntary movements, poor coordination, difficulty acquiring new information, and difficulty making judgements are some of the early indications and symptoms. In most cases the patients develop chorea and may develop dementia as well. These motions become more conspicuous as the disease evolves since the people who are affected have a hard time eating, speaking, or walking and they may encounter psychological changes and a reduction in their

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_2O_2), superoxide (O_2), 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 build-up of misfolded proteins [15,16].

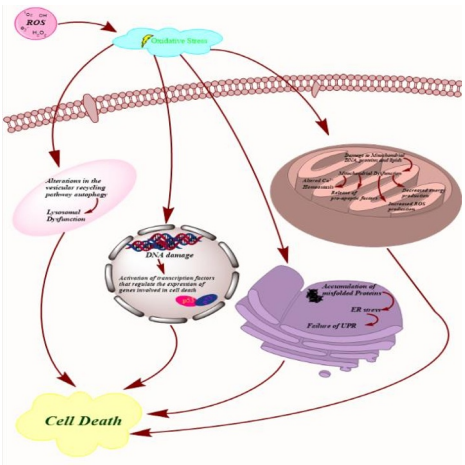

Fig1 The role of reactive oxygen species as signalling molecules in several physiological and pathological processesinvolving in HD

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.

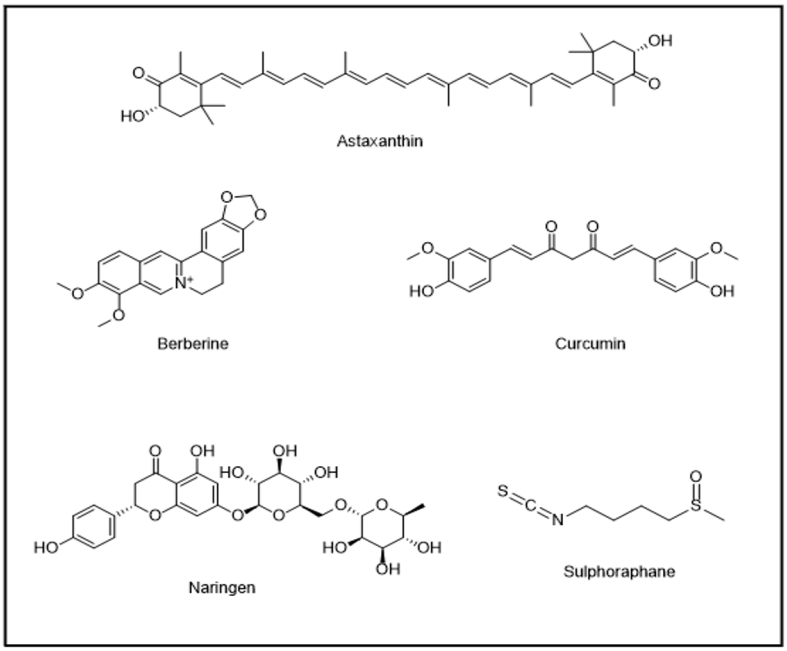

Fig2 Structure of the phytoconstituents directly associated with HD treatment

3.1 Astaxanthin (AST)

Reddish-orange carotenoid astaxanthin, a member of the xanthophyll group, has distinct effects on cell membrane and a variety of biological functions [18]. 3,3′-dihydroxy-4,4′-diketo-beta, beta-carotene is the molecular name for AST [19]. The three major sources of AST include a marine bacterium – *Agrobacterium aurantiacum*, a red yeast – *Phaffiarhodozyma*, and a microalga – *Chlorococcum* [20]. Additionally, it transforms metal pro-oxidants into innocuous molecules and serves as a metal chelator. However, AST is impacted by environmental factors like pH, heat, or light exposure, just like many other carotenoids. As a result, it can have its structural makeup changed through isomerization, aggregation, or esterification, which will change its physiochemical characteristics.
The pathogenesis of the HD involves a number of processes, including oxidative stress, inflammation, and apoptosis. According to studies, AST can easily cross the blood-brain barrier to shield the brain against both short-term damage and long-term neurodegeneration. This molecule's neuroprotective effects include anti-oxidation, anti-inflammation, and anti-apoptosis (**Fig. 3**) [21].

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-inflammatory 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) signalling pathway, facilitating the phosphorylation of Bad and diminishing the initiation of Cyt c and caspase-3 signalling pathways [26].

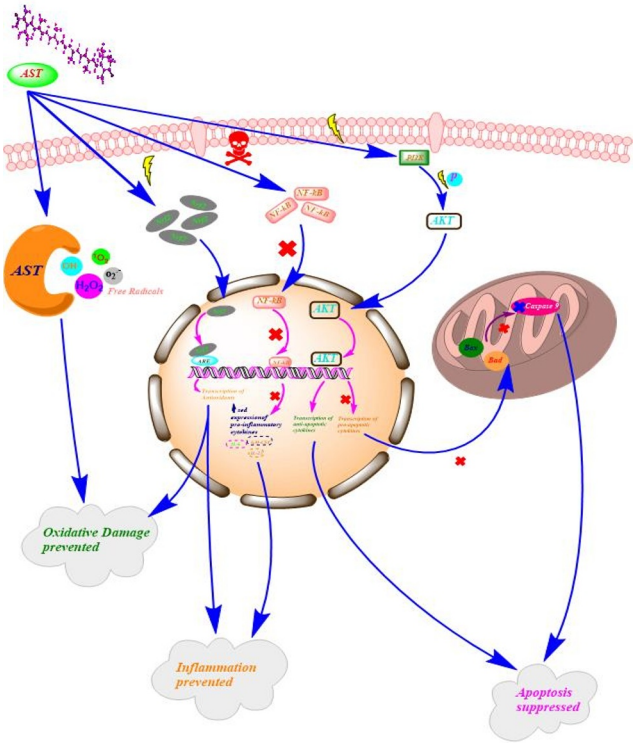

Fig3 Mechanism describing the neuroprotective activities of Astaxanthin. Firstly, it scavenges free radicals.Secondly, it suppresses inflammatory cytokine expression by inhibiting the NF-κB pathway. Also, it activates PI3K/Akt signalling pathway which helps suppress apoptosis

3.2 Berberine (BBR)

An isoquinoline alkaloid with 336.4 g/mol molecular weight 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 minimise 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 increasing promoter activity [30-41]. Demethyleneberberine, a metabolite of berberine, has been found to affect a number of the molecular processes involved in HD (**Fig. 4**) [42].

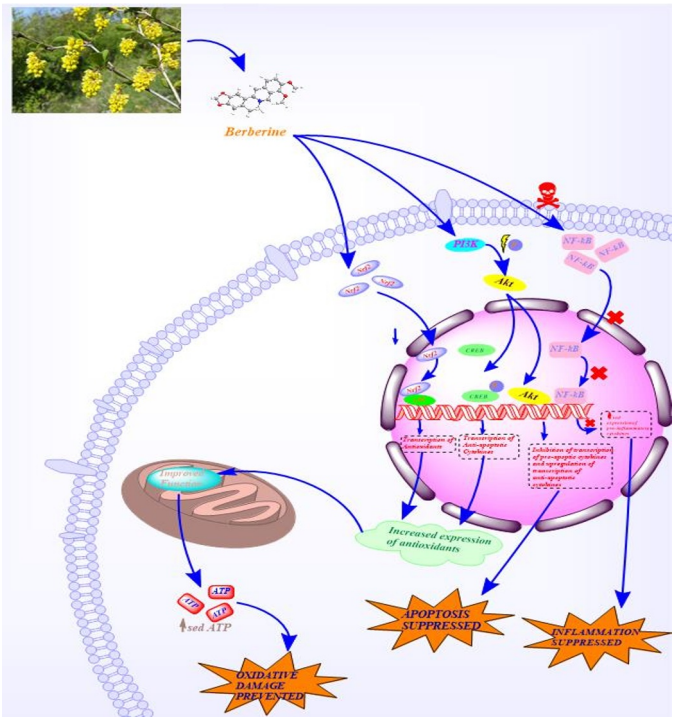

Fig4 Berberine induced neuroprotection by triggering Nrf2 pathway and P13K pathway

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*a, *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 poyphenolic 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].

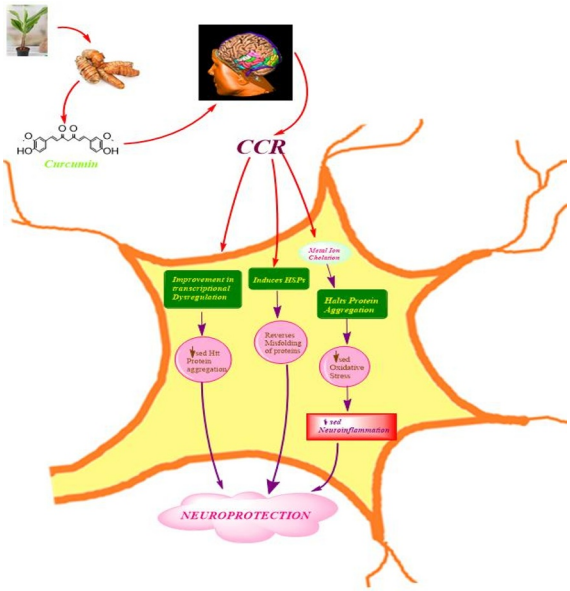

Fig5 Effects of curcumin at the cellular level where Curcumin leads to metal chelation and reduction in oxidative stress which are indeed one of the key mechanisms for the prevention or the treatment of neurodegenerative disorders including HD. The presence of one active methylene (CH_2) group and two 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-flavonone-7-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 moeity 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-NP(3-nitropropionic acid) 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 -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, oxido-nitrosative stress, and mitochondrial complex activity [75].

Recent investigations on aglycone moeity 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 (antioxident 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 moeity naringenin as powerful nutraceutical agents in HD treatment.

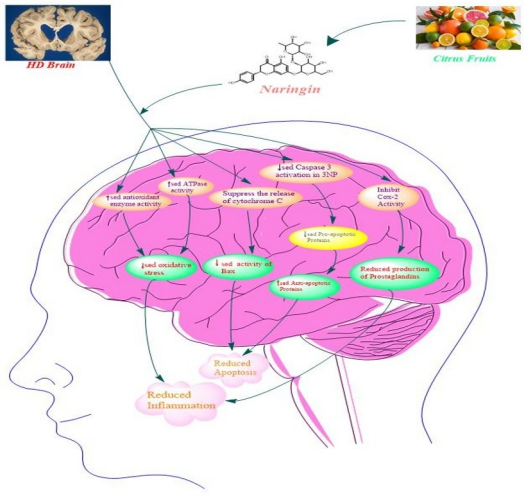

Fig6 Naringin treatment significantly enhance level of antioxidant enzymes such superoxide dimutase and catalase followed by potent free radical scavenging activity leading to reduction in level of oxidative stress and inflammation. ATPase activity can indirectly contribute to the reduction of inflammation through it's role in maintaining Ion balance and energy supply in cell. It exhibit apoptotic effect by suppressing the release of cyt c from mitochondria and reduce action of Bax, thereby inhibiting it's proapoptotic effect and help 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 caspace 3 activation in presence of 3-nitropropionic acid (3NP) can lead to decrease in proapoptotic proteins (Bax, Bad). NF-kappa B is known for its anti-apoptotic properties, when activated, 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 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 hydrolyze 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 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 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, [93,94] 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 [100-102]. The IB proteins are ubiquitinated and degraded when

an infection factor activates certain immunological signalling pathways, which causes NF-κB to be translocated to the nucleus where NF-κB attaches to DNA and triggers the production of proinflammatory cytokines like TNF(tumour necrosis factor), IL-1(interleukin 1), and IL-6 (interleukin 6) as well as PGE2(prostaglandin E2), iNOS(inducible nitric oxide synthase), COX-2 and others[103,104]. Hence, SFN exerts anti-inflammatory properties by decreasing NF-κB expression, its nuclear translocation, and hence preventing DNA-binding [105,106]. Besides using the NF-κB pathway, SFN supresses 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].

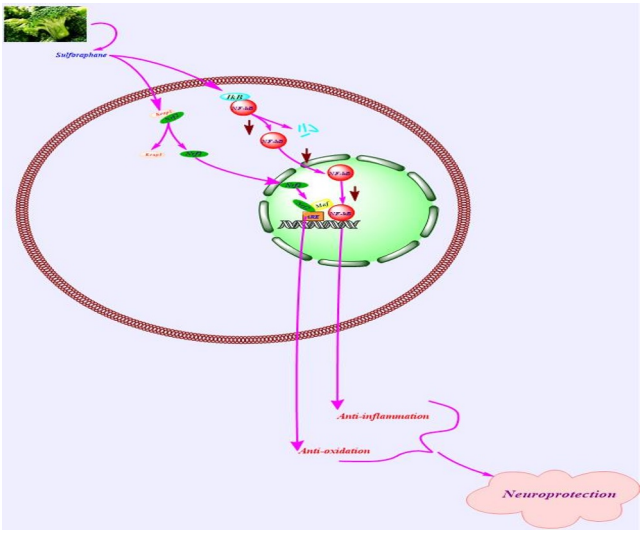

Fig7 Sulforaphane controls the inflammatory response by a mechanism linked to NF-κB inhibition for the prevention of neurodegeneration in HD

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. Pre-clinical 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

[1] Li, Shi-Hua, and Xiao-Jiang Li. "Huntingtin–protein interactions and the pathogenesis of Huntington's disease." TRENDS in Genetics 20, no. 3 (2004): 146-154.

[2] Behl, Tapan, Dapinder Kaur, Aayush Sehgal, Sukhbir Singh, Neelam Sharma, Gokhan Zengin, Felicia Liana Andronie-Cioara, Mirela Marioara Toma, Simona Bungau, and Adrian Gheorghe Bumbu. "Role of monoamine oxidase activity in Alzheimer's disease: an insight into the therapeutic potential of inhibitors." Molecules 26, no. 12 (2021): 3724.

[3] Zheng, Zhiqiang, and Marc I. Diamond. "Huntington disease and the huntingtin protein." Progress in molecular biology and translational science 107 (2012): 189-214.
[4] Ross, Christopher A., Elizabeth H. Aylward, Edward J. Wild, Douglas R. Langbehn, Jeffrey D. Long, John H. Warner, Rachael I. Scahill et al. "Huntington disease: natural history, biomarkers and prospects for therapeutics." Nature Reviews Neurology 10, no. 4 (2014): 204-216.
[5] Kay, Chris, Michael R. Hayden, and Blair R. Leavitt. "Epidemiology of Huntington disease." Handbook of clinical neurology 144 (2017): 31-46.
[6] Pringsheim, Tamara, Katie Wiltshire, Lundy Day, Jonathan Dykeman, Thomas Steeves, and Nathalie Jette. "The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis." Movement Disorders 27, no. 9 (2012): 1083-1091.
[7] Chen, Xueping, Chunyan Guo, and Jiming Kong. "Oxidative stress in neurodegenerative diseases." Neural regeneration research 7, no. 5 (2012): 376.
[8] Li, Robert, Zhenquan Jia, and Michael A. Trush. "Defining ROS in biology and medicine." Reactive oxygen species (Apex, NC) 1, no. 1 (2016): 9.
[9] Tabassum, Rubaiya, and Na Young Jeong. "Potential for therapeutic use of hydrogen sulfide in oxidative stress-induced neurodegenerative diseases." International Journal of Medical Sciences 16, no. 10 (2019): 1386.
[10] Cooke, Marcus S., Mark D. Evans, Miral Dizdaroglu, and Joseph Lunec. "Oxidative DNA damage: mechanisms, mutation, and disease." The FASEB Journal 17, no. 10 (2003): 1195-1214.
[11] Hong, Sung-Yong, Ludmila V. Roze, and John E. Linz. "Oxidative stress-related transcription factors in the regulation of secondary metabolism." Toxins 5, no. 4 (2013): 683-702.
[12] Pivtoraiko, Violetta N., Sara L. Stone, Kevin A. Roth, and John J. Shacka. "Oxidative stress and autophagy in the regulation of lysosome-dependent neuron death." Antioxidants & redox signaling 11, no. 3 (2009): 481-496.
[13] Paradies, Giuseppe, Valeria Paradies, Francesca M. Ruggiero, and Giuseppe Petrosillo. "Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease." World journal of gastroenterology: WJG 20, no. 39 (2014): 14205.
[14] Kumar, Puneet, Mandeep Kumar, Onkar Bedi, Manisha Gupta, Sachin Kumar, Gagandeep Jaiswal, Vikrant Rahi et al. "Role of vitamins and minerals as immunity boosters in COVID-19." Inflammopharmacology 29, no. 4 (2021): 1001-1016.
[15] Haynes, Cole M., Eric A. Titus, and Antony A. Cooper. "Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death." Molecular cell 15, no. 5 (2004): 767-776.
[16] Chong, Wai Chin, Madhur D. Shastri, and Rajaraman Eri. "Endoplasmic reticulum stress and oxidative stress: a vicious nexus implicated in bowel disease pathophysiology." International journal of molecular sciences 18, no. 4 (2017): 771.
[17] Lu, Meng-Chen, Jian-Ai Ji, Zheng-Yu Jiang, and Qi-Dong You. "The Keap1–Nrf2–ARE pathway as a potential preventive and therapeutic target: an update." Medicinal research reviews 36, no. 5 (2016): 924-963.
[18] Wu, Haijian, Huanjiang Niu, Anwen Shao, Cheng Wu, Brandon J. Dixon, Jianmin Zhang, Shuxu Yang, and Yirong Wang. "Astaxanthin as a potential neuroprotective agent for neurological diseases." Marine drugs 13, no. 9 (2015): 5750-5766.
[19] Brotosudarmo, Tatas Hardo Panintingjati, Leenawaty Limantara, and Edi Setiyono. "Structures of astaxanthin and their consequences for therapeutic application." International Journal of Food Science 2020 (2020).
[20] Singh, Pradeep, Garima Mishra, Mulugeta Molla, Yohannes Shumet Yimer, Woretaw Sisay, Yared Andargie, and Amien Ewunetie. "Dietary and nutraceutical-based therapeutic approaches to combat the pathogenesis of Huntington's disease." Journal of Functional Foods 92 (2022): 105047.
[21] Kumar, Amit, and Rajiv R. Ratan. "Oxidative stress and Huntington's disease: The good, the bad, and the ugly." Journal of Huntington's disease 5, no. 3 (2016): 217-237.
[22] Behl, Tapan, Gagandeep Kaur, Aayush Sehgal, Shaveta Bhardwaj, Sukhbir Singh, Camelia Buhas, Claudia Judea-Pusta, Diana Uivarosan, Mihai Alexandru Munteanu, and Simona Bungau. "Multifaceted role of matrix metalloproteinases in neurodegenerative diseases: Pathophysiological and therapeutic perspectives." International Journal of Molecular Sciences 22, no. 3 (2021): 1413.
[23] Kumar, Sunil, and S. V. Singh. "Inhibition of NF-κBsignaling pathway by astaxanthin supplementation for prevention of heat stress–induced inflammatory changes and apoptosis in Karan Fries heifers." Tropical animal health and production 51 (2019): 1125-1134.
[24] Chen, Yuqiong, Su Li, Yuxuan Guo, Hang Yu, Yandong Bao, Xin Xin, Huimin Yang, Xinzhu Ni, Nan Wu, and Dalin Jia. "Astaxanthin attenuates hypertensive vascular remodeling by protecting vascular smooth muscle cells from oxidative stress-induced mitochondrial dysfunction." Oxidative Medicine and Cellular Longevity 2020 (2020): 1-19.
[25] Pereira, Carolina Parga Martins, Ana Carolina Remondi Souza, Andrea Rodrigues Vasconcelos, and Pietra Sacramento Prado. "Antioxidant and anti-inflammatory mechanisms of action of astaxanthin in cardiovascular diseases." International journal of molecular medicine 47, no. 1 (2021): 37-48.
[26] Si, Pan, and Chenkai Zhu. "Biological and neurological activities of astaxanthin." Molecular Medicine Reports 26, no. 4 (2022): 1-12.

[27] Jiang, Wenxiao, Wenjie Wei, Marta A. Gaertig, Shihua Li, and Xiao-Jiang Li. "Therapeutic effect of berberine on Huntington's disease transgenic mouse model." PloS one 10, no. 7 (2015): e0134142.
[28] Kumar, Anil, Kanwaljit Chopra, Madhurima Mukherjee, Raghavender Pottabathini, and Dinesh K. Dhull. "Current knowledge and pharmacological profile of berberine: an update." European journal of pharmacology 761 (2015): 288-297.
[29] Cai, Zhiyou, Chuanling Wang, and Wenming Yang. "Role of berberine in Alzheimer's disease." Neuropsychiatric disease and treatment (2016): 2509-2520.
[30] Jiang, WenXiao, ShiHua Li, and XiaoJiang Li. "Therapeutic potential of berberine against neurodegenerative diseases." Science China Life Sciences 58 (2015): 564-569.
[31] Hsu, Ya-Yun, Cheng-Sheng Chen, Sheng-Nan Wu, Yuh-Jyh Jong, and Yi-Ching Lo. "Berberine activates Nrf2 nuclear translocation and protects against oxidative damage via a phosphatidylinositol 3-kinase/Akt-dependent mechanism in NSC34 motor neuron-like cells." European Journal of Pharmaceutical Sciences 46, no. 5 (2012): 415-425.
[32] Zhang, Xiaolin, Xiangjian Zhang, Chaohui Wang, Yanhua Li, Lipeng Dong, Lili Cui, Lina Wang et al. "Neuroprotection of early and short-time applying berberine in the acute phase of cerebral ischemia: up-regulated pAkt, pGSK and pCREB, down-regulated NF-κB expression, ameliorated BBB permeability." Brain research 1459 (2012): 61-70.
[33] Hu, Jun, Yushuang Chai, Yugang Wang, Michael M. Kheir, Huiying Li, Zhiyi Yuan, Hongjiao Wan, Dongming Xing, Fan Lei, and Lijun Du. "PI3K p55γ promoter activity enhancement is involved in the anti-apoptotic effect of berberine against cerebral ischemia–reperfusion." European Journal of Pharmacology 674, no. 2-3 (2012): 132-142.
[34] Zhou, Xi-Qiao, Xiao-Ning Zeng, Hui Kong, and Xiu-Lan Sun. "Neuroprotective effects of berberine on stroke models in vitro and in vivo." Neuroscience Letters 447, no. 1 (2008): 31-36.
[35] Cui, Hu-Shan, Kinzo Matsumoto, Yukihisa Murakami, Hitomi Hori, Qi Zhao, and Ryosuke Obi. "Berberine exerts neuroprotective actions against in vitro ischemia-induced neuronal cell damage in organotypic hippocampal slice cultures: involvement of B-cell lymphoma 2 phosphorylation suppression." Biological and Pharmaceutical Bulletin 32, no. 1 (2009): 79-85.
[36] Lim, Jung Su, Hyosup Kim, YoonSeok Choi, Hyockman Kwon, Ki Soon Shin, Insil Joung, Mijung Shin, and Yunhee Kim Kwon. "Neuroprotective effects of berberine in neurodegeneration model rats induced by ibotenic acid." Animal Cells and Systems 12, no. 4 (2008): 203-209.
[37] Zhang, Jing, Jun-Qing Yang, Bai-Cheng He, Qi-Xin Zhou, Hua-Rong Yu, Yong Tang, and Bei-Zhong Liu. "Berberine and total base from rhizomacoptis chinensis attenuate brain injury in an aluminum-induced rat model of neurodegenerative disease." Saudi medical journal 30, no. 6 (2009): 760-766.
[38] Hong, Jeong-Seok, Yeun-Kyung Chu, Hyung Lee, Byung-Hoon Ahn, Jae-Hyung Park, Mi-Jung Kim, Sunghye Lee et al. "Effects of berberine on hippocampal neuronal damage and matrix metalloproteinase-9 activity following transient global cerebral ischemia." Journal of Neuroscience Research 90, no. 2 (2012): 489-497.
[39] Benaissa, F., H. Mohseni-Rad, P. Rahimi-Moghaddam, and Massoud Mahmoudian. "Berberine reduces the hypoxic-ischemic insult in rat pup brain." Acta PhysiologicaHungarica 96, no. 2 (2009): 213-220.
[40] Lee, Taehwan, Hwon Heo, and Yunhee Kim Kwon. "Effect of berberine on cell survival in the developing rat brain damaged by MK-801." Experimental Neurobiology 19, no. 3 (2010): 140.
[41] Bhutada, Pravinkumar, Yogita Mundhada, Kuldeep Bansod, Santosh Tawari, Shaktipal Patil, Pankaj Dixit, Sudhir Umathe, and Dharmendra Mundhada. "Protection of cholinergic and antioxidant system contributes to the effect of berberine ameliorating memory dysfunction in rat model of streptozotocin-induced diabetes." Behavioural brain research 220, no. 1 (2011): 30-41.
[42] P.K. Singh, B. Gorain, H. Choudhury, S.K. Singh, P. Whadwa, S. Sahu, M. Gulati, P. Kesharwani, "Macrophage targeted amphotericin B nanodelivery systems against visceral leishmaniasis," Materials Science and Engineering: B, vol. 258, p. 114571, 2020.
[43] Bao, Wei, Ke Li, Shuang Rong, Ping Yao, Liping Hao, Chenjiang Ying, Xiping Zhang, Andreas Nussler, and Liegang Liu. "Curcumin alleviates ethanol-induced hepatocytes oxidative damage involving heme oxygenase-1 induction." Journal of ethnopharmacology 128, no. 2 (2010): 549-553.
[44] Lobo, Richard, Kirti S. Prabhu, Annie Shirwaikar, and Arun Shirwaikar. "Curcuma zedoariaRosc.(white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties." Journal of Pharmacy and Pharmacology 61, no. 1 (2009): 13-21.
[45] Rajamma, Angel Gabriel, Vimala Bai, and Bala Nambisan. "Antioxidant and antibacterial activities of oleoresins isolated from nine Curcuma species." Phytopharmacology 2, no. 2 (2012): 312-317.
[46] Tohda, Chihiro, Natsuki Nakayama, Fumiyuki Hatanaka, and Katsuko Komatsu. "Comparison of anti-inflammatory activities of six Curcuma rhizomes: a possible curcuminoid-independent pathway mediated by Curcuma phaeocaulis extract." Evidence-Based Complementary and Alternative Medicine 3 (2006): 255-260.
[47] Ullah, Faheem, Andy Liang, Alejandra Rangel, Erika Gyengesi, Garry Niedermayer, and Gerald Münch. "High bioavailability curcumin: an anti-inflammatory and neurosupportive bioactive nutrient for neurodegenerative diseases characterized by chronic neuroinflammation." Archives of Toxicology 91 (2017): 1623-1634..

[48] Witika, Bwalya Angel, Pedzisai Anotida Makoni, Scott Kaba Matafwali, Larry Lawrence Mweetwa, GinnethonChaambaShandele, and Roderick Bryan Walker. "Enhancement of biological and pharmacological properties of an encapsulated polyphenol: Curcumin." Molecules 26, no. 14 (2021): 4244.
[49] Darvesh, Altaf S., Richard T. Carroll, Anupam Bishayee, Nicholas A. Novotny, Werner J. Geldenhuys, and Cornelis J. Van der Schyf. "Curcumin and neurodegenerative diseases: a perspective." Expert opinion on investigational drugs 21, no. 8 (2012): 1123-1140..
[50] Oppenheimer, Albert. "Turmeric (curcumin) in biliary diseases." The Lancet 229, no. 5924 (1937): 619-621.
[51] Labanca, Fabiana, Hammad Ullah, Haroon Khan, Luigi Milella, Jianbo Xiao, Zora Dajic-Stevanovic, and Philippe Jeandet. "Therapeutic and mechanistic effects of curcumin in Huntington's disease." Current Neuropharmacology 19, no. 7 (2021): 1007-1018.
[52] Márquez, Lucía, Borja García-Bueno, José LM Madrigal, and Juan C. Leza. "Mangiferin decreases inflammation and oxidative damage in rat brain after stress." European Journal of Nutrition 51 (2012): 729-739.
[53] Bhat, Abid, Arehally M. Mahalakshmi, Bipul Ray, Sunanda Tuladhar, Tousif A. Hediyal, Esther Manthiannem, Jagadeeswari Padamati, Ramesh Chandra, Saravana B. Chidambaram, and Meena K. Sakharkar. "Benefits of curcumin in brain disorders." BioFactors 45, no. 5 (2019): 666-689.
[54] Scapagnini, Giovanni, Calogero Caruso, and Vittorio Calabrese. "Therapeutic potential of dietary polyphenols against brain ageing and neurodegenerative disorders." Adv Exp Med Biol 698 (2010): 27-35.
[55] Sumanont, Yaowared, Yukihisa Murakami, MichihisaTohda, OpaVajragupta, Kinzo Matsumoto, and Hiroshi Watanabe. "Evaluation of the nitric oxide radical scavenging activity of manganese complexes of curcumin and its derivative." Biological and Pharmaceutical Bulletin 27, no. 2 (2004): 170-173.
[56] Kant, Vinay, Anu Gopal, Nitya N. Pathak, Pawan Kumar, Surendra K. Tandan, and Dinesh Kumar. "Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats." International immunopharmacology 20, no. 2 (2014): 322-330.
[57] Song, Zhimei, Runliang Feng, Min Sun, Chenyu Guo, Yan Gao, Lingbing Li, and Guangxi Zhai. "Curcumin-loaded PLGA-PEG-PLGA triblock copolymeric micelles: Preparation, pharmacokinetics and distribution in vivo." Journal of colloid and interface science 354, no. 1 (2011): 116-123.
[58] Wanninger, Simon, Volker Lorenz, Abdus Subhan, and Frank T. Edelmann. "Metal complexes of curcumin–synthetic strategies, structures and medicinal applications." Chemical Society Reviews 44, no. 15 (2015): 4986-5002.
[59] Maiti, Panchanan, and Gary L. Dunbar. "Use of curcumin, a natural polyphenol for targeting molecular pathways in treating age-related neurodegenerative diseases." International journal of molecular sciences 19, no. 6 (2018): 1637.
[60] Hickey, Miriam A., Chunni Zhu, Vera Medvedeva, Renata P. Lerner, Stefano Patassini, Nicholas R. Franich, Panchanan Maiti et al. "Improvement of neuropathology and transcriptional deficits in CAG 140 knock-in mice supports a beneficial effect of dietary curcumin in Huntington's disease." Molecular Neurodegeneration 7, no. 1 (2012): 1-16.
[61] Selkoe, Dennis J. "Cell biology of protein misfolding: the examples of Alzheimer's and Parkinson's diseases." Nature cell biology 6, no. 11 (2004): 1054-1061.
[62] Kakkar, Vaishali, Melanie Meister-Broekema, Melania Minoia, Serena Carra, and Harm H. Kampinga. "Barcoding heat shock proteins to human diseases: looking beyond the heat shock response." Disease models & mechanisms 7, no. 4 (2014): 421-434..
[63] Dou, Fei, William J. Netzer, Kentaro Tanemura, Feng Li, F. Ulrich Hartl, Akihiko Takashima, Gunnar K. Gouras, Paul Greengard, and Huaxi Xu. "Chaperones increase association of tau protein with microtubules." Proceedings of the National Academy of Sciences 100, no. 2 (2003): 721-726..
[64] Wyttenbach, Andreas, Jenny Carmichael, Jina Swartz, Robert A. Furlong, Yolanda Narain, Julia Rankin, and David C. Rubinsztein. "Effects of heat shock, heat shock protein 40 (HDJ-2), and proteasome inhibition on protein aggregation in cellular models of Huntington's disease." Proceedings of the National Academy of Sciences 97, no. 6 (2000): 2898-2903..
[65] Sherman, Michael Y., and Alfred L. Goldberg. "Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases." Neuron 29, no. 1 (2001): 15-32.
[66] Zhang, Yu-Qian, and Kevin D. Sarge. "Celastrol inhibits polyglutamine aggregation and toxicity though induction of the heat shock response." Journal of molecular medicine 85 (2007): 1421-1428.
[67] Davenport J, Manjarrez JR, Peterson L, Krumm B, Blagg BS, Matts RL. Gambogic acid, a natural product inhibitor of Hsp90. J Nat Prod 2011;74(5):1085-92.
[68] Maiti, Panchanan, and Gary L. Dunbar. "Comparative neuroprotective effects of dietary curcumin and solid lipid curcumin particles in cultured mouse neuroblastoma cells after exposure to Aβ42." International Journal of Alzheimer's Disease 2017 (2017).
[69] Majumder, B. "Activation of heat shock protein induced by curcumin to prevent Huntington disease-an analytical approach in the context of protein vibration." International Journal of Biophysics 8 (2018): 1-8.
[70] Alam, M. Ashraful, Nusrat Subhan, M. Mahbubur Rahman, Shaikh J. Uddin, Hasan M. Reza, and Satyajit D. Sarker. "Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action." Advances in Nutrition 5, no. 4 (2014): 404-417.

[71] Chen, Rui, Qiao-Ling Qi, Meng-Ting Wang, and Qi-Yan Li. "Therapeutic potential of naringin: an overview." Pharmaceutical biology 54, no. 12 (2016): 3203-3210.
[72] Mekhilef, Saad, Rahman Saidur, and Masoud Kamalisarvestani. "Effect of dust, humidity and air velocity on efficiency of photovoltaic cells." Renewable and sustainable energy reviews 16, no. 5 (2012): 2920-2925.
[73] Gopinath, Kulasekaran, and Ganapasam Sudhandiran. "Protective effect of naringin on 3-nitropropionic acid-induced neurodegeneration through the modulation of matrix metalloproteinases and glial fibrillary acidic protein." Canadian journal of physiology and pharmacology 94, no. 1 (2016): 65-71.
[74] Gopinath, K., and G. Sudhandiran. "Naringin modulates oxidative stress and inflammation in 3-nitropropionic acid-induced neurodegeneration through the activation of nuclear factor-erythroid 2-related factor-2 signalling pathway." Neuroscience 227 (2012): 134-143.
[75] Cui, Jian, Gang Wang, Amit D. Kandhare, Anwesha A. Mukherjee-Kandhare, and Subhash L. Bodhankar. "Neuroprotective effect of naringin, a flavone glycoside in quinolinic acid-induced neurotoxicity: possible role of PPAR-γ, Bax/Bcl-2, and caspase-3." *Food and chemical toxicology* 121 (2018): 95-108.
[76] Wang, Kaihua, Zhenzhen Chen, Longjian Huang, Bing Meng, Xinmei Zhou, Xiaodong Wen, and Ding Ren. "Naringenin reduces oxidative stress and improves mitochondrial dysfunction via activation of the Nrf2/ARE signaling pathway in neurons." International Journal of Molecular Medicine 40, no. 5 (2017): 1582-1590.
[77] Salman, Mohd, Pooja Sharma, Md Iqbal Alam, Heena Tabassum, and Suhel Parvez. "Naringenin mitigates behavioral alterations and provides neuroprotection against 3-nitropropinoic acid-induced Huntington's disease like symptoms in rats." Nutritional Neuroscience 25, no. 9 (2022): 1898-1908.
[78] Liu, Yanying, Casey L. Hettinger, Dong Zhang, Khosrow Rezvani, Xuejun Wang, and Hongmin Wang. "Sulforaphane enhances proteasomal and autophagic activities in mice and is a potential therapeutic reagent for Huntington's disease." Journal of neurochemistry 129, no. 3 (2014): 539-547.
[79] Matusheski, Nathan V., John A. Juvik, and Elizabeth H. Jeffery. "Heating decreases epithiospecifier protein activity and increases sulforaphane formation in broccoli." Phytochemistry 65, no. 9 (2004): 1273-1281.
[80] Schepici, Giovanni, Placido Bramanti, and Emanuela Mazzon. "Efficacy of sulforaphane in neurodegenerative diseases." International journal of molecular sciences 21, no. 22 (2020): 8637.
[81] Liu, Fangkun, Jing Huang, Gangrui Hei, Renrong Wu, and Zhixiong Liu. "Effects of sulforaphane on cognitive function in patients with frontal brain damage: study protocol for a randomised controlled trial." BMJ open 10, no. 10 (2020): e037543.
[82] Santín-Márquez, R., Alarcón-Aguilar, A., López-Diazguerrero, N.E., Chondrogianni, N. and Königsberg, M., 2019. Sulforaphane-role in aging and neurodegeneration. Geroscience, 41, pp.655-670.
[83] Hu, Chenqi, Aimee L. Eggler, Andrew D. Mesecar, and Richard B. Van Breemen. "Modification of keap1 cysteine residues by sulforaphane." Chemical research in toxicology 24, no. 4 (2011): 515-521.
[84] Uddin, Md Sahab, Abdullah Al Mamun, Md Jakaria, Shanmugam Thangapandiyan, Jamil Ahmad, Md Ataur Rahman, Bijo Mathew, Mohamed M. Abdel-Daim, and Lotfi Aleya. "Emerging promise of sulforaphane-mediated Nrf2 signaling cascade against neurological disorders." Science of the Total Environment 707 (2020): 135624.
[85] Zalachoras, Ioannis, Fiona Hollis, Eva Ramos-Fernández, Laura Trovo, Sarah Sonnay, Eveline Geiser, Nicolas Preitner, Pascal Steiner, Carmen Sandi, and Laia Morató. "Therapeutic potential of glutathione-enhancers in stress-related psychopathologies." Neuroscience &Biobehavioral Reviews 114 (2020): 134-155.
[86] Dinkova-Kostova, Albena T., Rumen V. Kostov, and Peter Canning. "Keap1, the cysteine-based mammalian intracellular sensor for electrophiles and oxidants." Archives of biochemistry and biophysics 617 (2017): 84-93.
[87] Pu, Die, Yuxing Zhao, Jinliang Chen, AnkangLv, Shiyu Zhu, Cheng Luo, Kexiang Zhao, and Qian Xiao. "Protective effects of sulforaphane on cognitive impairments and AD-like lesions in diabetic mice are associated with the upregulation of Nrf2 transcription activity." Neuroscience 381 (2018): 35-45.
[88] Zgorzynska, Emilia, Barbara Dziedzic, and Anna Walczewska. "An overview of the Nrf2/ARE pathway and its role in neurodegenerative diseases." International Journal of Molecular Sciences 22, no. 17 (2021): 9592.
[89] Shang, Guoguo, Xinjun Tang, Pan Gao, Fanli Guo, Hongpeng Liu, Zhonghua Zhao, Qi Chen, Tao Jiang, Nong Zhang, and Hui Li. "Sulforaphane attenuation of experimental diabetic nephropathy involves GSK-3 beta/Fyn/Nrf2 signaling pathway." The Journal of Nutritional Biochemistry 26, no. 6 (2015): 596-606.
[90] A. Verma, B. Kaur, S. Venugopal, P. Wadhwa, S. Sahu, P. Kaur, D. Kumar, A. Sharma, "Tetrazole: A privileged scaffold for the discovery of anticancer agents," Chemical Biology & Drug Design, vol. 100, no. 3, 419-42, 2022.
[91] Kubo, Eri, Bhavana Chhunchha, Prerna Singh, Hiroshi Sasaki, and Dhirendra P. Singh. "Sulforaphane reactivates cellular antioxidant defense by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress." Scientific reports 7, no. 1 (2017): 14130.
[92] Magesh, Sadagopan, Yu Chen, and Longqin Hu. "Small molecule modulators of K eap1-N rf2-ARE pathway as potential preventive and therapeutic agents." Medicinal research reviews 32, no. 4 (2012): 687-726.
[93] Zhao, Fangfang, Jianlei Zhang, and Na Chang. "Epigenetic modification of Nrf2 by sulforaphane increases the antioxidative and anti-inflammatory capacity in a cellular model of Alzheimer's disease." European journal of pharmacology 824 (2018): 1-10.

[94] Soane, Lucian, Wei Li Dai, Gary Fiskum, and Linda L. Bambrick. "Sulforaphane protects immature hippocampal neurons against death caused by exposure to hemin or to oxygen and glucose deprivation." Journal of neuroscience research 88, no. 6 (2010): 1355-1363.
[95] Lee, Chan, Gyu Hwan Park, Seong-Ryong Lee, and Jung-Hee Jang. "Attenuation of-amyloid-induced oxidative cell death by sulforaphane via activation of NF-E2-related factor 2." Oxidative medicine and cellular longevity 2013 (2013).
[96] Alfieri, Alessio, Salil Srivastava, Richard CM Siow, Diana Cash, Michel Modo, Michael R. Duchen, Paul A. Fraser, Steven CR Williams, and Giovanni E. Mann. "Sulforaphane preconditioning of the Nrf2/HO-1 defense pathway protects the cerebral vasculature against blood–brain barrier disruption and neurological deficits in stroke." Free Radical Biology and Medicine 65 (2013): 1012-1022.
[97] Sedlak, Thomas W., Bindu D. Paul, Gregory M. Parker, Lynda D. Hester, Adele M. Snowman, Yu Taniguchi, Atsushi Kamiya, Solomon H. Snyder, and Akira Sawa. "The glutathione cycle shapes synaptic glutamate activity." Proceedings of the National Academy of Sciences 116, no. 7 (2019): 2701-2706.
[98] He, Feng, Xiaoli Ru, and Tao Wen. "NRF2, a transcription factor for stress response and beyond." International journal of molecular sciences 21, no. 13 (2020): 4777.
[99] Quispe, Ruth Liliám, Michael Lorenz Jaramillo, Leticia Selinger Galant, Daiane Engel, Alcir Luiz Dafre, João Batista Teixeira da Rocha, Rafael Radi, Marcelo Farina, and Andreza Fabro de Bem. "Diphenyl diselenide protects neuronal cells against oxidative stress and mitochondrial dysfunction: Involvement of the glutathione-dependent antioxidant system." Redox biology 20 (2019): 118-129.
[100] Nadeem, Ahmed, Sheikh F. Ahmad, Naif O. Al-Harbi, Sabry M. Attia, Saleh A. Bakheet, Khalid E. Ibrahim, Faleh Alqahtani, and Mohammed Alqinyah. "Nrf2 activator, sulforaphane ameliorates autism-like symptoms through suppression of Th17 related signaling and rectification of oxidant-antioxidant imbalance in periphery and brain of BTBR T+ tf/J mice." Behavioural brain research 364 (2019): 213-224.
[101] Saha, Sarmistha, Brigitta Buttari, Emiliano Panieri, Elisabetta Profumo, and Luciano Saso. "An overview of Nrf2 signaling pathway and its role in inflammation." Molecules 25, no. 22 (2020): 5474.
[102] Subedi, Lalita, Jae Hyuk Lee, Silvia Yumnam, Eunhee Ji, and Sun Yeou Kim. "Anti-inflammatory effect of sulforaphane on LPS-activated microglia potentially through JNK/AP-1/NF-κB inhibition and Nrf2/HO-1 activation." Cells 8, no. 2 (2019): 194.
[103] Behl, Tapan, Keshav Kumar, Ciprian Brisc, Marius Rus, Delia Carmen Nistor-Cseppento, Cristiana Bustea, Raluca Anca Corb Aron et al. "Exploring the multifocal role of phytochemicals as immunomodulators." Biomedicine & Pharmacotherapy 133 (2021): 110959.
[104] Sun, Jing, and Guangxian Nan. "The mitogen-activated protein kinase (MAPK) signaling pathway as a discovery target in stroke." *Journal of Molecular Neuroscience* 59 (2016): 90-98.
[105] Hernández-Rabaza, Vicente, Andrea Cabrera-Pastor, Lucas Taoro-González, Michele Malaguarnera, Ana Agustí, Marta Llansola, and Vicente Felipo. "Hyperammonemia induces glial activation, neuroinflammation and alters neurotransmitter receptors in hippocampus, impairing spatial learning: reversal by sulforaphane." *Journal of neuroinflammation* 13 (2016): 1-11.

[106] Sanjay W., Digvijay G., Walmik S., and Hitesh Vasudev, Plasticity Index a measure of dry sliding wear for Ni-based coating, *Surface review and letters;* https://doi.org/10.1142/S0218625X23400103

[107] 63 Sharma, S. and Kumar, A., 2021. Recent advances in metallic corrosion inhibition: A review. *Journal of Molecular Liquids*, *322*, p.114862.
[108] 64 Garg, S.S., Gupta, J., Sharma, S. and Sahu, D., 2020. An insight into the therapeutic applications of coumarin compounds and their mechanisms of action. *European Journal of Pharmaceutical Sciences*, *152*, p.105424.
[109] 65 Kumar, H., Bhardwaj, K., Nepovimova, E., Kuča, K., Singh Dhanjal, D., Bhardwaj, S., Bhatia, S.K., Verma, R. and Kumar, D., 2020. Antioxidant functionalized nanoparticles: A combat against oxidative stress. *Nanomaterials*, *10*(7), p.1334.
[110] 66.Prashar, D., Jha, N., Jha, S., Lee, Y. and Joshi, G.P., 2020. Blockchain-based traceability and visibility for agricultural products: A decentralized way of ensuring food safety in india. *Sustainability*, *12*(8), p.3497.