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Review article

Natural antioxidants for neuroinflammatory disorders and possible involvement of Nrf2 pathway: A review

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ABSTRACT

The transcription factor Nrf2 (nuclear factor-erythroid 2 p45-related factor 2) play a crucial role in cellular redox and metabolic system. Activation of Nrf2 may be an effective therapeutic approach for neuroinflammatory disorders, through activation of antioxidant defences system, lower the inflammation, line up the mitochondrial function, and balancing of protein homeostasis. Various recent studies revealed that many of active substance obtained from plants have been found to activate the Nrf2 and to exert neuroprotective effects in various experimental models, raising the possibility that activation of Nrf2 may be an effective therapeutic approaches for neuroinflammatory disorders. The objective of this review was to evaluate the neuroprotective property of natural substance against neuroinflammatory disorders by reviewing the studies done till today. The outcomes of various *in vitro* and *in vivo* examinations have shown that natural compounds producing neuroprotective effects in neuronal system *via* activation of Nrf2. Herein, we also reviewed the studies to understand the role of Nrf2 for curing CNS disorders. Here we can conclude, herbal/natural moieties having potency to fight and prevent from neuroinflammatory disorders due to their abilities to activate Nrf2 pathway.

1. Introduction

Neuroinflammation is nervous system inflammation that is prevalent in many neurodegenerative disorders such as Alzheimer's disease, Parkinson 's disease, Huntington 's disease, Amyotrophic lateral sclerosis (ALS) etc., characterised by microglia activation, inflammatory mediator release and reactive oxygen species (ROS) generation [1]. Studies have shown that neuroinflammation plays a crucial role in neurodegenerative disease growth. In several neurodegenerative diseases, neuroinflammation targeting is important because it aims to speed up interpretation of the immune process involved in neurodegenerative diseases [2]. Risk factors for neuroinflammation formation are distinct and are full responses that contribute to vascular compromise, oxidative stress and eventually lead to further formation of neurodegenerative diseases contributing to brain injury. The role of nuclear factor Erythroid 2-related factor 2 (Nrf2) is altered in many neurodegenerative diseases [3, 4].

Current studies have shown that there are several compounds isolated from natural plants that can delay neuronal damage and degenerative progression by inhibition of free radical generation and inflammation by activation of Nrf2, so they have attracted considerable attention as pharmacological treatments targeting neurodegenerative disorders [5]. Herbs or natural compounds have been known to control neurodegenerative diseases associated with neuroinflammation through antioxidant and anti-inflammatory activity [6]. Numerous natural substances are currently able to suppress neuroinflammation through the Nrf2-Responsive Antioxidant Element (ARE) pathway [7]. Many researchers are therefore focused on the pharmacological activation of Nrf2 in order to ameliorate neurodegenerative diseases. A number of studies have indicated that natural plants and their active components can counteract the progression of neurodegenerative diseases by activating Nrf2 [8]. Nrf2 is a transcription factor that controls antioxidant enzymes that protects against cellular system damage due to free radicle overproduction and is derived from Nuclear Factor. The gene Erythroid 2 Like 2 (NFE2L2) belongs to the family cap'n' transcription factor family [9]. Nrf2 exists in the cytoplasm with an inhibitory Nrf2 kelch protein such as ECH-associated protein1 (keap1) in the resting state. The levels of Nrf2 and its activation were basically regulated by keap1. At the level of free radicles, keap1 releases Nrf2 by altering main keap1 cysteine residues, facilitating the dissociation of the inhibitory complex and inducing its nuclear translocation sequentially [10]. The two pathways involved in Nrf2 activation are keap1 confirmation modification and Nrf2

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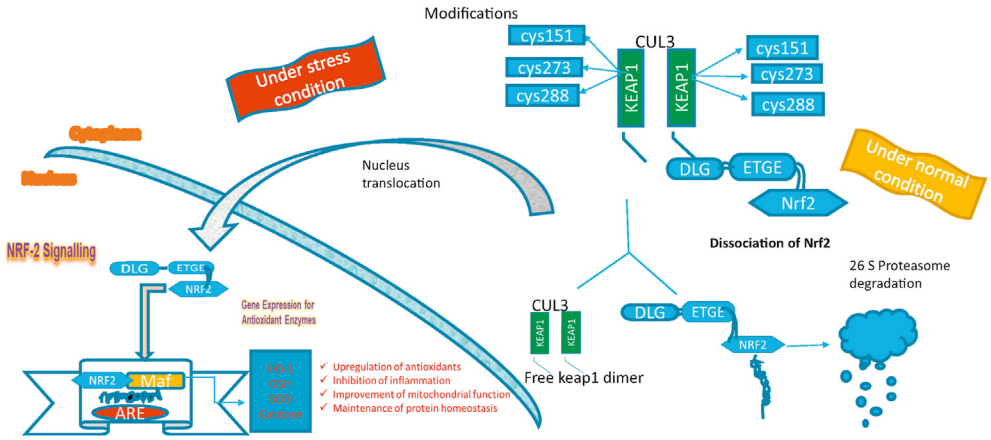


Figure 1. Physiology of Nrf2 activation in both normal and stress conditions. In normal conditions, Nrf2 is associated with Keap1 by its two motifs (ETGE and DLG) that leads to CUL3-mediated ubiquitination followed by proteasome degradation. In oxidative stress, Nrf2 dissociates from Keap1, translocates to the nucleus and activates the ARE-gene system. KEAP1 = Kelch-like ECH-associated protein 1, CUL3 = Cullin 3, DLG = DLG motifs, ETGE = ETGE motifs, NRF2 = Nuclear factor erythroid 2-related factor 2, ARE = Antioxidant response element, HO1 = *Haem oxygenase*-1, GSH = Glutathione, SOD = Superoxide dismutase.

phosphorylation. Nrf2 accumulates gene-dependent expression in the nucleus regulated by the basal antioxidant response factor and maintains cellular homeostasis. During the expression of Nrf2 target genes such as superoxide dismutase (SOD), heme oxygenase-1 (HO-1), glutathione (GSH), catalase (CAT), Uridine 5′-diphospho-glucuronosyltransferase (UDP-glucosyltransferase), Nrf2 forms a heterodimer in the nucleus with its partner musculoaponeurosis fibromatosis (sMaf) binding to ARE [9]. This is the Nrf2 conical pathway. Alternatively, non-conical mechanisms can disturb the interaction of keap1 and Nrf2 [11,12]. Figure 1 demonstrating the basic physiology of Nrf2 activation in both normal and stress conditions.

2. Nrf2-ARE signaling pathway in neuroprotection

Nrf2 is a transcription factor that stimulates a large number of cytoprotective and detoxifying genes to express them. The protective function of the Nrf2-ARE pathway in neurodegenerative conditions is illustrated by a lot of data, as it reduces ROS and neuroinflammation. An intrinsic mechanism of defense against cellular oxidative damage is the Nrf2-ARE pathway. Antioxidant enzymes are regulated by Nrf2 and proteins are involved in detoxification, repair and removal of damaged tissues and organelles and inflammation. Nrf2 blocks the transcription of proinflammatory cytokine encoding genes and suppresses proinflammatory responses after UV radiation or lipopolysacchride (LPS) exposure. A variety of antioxidant enzymes and proteins that exert cytoprotective enhancement of neurological phenotypes in disease models after the induction of antioxidant activities based on Nrf2 are expressed in the Nrf2 Regulations. The levels of Nrf2 are primarily regulated by ubiquitination and proteosomal degradation. Activation of Nrf2 contributes to upregulation of proteins involved in the synthesis of glutathione, the major antioxidant intracellular small molecule, and nicotinamide adenine dinucleotide phosphate (NADPH), which produces oxidised glutathione disulfide (GSSG) reduction equivalents for the regeneration of reduced glutathione (GSH). Nrf2 activation counterbalances mitochondrial ROS production and defends toxins released by mitochondria [13, 14]. Similarly, in numerous *in vitro* and *in vivo* studies, other researchers have tested the neuroprotective efficacy of ARE-Nrf2 pathways and it has been shown that many natural and synthetic compounds exhibit profound neuroprotective effects based on Nrf2-ARE. It was therefore assessed that the chemically induced ARE-mediated transcriptional response as well as the chemo preventive efficacy of these compounds is absolutely abolished in Nrf2 knock-out mice and Nrf2 disrupted cells [15, 16].

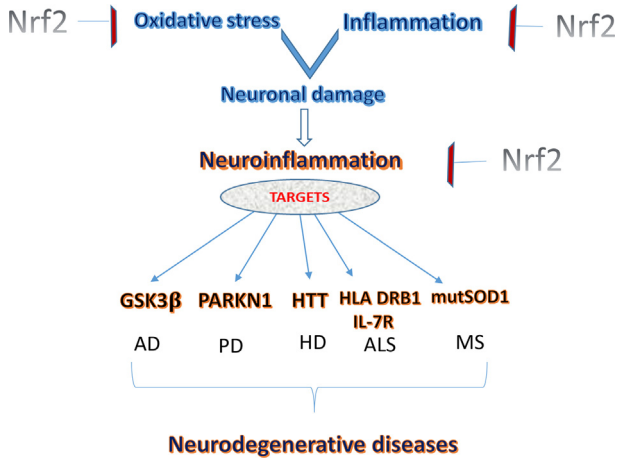


Figure 2. Nrf 2 pathway as a target in different neurodegenerative diseases. Nrf2 mediated oxidative stress and inflammations causes neuronal damages lead to deregulation of various proteins responsible for subsequent neurodegenerative diseases. Nrf 2 = Nuclear factor erythroid 2-related factor 2, GSK3β = Glycogen synthase kinase 3 beta, AD = Alzheimer's disease, PD = Parkinson's disease, HD = Huntington's disease, ALS = Amyotrophic lateral sclerosis, MS = Multiple sclerosis.

3. Role of Nrf2 signaling in countering neurodegenerative diseases

The important global health issues associated with ageing are neurodegenerative diseases. For different neurodegenerative diseases underlying ROS overproduction and inflammation, pharmacological activation of Nrf2 is a promising therapeutic strategy. *Via* upregulation of antioxidant defenses, inflammation inhibition, enhancement of mitochondrial function and maintenance of protein homeostasis, Nrf2 activation mitigates several pathogenic processes involved in neurodegenerative diseases. Enhanced antioxidant activities based on Nrf2 play a crucial role in the pathological enhancement of neurodegenerative diseases, as Nrf2 controls the expression of a spectrum of antioxidant enzymes and proteins [17]. Nrf2 has been involved in the regulation of the mechanism of cellular defense by altering mitochondrial function. Enabled Nrf2 preserves ROS mitochondrial production and protects it from toxins released by mitochondria [18]. The involvement of Nrf2 signalling in the maintenance of inflammatory mediator development has been identified, explaining the mechanism of transcriptional repression of pro-inflammatory cytokines (TNF-alpha, IL-1, IL6, IL-8, MCP-1) in microglia, macrophages, monocytes and astrocytes after activation of Nrf2 [19].

In neurodegenerative disorders, Nrf2-HO-1 is downregulated [17, 20]. These are the primary cellular mechanisms which regulate genes

Table 1. List of natural substances that modulate Nrf2 pathway in neurodegenerative diseases.

S. No.	Compound	Botanical name	Mechanism	Model of disease	Used doses	Ref.
1	Amygdaline	*Artemisia amygdalina*	*Artemisia amygdalina* up regulates Nrf2 pathway through inhibition of KEAP1 which further leads to activation of antioxidant machinery.	*in vitro* N2a and SH-SY5Y cells	100 μg/ml	[36]
2	Andalucín	*Artemisia lannta*	Andalucín promotes Nrf2 mediated HO-1 levels by blocking the p65-p300 interaction in LPS treated BV2 microglia.	*in vitro* BV2 cells	5–20 μM	[31]
3	Andrographolide	*Andrographus Paniculata*	Andrographolide increases Nrf2 expression in CYS151 independent manner but likely KEAP1 dependent manner.	*in vitro* HEK293T cells	7.5 μM	[34]
4	Astragaloside IV	*Radix Astragali Seu Hedysari*	Astragaloside IV protected the integrity of BBB in LPS induced mice, the mechanism of which might be mediated *via* activating Nrf2 signalling pathway	*in vivo* Mice	40 μM	[83, 84]
5	Caffeic acid	Propolis Extract	Caffeic acid increases the expression of Nrf2 and HO-1, which is probably mediated by GSKβ activity.	*in vivo* Male C57B1/6 Mice	10 mg/kg	[70]
6	Cannabidiol	*Cannabis sativa*	Activation of Nrf2-hmox1 and Nrf2/ATF4 pathways to control LPS-induced activation of microglial cells.	*in vitro* BV2 cells	10 μM	[41]
7	Cardamonin	*Alpinia katsumadai*	The mechanism underlying the activation of Nrf2 by CD might involve the oxidation/alkylation of key thiols in KEAP1 and/or phosphorylation of Nrf2.	*in vitro* PC12 cells	10 μM	[29]
8	Carnosic acid	*Rosmarinus officinalis*	Neurons protection from oxidative stress and excitotoxicity through keap1/Nrf2 transcriptional pathway	*in vitro*	3 μmol/L	[88]
9	Curcumin	*Curcuma longa*	Protects neurons from ischemic injury through Akt/Nrf2 pathway.	*in vivo*	5 mg/kg	[100]
10	Fumaric acid	Dimethyl Fumarate DMF	Fumaric acid activates Nrf2 through Modification of keap1 cysteine residue 151 and thus leads to stabilization of Nrf2.	*in vivo* C57/BL6 mice	15 mg/kg	[101]
11	Hesperetin	*Citrus* Fruit Species	Hesperetin significantly upregulated the expression of Nrf2 and HO-1.	*in vitro,* HT22 and BV2 cells	5 μM	[102]
12	Icariin	*Epimedii Herba*	Icariin increases the translocation of Nrf2 from cytoplasm to nucleus and also enhance the protein expression of HO-1 as well as NQO1.	*in vitro* BV2 cells	0.1 μM	[103]
13	Lycopene	*Solanum lycopersicum*	Lycopene restore Nrf2, upregulate expression of HO-1 and BDNF in H_2O_2 treated SH-SY5Y cells	*in vitro* SH-SY5Y cells	5 μM	[96]
14	Nardochinoid C	*Nardostachys chinensis*	Activation of Nrf2/HO-1 by nardochinoid c inhibit inflammation and oxidative stress in LPS activated macrophages	*in vitro* *RAW 264.7* cells	20 μM	[79]
15	Narngenin	*Citrus paradise*	Narngenin showed neuroprotective effects against MPTP- induced oxidative stress.	Male C57BL/6J mice	100 mg/kg	[45]
16	Quercetin	*Morus alba*	Quercetin counteracts neuroinflammation by activating Nrf2/HO-1 and inhibiting NF-kB signalling in SK-N-MC cell lines.	*in vitro* and *in vivo*	20 μg/mL	[76]
17	Schisantherin A	*Schisandra Sphenanthera*	Schisantherin A induce accumulation of Nrf2 in the nucleus and its activation mediated by ERK phosphorylation.	*in vitro* BV2 cells	50 μM	[91]
18	Sophoraflavanone G	*Sophora Alopecuroides*	Sophoraflavanone downregulated phosphorylated MAPK, JAK/STAT	*in vitro* BV2 cells	10 μM	[97]

(*continued on next page*)

Table 1 (*continued*)

S. No.	Compound	Botanical name	Mechanism	Model of disease	Used doses	Ref.
			and upregulated HO-1 *via* Nrf2 transcription factor in LPS activated BV2 cells.			
19	Tenuigenin	*Polygala Tenuifolia*	Tenuigenin upregulates Nrf2 in dose dependent manner. It inhibit neuro-inflammation by upregulating the expression of keap1-Nrf2 signalling pathway.	*in vitro*, BV2 cells and *in vivo* male ICR mice	1–4 μM 5–20 mg/kg	[82]

that are antioxidant and cytoprotective. In multiple pathological disorders such as Alzheimer's disease, Parkinson 's disease etc., neuroprotective activity of Nrf2 mediated haemoxygenase1 (HO-1) induction has been demonstrated [21]. The rate-limiting enzyme, HO-1, is closely regulated by Nrf2. Promising methods for the initiation and development of neurodegenerative diseases are Nrf2 activation and elevation of HO-1 in microglia [22]. Figure 2 demonstrating about targets of Nrf2 pathway in different neurodegenerative diseases. Similarly, it has been shown that the interaction between the nuclear factor kappa-light-chain-enhancer of activated B cells controlling the production of cytokines and the NRF2-ARE system is also involved in neurodegenerative and neuroinflammatory disorders [23]. Stimulation of the ARE-mediated activity of Nrf2 can lead to suppression of the neurodegenerative process by inhibition of ROS generation and inhibition of redox-sensitive expression of inflammatory mediators, based on the available literature on the Nrf2-ARE signaling pathway. The fact that the Nrf2-ARE signaling pathway may be potential developmental therapeutic targets and the quest for new promising agents for better treatment of neurodegenerative diseases is identified [22].

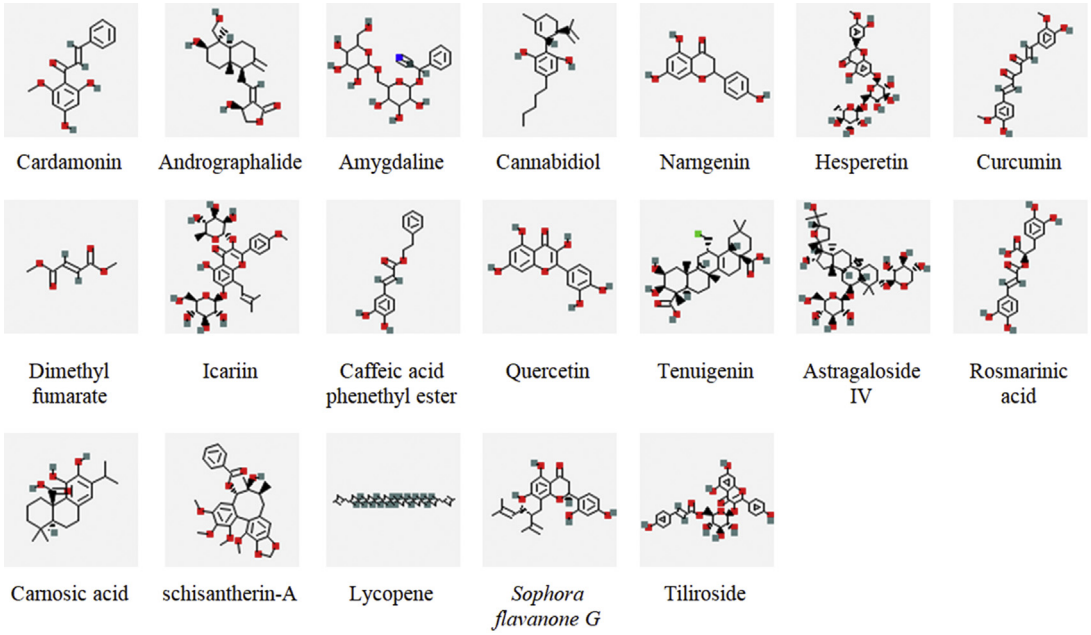
4. Natural substances induced Nrf2 activation in neurodegenerative diseases

Recent studies have shown that certain natural substances or derived compounds are capable of defending neuronal cells against oxidative stress and ameliorating various chronic diseases. In addition, few researchers have investigated the possibility of combining different herbal plants with Keap1-Nrf2 Pathway activation for the treatment of neurodegenerative disease [24]. The Table 1 contains available natural substances and their effective moiety which is responsible to activate the Nrf2 pathway and gives protection against neuroinflammatory disorders. Table 2 represent the structure of active moiety obtained from various natural sources and are responsible for modulate the activity of Nrf2 in order to produce neuroprotective action.

4.1. *Alpinia katsumadai*

Cardamonin (CD) is chalconoid which belongs to the *Zingiberaceous* family, isolated from Alpinia species such as *Alpinia katsumadai*. A broad range of pharmacological activities such as antioxidant, anti-inflammatory, antineoplastic, anti-infectious, vasorelaxant, hypoglycaemic and autophagy induction have been investigated [25]. It has been documented in recent studies that CD is an efficient small molecule activator of Nrf2. The study paper indicated that the mechanisms underlying CD activation of Nrf2 might include the oxidation/alkylation of main thiols in Keap1 and/or Nrf2 phosphorylation [26, 27]. Some other study findings showed that neuroinflammation was caused by dose-dependently CD upregulated phase11 enzymes governed by Nrf2 in PC12 cells with H_2O_2. This promotes the use of CD as a possible candidate for the prevention of neurodegenerative diseases induced by oxidative stress prevention [28, 29].

Table 2. Structures of natural compounds obtained from herbal sources and effective in neuroprotection by acting through Nrf2 pathway.



4.2. Andrographus paniculata

Andrographalide was isolated from the plant *Andrographus paniculata*, a major labdane diterpenoid commonly known as Kalmegh [30]. It is an herbaceous plant belonging to the family *Acanthaceae*. Immunostimulatory, antitumor, antibacterial, antidiabetic, and neuroprotective activities in the treatment of stroke have been recorded [31]. Andrographalide upregulates of the Nrf2 route have been documented in recent studies. Effects of neuroprotective behaviour in the treatment of stroke were shown by Andrographalides. Upregulation of Nrf2 by andrographalide depending on the existence of cysteine residue 151 in keap1 has been documented in recent studies, resulting in keap1 dependent Nrf2 degradation [32]. Mostly, they possess an antioxidant response and produce cytoprotective results. *Via* activating p38 by mitogen-activated protein kinases (MAPK) and extracellular signal-regulated kinases (ERK) phosphorylation in *in vitro* assays, andrographolides express Nrf2 and HO-1 in astrocytes [33, 34, 35].

4.3. Artemisia amygdalina

Amygdaline is a member of the *Asteraceae* family of *Artemisia amygdalina*, a critically endangered endemic species of the Kashmir Himalayas. Anti-inflammatory, antioxidant, anti-diabetic, immunomodulatory and neuroprotective activities have already been recorded [36]. In folk medicine, it is the most commonly used medicinal herb. Amygdaline from *Artemisia amygdalina* induces oxidative stress against H_2O_2-induced toxicity in differentiated N2a and SH-SY5Y cells. Studies have shown that this plant provides neuroprotection by upregulating the Nrf2 path [37]. Activation of Nrf2 causes inhibition of keap1, which also leads to activation of the antioxidant response and induction of the neuroprotective effects of OH-1 enzymes [38, 39].

4.4. Cannabis sativa

Cannabis sativa has been known for its medicinal properties since ancient times. The key non-psychotropic constituent of *Cannabis sativa* is the cannabinoid. Cannabidiol (CBD), which is currently being studied as a possible therapeutic alternative for various neurodegenerative diseases. Evidence indicates that CBD has properties that are antioxidant, anti-apoptotic and neuroprotective. A substantial reduction in Aβ mediated neuronal cell death can be accounted for by CBD. Activation of microglial cells by activation of Nrf2-hmox1 and Nrf2/ATF4 pathways in LPS induced by CBD providing neuroprotection*in vitro* model [40]. CBD decreases Aβ-induced neuroinflammation and facilitates hippocampal neurogenesis through PPARc participation in the Alzheimer's disease model of *in vivo Sprague dawley* rat. Recent research has shown that distilled CBD alone counteracts neuronal apoptosis in the multiple sclerosis experimental model [41, 42].

4.5. Citrus paradise

In citrus fruits such as *Citrus paradise* and *Citrus sinensis,* Narngenin is a strong flavonoid found to be abundant. It has strong antioxidant, anti-inflammatory and neuroprotective properties [5, 43]. The study shows that narngenin has prevented neurotoxicity caused by 6-hydroxydopamine (6-OHDA) by triggering the Nrf2-ARE signaling pathway. Another NGN research has demonstrated neuroprotective effects in the mouse model against MPTP-mediated parkinson's disease and also against toxicity induced by Aβ in PC12 nerve cells [44, 45, 46].

4.6. Citrus fruit species

Hesperetin is a flavanone glycoside and a broad variety of pharmacological activities such as antioxidant, anti-inflammatory and neuroprotective in various models of neurodegenerative diseases have been shown from hesperidin contained in citrus fruit organisms [47]. Recent studies have indicated that hesperetin hinders initiation, neuroinflammation progression and may act as a potential neuroprotective agent against neurodegenerative diseases such as alzheimer's disease, memory decline [48]. Recent studies have indicated that hesperetin confers neuroprotection in the Aβ mouse model for alzheimer's disease by controlling NRF2/TLR4/NF-kB signaling [49].

4.7. Curcuma longa

The main active ingredient of *Curcuma longa*, widely used as a turmeric powder, is curcumin. Epidemiological studies have shown that the occasional dietary consumption of turmeric in rural areas of India decreases the incidence of Alzheimer's disease. 5–30 μM curcumin has been shown to suppress Aβ in the transgenic mouse model of Alzheimer's disease [50]. The study found that curcumin could reduce the expression of IL-1β, IL-6 and TNF-alpha induced by Aβ 42 in microglia, depending on its concentration [51]. In an *in vitro* model of ischemia/reperfusion, curcumin has neuronal defense against oxidative stress and inflammation by inducing Nrf2 activation and HO-1 expression in the PI3K/Akt pathway activation system. Recent studies have shown that curcumin defends PC12 cell lines against *in vitro* and *in vivo* models of cholesterol-induced neurotoxicity [52]. Curcumin was found to suppress TNF-alpha and caspase3 levels, the neuroinflammatory mediators, by growing BDNF levels in another research rat model of olfactory-bulb ablation [53].

4.8. Dimethyl fumarate

Dimethyl fumarate (DMF) is a trans-butenedioic acid, an alkylating metabolite that occurs naturally. This is an electrophilic compound [54] which is reported to have neuroprotective and immunomodulatory properties through Nrf2 activation [55]. It (DMF; Tecfidera/BG-12) has recently been approved by the FDA for multiple sclerosis therapy, commonly referred to as BG-12, on the basis of its neuroprotective and anti-inflammatory impact [56]. A further research study showed that DMF activates the Nrf2 pathway by depleting intracellular GSH levels and reducing dose-dependent cell viability *via* the S-alkylation mechanism to generate neuroprotection by up-regulating antioxidant response in MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced experimental parkinson-like disease model MPTP [57].

4.9. Elephantopus scaber

Elephantopus scaber (ESEAF), usually referred to as the foot of an elephant, is a folk medicine typically used for wound healing, fever and hepatoprotective agents. It has many functions, such as anti-cancer, anti-diabetic, anti-inflammatory and antioxidant properties. It has been scientifically proven in different *in vivo* models to show anti-inflammatory and antioxidant impact. Scientific research, however, has shown that ESEAF exhibits anti-neuroinflammatory effects on LPS-induced neuronal immune cell (BV2) inflammation. Activation of the Nrf2/HO-1 pathway by ESEAF has been reported to reduce oxidative stress and inflammation in neurodegenerative diseases [58]. This indicates that by inducing activation of Nrf2/HO-1 protein expression, ESEAF demonstrates anti-neuroinflammatory impact. The potential for developing ESEAF as a potential therapeutic agent for the treatment of microglial induced neuroinflammatory diseases has therefore been further substantiated by these results [59, 60].

4.10. Epimedii herba

Icariin (ICA) is a natural flavonoid extracted from the *Epimedium Herba* species, a Chinese herbal medicine known as Ying Yang Huo [61]. It displays a number of pharmacological activities such as antioxidants, anti-inflammatory, anti-aging [62]. Recent studies show that by activating the Nrf2 signalling pathway, ICA granted neuroprotective safety

against brain ischemic injury and neurodegenerative diseases [63]. ICA decreases neuroinflammation and exerts Nrf2 pathway dopamine neuroprotection and also improves neurogenesis, enhancing unique working memory. A further research paper reported that by triggering the antioxidant defense, ICA exercised neuroprotection against oxygen-glucose deprivation-induced neurotoxicity. Furthermore, ICA enhanced the unique learning and memory capacities of rats in LPS-induced brain dysfunction by reducing proinflammatory mediators [64].

4.11. *Zingiber officinale*

Ginger has been generally utilized as a well known zest or food supplement and has been similarly rumored for its therapeutic properties for quite a long time. 6-Dehydrogingerdione (6-DG), one of the significant parts of dietary ginger, has gotten broad consideration because of its different pharmacological exercises, for example, restraint of lipid peroxidation [65]. 6-DG is viable in forestalling oxidative pressure prompted neuronal cell harm. Its neuroprotection include its ability in straightforwardly killing free revolutionaries and actuating endogenous cell cancer prevention agent guard. Its hydroxyl bunch is basic for the immediate cancer prevention agent movement, though the, β-unsaturated ketone structure is fundamental for initiation of the Keap1-Nrf2-ARE pathway in cells [66].

4.12. *Honey bee hives*

Caffeic acid phenethyl ester (CAPE) is a main active component of propolis extract, commonly called phenyl ethyl caffeate, which is derived from *honey bee hives*. Various biological activities have been shown to have diverse effects, such as antimicrobial, anti-inflammatory, antitumor, antiviral, cytotoxic, anti-carcinogenic, immunomodulatory and neuroprotective [67]. The available studies indicate that it is an efficient moiety against various pathologies such as inflammation, oxidative stress, cancer, diabetes, neurodegeneration and anxiety, according to the literature quest. Studies have shown that CAPE has neuroprotective operation [68]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is released after stimulation with CAPE from its suppressor Kelch-like ECH-associated protein 1 (Keap1) and translocated to the nucleus, activating expression of HO-1 leading to neuroprotection. In addition, anti-inflammatory effects are provided by NF-kBinhibition [69, 70].

4.13. *Inula helenium*

Costunolide (COS) is a natural sesquiterpene lactone originally isolated from *Inula helenium* (Compositae). Costunolide (COS) belongs to the sesquiterpene lactone family and is abundant in Compositae, such as *Laurus nobilis* and *Saussurea lappa*. It has been reported that COS exhibits a range of pharmacological properties. It has been shown that COS provides neuroprotection *via* activating the Nrf2 signaling pathway in PC12 cells. Furthermore, COS attenuates the cellular reactive oxygen species level and restores cellular thiol homeostasis, supporting that COS was involved in maintaining the cellular redox balance [71].

4.14. *Loranthus parasiticus merr*

Loranthus parasiticus Merr is an essential traditional Chinese medicinal plant known as Sang ji sheng in Chinese and belongs to the *Loranthaceae* family [72]. Important pharmacological activities such as neuroprotective, tranquillizing, anticancer, antihepatotoxic, diuretic, immunomodulatory, antioxidant and anti-nephrotoxicity activities have been shown through different studies to date [72, 73]. Latest researches have stated that two types of *L. parasiticus* LPEE (*L. parasiticus* ethanol extract) and *L. parasitic s*aqueous fraction (*L. parasitic s*aqueous fraction) have been evaluated and demonstrated dose-dependent antioxidant properties through Nrf2/HO-1 protein expression and neuroprotective activity on NG-108-15 hybridoma cells against induced free radicle generation [74, 75].

4.15. *Morus Alba*

Quercetin is a significant glycoside of flavonol derived from *Morus Alba*, generally referred to as mulberry. It has antioxidant properties and is anti-inflammatory. This enhances neuroprotection by scavenging free radicals through their antioxidant properties. It has been studied as a lead compound exhibiting neuroprotective effects in the animal model of neurodegeneration because of its anti-inflammatory property. Recently, neuroinflammation-associated markers induced by quercetin attenuated LPS counteract neuroinflammation by activating Nrf2/HO-1 and inhibitory NF-kB signalling in SK-N-MC cell lines in both *in vitro* and *in vivo* models [76].

4.16. *Nardostachys Chinensis*

Nardochinoid C (DC) is a new *Nardostachys Chinensis* isolated compound. Neuroprotection and cardiovascular effects occur in the roots and rhizomes of *Nardostachys Chinensis*. It has antioxidant properties and anti-inflammatory properties. Recent studies have shown that DC substantially decreases oxidative stress and releases macrophages triggered by LPS proinflammatory mediators [77, 78]. Mechanism studies have reported that DC activated the Nrf2 signalling pathway primarily, increased antioxidant protein HO-1 levels and thus induced anti-inflammatory antioxidant effects. The activation of the antioxidant pathway mediated by Nrf2 has a neuroprotective effect, and antioxidants can promote the anti-inflammatory effects of DC [79].

4.17. *Olives*

Hydroxytyrosol (3,4-dihydroxyphenylethanol), a normally happening polyphenol in table olives and other dietary plants, is available in an especially high fixation either in a free or esterified structure in additional virgin olive oils, wherein it represents up to 70%–80% of the absolute phenolic portions [80]. Hydroxytyrosol gives double neuroprotection and cell cancer prevention agent guard as both a free extreme forager and Nrf2 activator, recommending the likely drug utilization of HT for the therapy of neurodegenerative issues [81].

4.18. *Polygala Tenuifolia*

Tenuigenin is a bioactive component that is mostly recognised from the roots of *Polygala Tenuifolia* and has pharmacological activities such as anti-inflammatory effects. It has recently been stated by Xiaokun Wang that TGN activates the dose-dependent Nrf2-ARE pathway, which is subsequently upregulated by HO-1. These findings suggest that TGN induces anti-inflammatory effects by Nrf2-ARE pathway activation. TGN activation of Nrf2 decreases inflammation and cytokines in brain tissue [82].

4.19. *Radix astragali seu hedysari*

Radix astragali seu hedysari (huangqi), an essential herb widely used in traditional Chinese medicine, is a major component of Astragaloside IV. The paper by H.L wang et al, review evaluated the recent findings on the neuroprotective effects of astragaloside IV. They suggest based on their review, that astragaloside IV enhances neurological deficits in the experimental model of cerebral ischemia. Results showed that astragaloside IV preserved the integrity of BBB in mice induced by LPS, whose function could be regulated by the activation of the Nrf2 signalling pathway. Such results indicated that astragaloside IV could be a potent neuroprotective drug [83, 84].

4.20. Rosmarinic acid

Rosmarinic acid, a polyphenolic phytochemical compound, is commonly used as a flavouring agent and preservative in the food industry. It has properties that are anti-oxidative, anti-viral, immunomodulatory and anti-apoptotic. Some preclinical studies have shown that Rosmarinic acid provokes neuroprotection through Nrf2 and HO-1 signalling in the mouse model of ischaemic stroke. The activation of the Akt/Nrf2/HO-1 pathway provides rosmarinic acid with a valuable target to protect the brain against acute ischaemic injury. HO-1 has been highlighted as an important downstream Nrf2/ARE signaling pathway enzyme for its successful neuroprotection against ischemic injury and other neurodegenerative diseases [85]. In the G93A-SOD1 transgenic mouse model of ALS, another investigator showed that rosmarinic acid alleviates neurological symptoms and also protects PC12 cells from Aβ-induced neurotoxicity in the Alzheimer's disease model [86, 87].

4.21. Rosmarinus officinalis

Carnosic acid (CA) is a normal pro-electrophilic compound transformed to its active form by oxidative stress, which in turn activates transcription based on Nrf2. Carnosic acid decreased dendritic spine loss in rat neurons exposed to neurotoxic oligo metric Aβ *in vitro* and *in vivo* models, enhanced learning and memory by carnosic acid treatment of human amyloid precursor protein (hApp)-J20 mice. CA triggers the keap1/Nrf2 transcriptional pathway by S-alkylation in recent studies by binding keap1 cysteine residues, thus shielding neurons from oxidative stress and excitoxicity in both *in vitro* and *in vivo* [88].

4.22. Schisandra sphenanther

During neuroinflammation, phytochemical-induced activation of Nrf2 signalling might have a modulatory effect on activation of NF-kB. Dibenzocycloctadiene lignin, from *Schisandra sphenanthera* fruits, is schisantherin-A (StA). In Chinese traditional medicine, it is generally used as a sedative, tonic, antitussive. It also has anti-inflammatory effects and can have behaviors that are neuroprotective. Its anti-inflammatory activities were based on activation of Nrf2 mediated by ERK phosphorylation [89]. Recently, it has been reported that StA attenuates antioxidant response by quenching ROS and regulates phase 2 antioxidant enzymes like HO-1 by stimulating the signalling mechanism of activation Nrf2 through ERK phosphorylation and could contribute to inactivation of NF-βB pathways in microglial cells activated by LPS BV2 [90,91]. The anti-inflammatory and antioxidant effects of StA are a preventive therapeutic potential for various neurodegenerative disorders [92].

4.23. Solanum lycopersicum

Lycopene is a natural carotenoid, a polyunsaturated hydrocarbon extracted from *Solanum lycopersicum*. Studies show that it has many pleiotropic effects, including antioxidants, anti-inflammatory and neuroprotective activities [93, 94]. Mediating the neuroprotective effects of lycopene through inhibition of ROS development, microglial activation, PPARγ, PI3K/AtK signalling mechanisms in CNS diseases has been established. In an experimental ischaemic model, its acts were shown to be due to upregulation of the Nrf2 pathway that leads to neuroprotection. Recently an *in vitro* study has confirmed that lycopene decreases neuronal damage caused by Aβ exposure by enhancing mitochondrial pathogenesis in primary cultured rat cortical neurons [95]. Other research paper showed results of lycopene restoring Nrf2, upregulating HO-1 and BDNF expression in SH-SY5Y cells treated with H_2O_2 [96].

4.24. Sophora alopecuroides

A major flavonoid obtained from *Sophora alopecuroides* is *Sophora flavanone G* (SG). Recent studies have shown that SG ameliorate microglia mediated neuroinflammation (BV2 cells) by the signaling pathways MAPK, JAK STAT and Nrf2/HO-1. Recent study have shown that SG ameliorate microglia mediated neuroinflammation (BV2 cells) by MAPK, JAK/STAT and Nrf2/HO-1. Mechanism studies have found that in LPS activated BV2 cells, SG down regulated phosphorylated MAPK, JAK/STAT and upregulated HO-1 via Nrf2 transcription factor. This suggests that SG can have strong anti-neuroinflammatory effects [97].

4.25. Tiliroside

Tiliroside is a dietary flavonoid extracted from various edible plants present in fruits, leaves, roots, and various components. The current states of research to date shows that 172 plant species come from 35 different families have been described. Antioxidant, anti-inflammatory, antidiabetic, anti-allergic, heptoprotective, anti-microbial, anti-proliferative, anti-neuroprotective activities have been documented in studies [98]. A new study shows that by targeting Nrf2 antioxidant pathways, tiliroside protected BV2 microglia from LPS/IFNγ mediated neuroinflammation and HT22 neuronal toxicity. *Via* the Nrf2 pathway, tiliroside greatly improves HO-1/NQO1 proteins and contributes to neuroprotection. In mouse hippocampal neurons, it also inhibits the NF-kB *via* SIRT1 pathway [99].

5. Conclusion

In different neurodegenerative diseases, neuroinflammation is a major process that has been widely described. In recent years, the Nrf2-ARE response has been described in many neurodegenerative diseases as a dysfunction of the cellular response to oxidative stress and neuroinflammation. The activation of the Nrf2-ARE pathway has therefore been identified as a key target for the development of new medicines for neurodegenerative diseases. In this sense, natural substances, which have been studied in recent years, are important sources of Nrf2 activators. Compounds examined here have shown promising results in *in vitro* and *in vivo* models that protect neurons from inflammation and oxidative stress. The anti-inflammatory, antioxidant and Nrf2 activating properties of these substances tested were connected to these findings. In conclusion, the first-line idea of the activation of Nrf2 was to use the Nrf2-ARE pathway as a main target to find real disease modifying drugs for neurodegenerative diseases. In summary, this study includes a variety of subjects concerned with the neuroprotective effects of different natural substances by stimulating the Nrf2-ARE pathway.

Declarations

Author contribution statement

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