Phytochemicals as substances that affect astrogliosis and their implications for the management of neurodegenerative diseases

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Abstract

Astrocytes are a multifunctional subset of glial cells that are important in maintaining the health and function of the central nervous system (CNS). Reactive astrocytes may release inflammatory mediators, chemokines and cytokines, as well as neurotrophic factors. There may be neuroprotective (e.g., cytokines, like IL-6 and TGF-b) and neurotoxic effects (e.g., IL-1β and TNF-a) associated with these molecules. In response to CNS pathologies, astrocytes go to a state called astrogliosis which produces diverse and heterogenic functions specific to the pathology. Astrogliosis has been linked to the progression of many neurodegenerative disorders. Phytochemicals are a large group of compounds derived from natural herbs with health benefits. This review will summarize how several phytochemicals affect neurodegenerative diseases (e.g., Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, and Parkinson's disease) and in basic medical and clinical studies and how they might affect astrogliosis in the process.

Keywords: Astrocytes, Neurodegenerative diseases, Phytochemicals, Herbal medicine, Central nervous system, health

Introduction

Astrocytes are a multifunctional subset of glial cells that are key to the structure and function of the brain. They are the key '*homeostatic cells*' that support the proper functioning and neuronal information transfer of the central nervous system (CNS)[1]. Astrocytes regulate synaptic function and plasticity by balancing neurotransmitters and ions. Moreover, they act as regulators of blood flow to the brain and neuronal energy metabolism. Furthermore, astrocytes are among the main respondents to toxic and traumatic injuries to the brain through an activation process called reactive astrogliosis. During reactive astrogliosis, astrocytes become hypertrophic and show increased expression of intermediate filament proteins such as glia fibrillary acidic protein (GFAP) and vimentin [2, 3]. GFAP is an intermediate filament protein and an important part of the astrocyte's cytoskeleton. It is used as a marker of astrocytes; however, the basal levels of GFAP are variable in healthy CNS [4]. Elevated GFAP levels have been found to occur in several experimental models involving astrogliosis [5, 6]. However, the GFAP alone is not a good marker for identifying different astrocytes in healthy and injured CNS. To overcome this, other astrocyte markers, such as aldehyde dehydrogenase-1 (Aldh1L1) and glutamine synthetase (GS), are used in combination with GFAP[7]. The pathological changes of astrocytes can be divided into two states or forms: 1) non-reactive or 2) reactive. The transformations in the non-reactive state include astrodegeneration and pathological remodeling. The reactive state is identified by changes in transcriptional regulation or biochemical, morphological, metabolic, and physiological remodeling, collectively called reactive astrocytes or reactive astrogliosis [8]. Reactive astrogliosis appears as hypertrophy and proliferation of astrocytes. In association with this, markers such as GFAP are upregulated. Reactive astrogliosis is seen in almost all neurological conditions. In every CNS pathology, reactive astrogliosis results in a wide range of pathology-specific changes, which

can resolve in various ways [9]. This process is regulated through a multifaceted and complex network of intrinsic and extrinsic factors as well as different cell surface receptors and intracellular signaling pathways. The function of reactive astrogliosis in various CNS pathological states provides for: metabolic support of vulnerable neurons, regulation of BBB permeability, remodeling of extracellular matrix (ECM), mobilizing progenitors, as well as immunomodulation, synaptic remodeling, and neurite outgrowth [10]. The overall result of astrogliosis is beneficial for the nervous tissue, the suppression of which exacerbates tissue damage [3, 11]. Despite its essential beneficial functions for the nervous system, astrogliosis exacerbates tissue damage when suppressed [3]. Morphologically reactive astrogliosis is classified into isomorphic and anisomorphic. Anisomorphic astrogliosis is characterized by preserving morphology, whereas isomorphic astrogliosis appears to change morphology. The astrocytes in isomorphic gliosis undergo hypertrophy with multiple biochemical and immunological changes, but the astroglial domain organization remains intact. Neurite growth and synaptogenesis are facilitated by isomorphic astrogliosis, which may lead to the regeneration of the neuronal network. Astrocytes return to their normal state after the pathology is resolved in isomorphic gliosis.

Anomomorphic gliosis results in hypertrophic astrocytes and a loss of normal domain organization due to astrocyte proliferation. A permanent glial scar results from anisomorphic gliosis because anisomorphic reactive astrocytes secrete chondroitin and keratin [3, 9].

The role of astrogliosis in neurodegenerative diseases

In neurodegenerative diseases, neurons gradually deteriorate, causing brain atrophy and cognitive decline. The biology of neuroglia in neurodegeneration is still poorly understood; however, profound homeostatic changes that accompany (and are probably related to) neurodegeneration tend to be caused by dysfunctional glia [2, 9, 12]. Increasing evidence indicates that inflammation

is activated in the early stages of neurodegenerative disorders. As a result, microglia and astrocytes are produced, as well as inflammatory mediators responsible for astrocytic hypertrophy and proliferation. In addition to astrocytes, microglia are a key player in defence against CNS pathologies. Microglial proliferation happens in almost all neurodegenerative disorders. This is associated with the secretion of a wide array of cytokines and chemokines. Microglia affect the development of neuronal networks and the progress of many diseases, such as AD, PD, multiple sclerosis, ALS, Huntington's disease, stroke, epilepsy, autism spectrum disorder, and schizophrenia [13]. Numerous neurodegenerative diseases, including Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD), are associated with neuroinflammatory processes [14, 15]. Neuroglial cells are considered an integral part of the pathophysiology of neurodegenerative disorders at the early stages [2, 9, 12]. Reactive astrocytes may release inflammatory mediators, chemokines and cytokines, as well as neurotrophic factors. There may be neuroprotective (e.g., cytokines, like IL-6 and TGF-b) as well as neurotoxic effects (e.g., IL-1β and TNF-a) that are associated with these molecules [16] [17].

Phytochemicals

Phytochemicals are compounds found in natural products that belong to the class of secondary metabolites. There is a wide range of phytochemicals, such as polyphenols, flavonoids, saponins, organosulfur compounds, vitamins, and steroidal saponins. The phytochemicals of plants play a major role in plant growth and physiology, from reproduction and symbiotic association to interacting with the environment as well as other organisms [18]. Phytochemicals such as terpenoids, phenolics, alkaloids and fiber have a variety of health benefits, including catalysts for biochemical reactions; substrates for fermentation by beneficial oral, digestive, or intestinal bacteria; enzyme inhibitors; ligands with agonistic and antagonistic properties towards cell surface

or intracellular receptors; substances that absorb and bind to undesirable substances in the intestine; having the capacity to scavenge reactive or toxic chemicals; cofactors of enzymatic reactions; they possess some growth factors for gastrointestinal bacteria; constituents that improve the absorption and or stability of important nutrients, and inhibiting harmful intestinal bacteria [19]. *In vitro* and *in vivo* studies have demonstrated that phytochemicals can treat various pathological conditions such as diabetes mellitus, malignancies, cardiovascular diseases, bacterial, viral and parasitic infections, spasmodic situations, ulcers and neurological disease [19, 20].

Herein, we attempt to provide a comprehensive view of phytochemicals' effects on the neuroprotective properties of astrogliosis.

Neuroprotective effects of phytochemicals on astrogliosis:

Curcumin

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a natural polyphenol and a crystalline compound which is found in the rhizome of *Curcuma longa* (turmeric) and others Curcuma spp. [21]. Curcumin has a bright orange-yellow appearance. It is an active component of *Curcuma longa* Linn. It is a natural food coloring agent commonly perceived to have a pleasant taste [22-24]. There is a long history of empirical use of curcumin in treating anorexia, hepatic disorders, and arthritis [25-29]. The pharmacological properties of curcumin are numerous [30-36], including antioxidant [37], immunomodulatory [38], anti-inflammatory [39-41], analgesic [42], antidiabetic [43], antimicrobial [44], and anticarcinogenic effects [45, 46].

In a lipopolysaccharide-induced PD model, curcumin administration inhibited astrocytic activation (GFAP) and decreased the activity of transcription factors such as NFkB, TNF-a, IL-1b, and IL-1a, as well as iNOS. In addition, curcumin reduced the protein activity of apoptotic markers (Bax,

Bcl-2, Caspase 3 and Caspase 9) and the expression of α-synuclein. As demonstrated by atomic absorption spectroscopy (AAS), curcumin stabilized the altered glutathione homeostasis and activated the NADPH oxidase complex. Additionally, curcumin prevented iron accumulation in dopaminergic neurons [47]. In a mouse model of PD induced by 6-OHDA, nigral tyrosine hydroxylase-immunoreactive (TH-IR) neurons, as well as microglial and astroglial reaction in the SNpc and the striatum, were diminished. Also, striatal TH-IR fibers were decreased in mice administrated by 6-OHDA. These changes were recovered following curcumin administration [48] (Table 1). The expression of RANTES is involved in the inflammatory cascade that leads to the neurodegeneration seen in AD [49]. Curcumin increased RANTES expression in primary cultured astrocytes, and the signaling pathways PI-3K and MAPK were activated. The curcumin inhibited the expression of iNOS in primary cultured astrocytes in non-stressed conditions. NMDA-exposed neurons cultured in curcumin-treated ACM showed increased RANTES expression and cell survival. The authors also demonstrated that RANTES expression in non-stimulated astrocytes provides neuroprotection using a small interfering RNA (siRNA) knockdown model [50]. In p25Tg mice, administration of p25 resulted in the activation of glial cells and the production of pro-inflammatory chemokines/cytokines. These changes were suppressed by the curcumin administration. Additionally, curcumin reduced the tau/amyloid pathology progression caused by p25, improving p25-induced cognitive deficits [51] (Table 1). In an *in vitro* study, primary mesencephalic astrocytes were stimulated by administrating 1-methyl-4-phenylpyridinium ions (MPP+). When MPP+-stimulated astrocytes were pretreated with curcumin, pro-inflammatory cytokines such as TNF-a, interleukin (IL-6), and reactive oxygen species (ROS) were reduced while IL-10 expression was increased. As a result of curcumin administration, antioxidant glutathione levels increased, and ROS production by MPP+ was suppressed. GFAP expression

was raised, and cell bodies were larger in astrocytes stimulated by MPP+. By pretreating with curcumin, MPP+ was inhibited from activating astrocytes. Moreover, curcumin inhibited TLR4 immunoreactivity, morphological activation, and downstream effectors NF-kB, IRF3, MyD88, and TIRF in MPP+-stimulated astrocytes [52].

Curcumin and its formulations have been used in clinical studies of different neurodegenerative diseases, including ALS [53, 54], AD [55, 56], and PD [57]. In addition, a comprehensive review by Mohsni et al. (2021) describes the effects of curcumin on the clinical outcome of these diseases in detail [58]. In summary, curcumin and its formulations improved the clinical outcome of patients with ALS, AD, and PD.

Thymoquinone

Thymoquinone (2-Isopropyl-5-methyl-1, 4-benzoquinone) is a major constituent of *Nigella sativa* of the family Ranunculaceae [59]. It is a naturally occurring quinone derivative called black caraway seed or black cumin. Nigella sativa L. is a flowering plant in countries adjoining the Mediterranean sea, India, Pakistan, and Iran [60]. Thymoquinone belongs to the class of monoterpene compounds, which are secondary metabolites. Thymoquinone constitutes about 54% of the volatile oil and its concentration has been reported to be between 18 and 25 µg/mL in the seed oil. Thymoquinone has a solid bright yellow color, scaly crystals, a melting point of 49–50 °C, and a characteristic intense smell of pepper [61]. Traditionally it has been used as a spice but also as a medicine. In addition, thymoquinone has [62], antioxidant [63], anti-inflammatory [64], and anti-bacterial [65] activity. Dariani et al. investigated the effects of thymoquinone in an intra-hippocampal kainite model of temporal lobe epilepsy in the rat. Epileptic rats showed increased nitrite, MDA and nitrate levels and decreased SOD content. However, these changes were reversed following the administration of thymoquinone. Furthermore, thymoquinone

improved neuronal loss in the CA1, CA3 and hilar regions and significantly reduced mossy fiber sprouting (MFS) and a number of reactive astrocytes (astrogliosis) [66] (Table 1).

Rosmarinic acid

Rosmarinic acid is a phenylpropanoid compound and an ester of caffeic acid and 3-(3,4-dihydroxyphenyl)lactic acid and it is found in plants belonging to the Lamiaceae family, including lemon balm (*Melissa officinalis* L.), rosemary (*Rosmarinus officinalis* L.), and spearmint (Mentha spp.) [67]. It has a yellowish-white crystalline appearance. Antioxidant [68], anti-inflammatory[69], and anticancer [70] properties are among the properties of rosmarinic acid. Researchers found that Aβ-42 led to increased levels of oxidative stress, monothiobarbituric acid reactive substances (TBARS) and 4-Hydroxy-2-nonenal (4-HNE), and reduced glutathione levels as well as antioxidant enzyme activity (GSH-Px, CAT, SOD). In addition, injection of Aβ-42 reduced acetylcholine (ACh) content and ACh esterase (AChE) activity. All these effects were prevented following RA treatment. Furthermore, RA administration attenuated astrocyte activation and Aβ staining. Administration of Aβ-42 impaired the auditory discrimination and echoic memory processes. This was evidenced by the suppressed response of MMN and theta power/coherence of AERPs following Aβ-42 injection. Treatment with RA recovered the suppressed AERP parameters following administration of Aβ-42 [71] (Table 1).

In a randomized placebo-controlled double-blind 24-week trial, the administration of *Melissa officinalis* (*M. officinalis*) extract containing rosmarinic acid improved the mean neuropsychiatric inventory questionnaire score in patients with mild dementia due to Alzheimer's disease. However, rosmarinic acid did not change the disease-related biomarkers [72]. A comprehensive review by Mahboubi (2019) addresses the effects of rosmarinic acid in clinical studies of AD [73].

Sesamin

In sesame seeds and sesame oil, sesamin is a major constituent [74, 75]. It is a bioactive phenolic compound and a major lignan in sesame seeds (Sesamum indicum L., Pedaliaceae). Raw sesame oil contains 0.5–1.1% sesamin and 0.2–0.6% sesamolin, which contribute to the medicinal properties of the oil. Sesamin possesses anti-inflammatory [76], antioxidant [76] and neuroprotective effects [77, 79]. In an animal model of PD induced by the administration of unilateral striatal 6-OHDA, sesamin treatment reduced the motor imbalance in the narrow beam test. Animals with PD showed increased brain oxidative stress, evidenced by elevated striatal MDA and ROS. Sesamin treatment lowered the levels of MDA and ROS and also increased the activity of SOD. Furthermore, animals with PD showed increased neuronal apoptosis (increased striatal caspase 3 activity and α-synuclein expression), which was suppressed following treatment with sesamin. Again, sesamin reduced the PD-induced increase of GFAP immunoreactivity and nigral neuronal apoptosis. In addition, tyrosine hydroxylase (TH) immunohistochemistry demonstrated that sesamin prevented damage to dopaminergic neurons [79] (Table 1).

Genistein

Genistein, 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one, is a phytoestrogen that belongs to the subgroup of isoflavone from the flavonoid family. It has a similar chemical structure to mammalian estrogens. Genistein is extracted from many plants such as Lupinus albus L. (lupine), Vicia faba L (fava bean), Glycine max (L.) Merr. (soybeans), Pueraria lobata (Willd.) Ohwi (kudzu), and Psoralea corylifolia L. (Psoralea) [80]. Data strongly indicates significant antioxidant and anti-inflammatory properties [81]. Genistein has been demonstrated to reduce memory impairment and neuronal cell apoptosis induced by Aβ1–40 [82, 83]. In one study, rats were injected with amyloid peptide in their hippocampus, which resulted in Aβ1–40 positive aggregates formation near the lateral blade of their dentate gyrus (DGlb). Later, in rats' hippocampus, iNOS-

expressing cells and astrogliosis were increased. Also, rats showed extensive neuronal degeneration in DGlb, CA1, and CA3. Genistein treatment inhibited the formation of Aβ1–40 positive aggregates and increased the number of nNOS+ neurons in the hippocampus. Additionally, the treatment with genistein decreased the extent of the astrogliosis [83]. After injecting Aβ1–40 into the brains of animals, astrocytes significantly increased in number, and GFAP-positive cells significantly increased, as did astrocytes in the hippocampus. Genistein treatment reduced the intensity of GFAP and the mean volume and area of astrocytes and inhibited their expansion [86] (Table 1). After 48 hours of pretreatment with 17-βestradiol or genistein, cells were treated for 24 hours with 5 μM Aβ. Aβ induced the production of inflammatory mediators, including COX-2, iNOS, IL-1β and TNF-α. Pretreatment with estradiol or genistein inhibits these changes in primary cultures of astrocytes, possibly through their anti-inflammatory activities. In Aβ-stimulated astrocytes, PPARs downregulate the expression of pro-inflammatory genes. It was found that Aβ, estradiol, and soybean isoflavone genistein increased PPAR-γ expression in cultured astrocytes [85]. In another study, genistein attenuated spatial recognition, discrimination, and memory deficits in rats exposed to LPS. In addition, the genistein-treated rats showed reduced hippocampal MDA, catalase and glutathione GSH in response to LPS. Furthermore, genistein reduced hippocampal levels of IL-6, NF-κB p65, TLR4, TNFα, COX2, iNOS, and GFAP, while increasing Nrf2 content in LPS-challenged rats. [86].

When Aβ1–40 was injected into the brain, there was a significant increase in GFAP intensity and enlargement of astrocytes in the hippocampus. This was indicated by improved results when including parameters for the nucleus, cell body, astrocyte (soma and branches), and territory (tissue covered by each astrocyte and the total number of branches). Genistein-treated rats showed reduced GFAP intensity elevation, and Aβ1–40-induced enlargement of astrocytes was markedly

decreased. The administration of genistein also reduced the risk of astrogliosis caused by mechanical injury caused by injection needle insertion into the brain [87]. SOD1-G93A mice administered Genistein had lower COX-2, TLR2, TLR4 and NF-kB p65 in their spinal cords, and their gliosis improved. Further, genistein administration increased spinal motor neuron viability and induced autophagy. A transgenic mouse model of ALS, SOD1-G93A, also improved ALS-related symptoms and slightly prolonged lifespan with genistein [88] (Table 1). Clinical studies have shown that genistein may delay the onset of Alzheimer's dementia in patients with prodromal Alzheimer's disease. In a double-blind, placebo-controlled, bicentric clinical trial, daily oral supplementation with 120 mg of genistein for 12 months on 24 prodromal AD patients significantly improved two neurocognitive tests (Complutense Verbal Learning Test and Rey Complex Figure Test). Also, genistein-treated patients showed lower uptake of amyloid-beta deposition in the anterior cingulate gyrus compared with the placebo-treated group [89].

Troxerutin

Troxerutin is a naturally occurring flavonoid in coffee, cereals, tea, and vegetables. It is also known as vitamin P4, derived from bioflavonoid rutin [90, 91]. Troxerutin is easily absorbed in the gastrointestinal tract (GIT), presenting low tissue toxicity. It has anti-oxidative and anti-inflammatory effects [90] and showed reno- [90] and hepato-protective [94] properties. In a rat model of Parkinson's disease induced by 6-OHDA, apomorphine administration caused motor asymmetry and increased latency to initiate the narrow beam task. Troxerutin treatment suppressed these pathological changes. However, administration of estrogen receptor β (ERβ) antagonists or phosphatidylinositol 3-kinase (PI3K) inhibitors eliminated the beneficial effects of troxerutin in narrow beam tasks. Troxerutin pretreatment decreased DNA fragmentation, reactive oxygen species, striatal MDA, and GFAP levels as the marker of astrogliosis. However, neither the

catalase activity nor the nitrite level was altered. Further, troxerutin prevented the death of neurons positive for tyrosine hydroxylase (TH) in the nigral part of the rat brain [93].

Luteolin

Luteolin (3,4,5,7-tetrahydroxy flavone) is a flavonoid found widely in broccoli, onion leaves, carrots, parsley, celery, sweet bell peppers, and chrysanthemum flowers [94]. Luteolin has multiple pharmacological activities, including antioxidant, anti-inflammatory, cardiovascular protection, and anti-carcinogenesis effects[95-97]. In mice treated with MPTP, apigenin and luteolin improved locomotor and muscular functions. Furthermore, apigenin and luteolin administration increased TH-positive cells and BDNF levels in MPTP-treated mice. In addition, the levels of GFAP in the SN of the brain were reduced in MPTP mice when apigenin and luteolin were administered [98] (Table 1). PD (tyrosine hydroxylase immunopositive) markers were decreased in rats treated with a composite containing palmitoylethanolamide (PEA) and luteolin (Lut) (Co-ultraPEALut). Additionally, Co-ultraPEALut administration induced astrocyte activation, pro-inflammatory cytokines, and inducible nitric oxide synthase levels. Using Western blot analysis and immunofluorescence staining, the co-ultraPEALut treatment led to an increase in autophagy. Pre-treatment of SH-SY5Y neuroblastoma cells with Co-ultraPEALut also maintained high Beclin-1 and p62 expression while inhibiting p70S6K expression [99]. In an in vitro and ex vivo organotypic AD model, Paterniti et al. found that co-ultraPEALut pre-treatment significantly reduced the expression of GFAP and inducible nitric oxide synthase. Furthermore, co-ultraPEALut pretreatment reduced apoptosis and restored neuronal nitric oxide synthase and BDNF [100].

Berberine

Berberine ($C_{20}H_{18}NO_4^+$) is a naturally occurring benzylisoquinoline alkaloid. It can be found in the roots, rhizomes, and stem bark of various herbs, including Berberis, Hydrastis canadensis, and

Coptidis rhizoma[101, 102]. Several anti-inflammatory, antitumor, antimalarial, antioxidative and cardioprotective properties have been identified [103-105]. By administering berberine, shortfalls in learning and retention of spatial memory in a long-term manner were significantly reduced. In a transgenic mouse AD model, BBR treatment decreased detergent-soluble and -insoluble β-amyloid levels and inhibited glycogen synthase kinase (GSK)-3 levels in the brain homogenates samples. GSK-3 is a major kinase involved in APP and tau phosphorylation. In an in vitro study, N2a mouse neuroblastoma cells which expressed human Swedish APP695 mutation (N2a-SwedAPP) were treated with berberine. By inhibiting the Akt/Glycogen synthase kinase 3 signaling pathway, berberine markedly decreased APP and tau levels and hyperphosphorylation [105] (Table 1). A study of lipopolysaccharide-induced learning and memory deficits in rats found that berberine restored hippocampal GFAP, 3-nitrotyrosine (3-NT), cyclooxygenase 2 (Cox 2), sirtuin 1, and p38 MAPK expression levels. However, there was no significant change in BDNF [106].

Baicalein

In the roots of *Scutellaria baicalensis* Georg, there is a flavonoid called baicalein, a chemical compound known as 5,6,7-trihydroxyflavone [107]. This compound has several pharmacological effects, including anti-inflammatory, antibacterial, antiviral, and anticarcinogenic properties [108, 109]. Baicalein can cross the blood-brain barrier due to its wide safety margin [110]. In a murine model of PD induced by 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP), dopaminergic neuron loss, microglial and microglial and astrocyte activation was attenuated following treatment with low doses of baicalein. Furthermore, baicalein inhibited MPTP-induced nuclear movement of NF-κB and the activation of JNK and ERK in the primary astrocytes [111]. In addition, the baicalein treatment significantly reduced the 6-OHDA-induced apoptosis of SH-SY5Y cells and

promoted neurite outgrowth in PC12 cells. Baicalein did not affect apomorphine (APO)-induced rotations in vivo experiments but markedly reduced muscle tremor in 6-OHDA-lesioned rats. Compared to the 6-OHDA group, the burst frequency and amplitude were 13.43% and 35.18%. TH-positive neurons were also enhanced by baicalein treatment. Baicalein was neuroprotective by attenuating astroglial responses in the substantia nigra in experimental parkinsonism induced by 6-hydroxydopamine (6-OHDA) [112]. In MPTP-treated mice, baicalein administration improved abnormal behavior, increased DA and 5-HT levels, increased dopaminergic neurons in the striatum, and reduced oxidative stress and astrocyte response [113] (Table 1).

Quercetin

Quercetin (QUR, C15H10O7), also known as 3,3′,4′,5,7-pentahydroxyflavone, is a flavonoid pigment which can be found in various fruits and vegetables such as apples, berries, chokeberries cilantro, dill, escapades, lingonberries, lovage, onions [114]. Its pharmacological effects include antioxidant, anti-inflammatory, antiviral, anticarcinogenic, antiplatelet aggregation, and psychostimulant effects [115, 116]. Administration of quercetin reduced extracellular β-amyloidosis, tauopathy, astrogliosis and microgliosis in the hippocampus and the amygdala. In addition, a significant decrease in the paired helical filament (PHF), β-amyloid (βA) 1–40 and βA 1–42 levels and a reduction in BACE1-mediated cleavage of APP (into CTFβ) were found. Moreover, quercetin improved performance on learning and spatial memory tasks and greater risk assessment behavior based on the elevated plus maze test on aged (21-24 months old) triple transgenic AD model (3xTg-AD) mice [117] (Table 1). SAMP8 mice were treated with nano-encapsulated quercetin in zein nanoparticles, which improved cognition and memory impairments and reduced hippocampal GFAP expression [118]. Quercetin reduced mitochondrial dysfunctions, oxidative stress, astrogliosis and pyknotic nuclei in the striatum and behavioral deficits in HD rats

[119]. There was a significant reduction in anxiety, motor coordination deficits, and gait despair in HD induced by 3-nitropropionic acid (3-NP). In contrast, quercetin decreased serotonin metabolism significantly while not affecting dopaminergic hypermetabolism. Although quercetin did not affect 3-NP-induced striatal neuronal lesion, it reduced microglia proliferation and increased astrocyte numbers in the lesion area (85). The consumption of a quercetin-rich diet (2 mg/g diet) during the early to middle stage of Alzheimer's disease pathological development decreased cognitive deficits as well as augmented Aβ clearance. It decreased astrogliosis in mice [120] (Table 1).

Naringenin

Several fruits and plants contain a flavonoid called naringenin [121]. Furthermore, it has anti-inflammatory, anticancer, analgesic, and neuroprotective properties [122, 123]. Naringenin conferred neurotrophic effects to support the viability of dopaminergic neurons in primary rat midbrain neuron-glia co-cultures in a dose- and time-dependent manner. Also, astrocytes play a role in the neurotrophic actions of Naringenin. In primary neuron-glia co-cultures and astroglia-enriched cultures, naringenin also released neurotrophic factors and induced astrogliosis.

It was suggested that activation of Nrf2 by astrocytes plays an important role in naringenin-mediated neurotrophic activities, which supports dopaminergic neurons. This hypothesis was supported by the following observations: 1) Naringenin increased the expression of Nrf2 mRNA and protein in neurons and astrocytes; 2) Nrf2-siRNA inhibited the release of naringenin-mediated astrogliosis and neurotrophic factors; 3—inhibition of naringenin-mediated neurotrophic effects on dopaminergic neurons by Nrf2-siRNA in the astrocytes [124].

Rutin

The flavonoid glycoside rutin is found in tea, passion flower, buckwheat, and apple [125]. Rutin is reputed for its numerous pharmacological actions, including antioxidant, anti-inflammatory, vasoprotective, anticarcinogenic, neuroprotective, antimicrobial, and cardioprotective effects [125-128]. Selenium and rutin coadministration provide neuroprotection by preventing oxidative stress, neuroinflammatory changes, and the apoptosis cascade. During a 3-NPA-induced HD-like symptoms model in mice, rutin and selenium coadministration suppressed astrocyte activation, improved BDNF levels, and improved cholinergic and monoaminergic transmission [129] (Table 1).

Resveratrol

Resveratrol (3,4′,5- trihydroxystilbene) is a phytoalexin found in many plants, including grapes, peanuts and berries [130]. Resveratrol has multiple pharmacological activities, including antioxidant, cardioprotective, anticancer, and neuroprotective effects [131-133], although findings have also been reported [134-136]. Resveratrol considerably reduced tau aggregation and oligomerization and prevented N2a cells from taking up extracellular tau oligomers. Resveratrol treatment significantly reduced phosphorylated tau levels, TNF-α, IL-1β, gliosis, and synaptic loss in the brains of PS19 mice in an in vivo study [137] (Table 1). Resveratrol induced astroglial BDNF and GDNF release by stimulating neurotrophic effects in DA neurons in a concentration- and time-dependent manner in primary midbrain neuron-glia cultures. In primary cultures without astrocytes, resveratrol failed to exhibit neurotrophic effects on DA neurons [138]. C6 astroglial cells responded to buthionine sulfoximine by releasing ROS/RNS and pro-inflammatory cytokines. However, buthionine also reduced glutamate-cycline ligase (GCL) activity, cystine uptake, GSH intracellular levels, GPX and glutathione reductase (GR) activities. By modulating oxidative and inflammatory responses, resveratrol prevented astroglial cell death induced by

buthionine sulfoximine. Anti-oxidative and anti-inflammatory effects of resveratrol were diminished following pharmacological inhibition of heme oxygenase 1 (HO-1) [139]. HO-1 is a key cellular defence against oxidative and inflammatory insults. The resveratrol decreased the levels of TNF-α, IL-1β, IL-6 and IL-18 that were induced by LPS in hippocampal astrocytes. A reduction in GSH content was also prevented by resveratrol in conjunction with preventing oxidative and nitrosative stress caused by LPS. Among the signaling pathways implicated in the protective effects of resveratrol are NFκB, HO-1, p38 and ERK [140]. In a study by Frosta et al., treatment with resveratrol-loaded lipid-core nanocapsules was compared with resveratrol-free treatment against intracerebroventricular injection of Aβ1-42. When rats were given Aβ1-42, their learning memory capacity was impaired, as was the amount of hippocampal synaptophysin [141]. Additionally, animals showed activated astrocytes and microglia, as well as JNK/GSK-3β activation and destabilization of β-catenin expression. Resveratrol prevented Aβ1-42's deleterious properties by using lipid-core nanocapsules, but it only produced partial benefits in combination with resveratrol. This may be due to the high levels of resveratrol found in brain tissue after being implanted with lipid-core nanocapsules [142].

Despite the scarcity of clinical studies for resveratrol in neurodegenerative diseases, several phase 2 clinical trials have shown the safety of resveratrol for use in mild to moderate AD patients. Also, in two clinical trials, AD patients treated with resveratrol for one year had lower levels of MMP-9, a matrix metalloproteinase (MMP), which its activity is associated with AD/neurodegeneration. In addition, these studies show that resveratrol can cross BBB, evidenced by significant amounts of resveratrol and its metabolites in the CSF [142, 143].

Capsaicin

The active ingredient in red and chilli peppers is capsaicin, a homovanillic acid. It has been shown to have analgesic [144], anti-inflammatory [145], antioxidant [146], and anti-obesity [147] effects. The capsaicin treatment reversed the PD symptoms in the MPTP mouse model in both nigrostriatal and striatal DA neurons. In addition, there were several mechanisms through which capsaicin enhanced behavioral recovery, including 1) restoring the loss of striatal dopamine, 2) inhibiting the expression of proinflammatory mediators in the substantia nigra, 3) reducing oxidative stress caused by microglial NADPH oxidase in the substantia nigra, and 4) decreasing astroglial MPO expression in the substantia nigra [148] (Table 1).

Conclusion

In numerous experimental models of neurodegenerative diseases, phytochemicals have been found to exert neuroprotective properties. Although herbal remedies are becoming increasingly popular, they require scientific validation before they become widely accepted and used. The blood-brain barrier must also be crossed for a neuroprotective agent to reach the target sites of the central nervous system [149, 150]. Passage through the blood-brain barrier is done by either paracellular transport between endothelial cells and through transcellular transport, involving passive or active mechanisms[151]. This creates a bottleneck that stops the crossing of approximately 98% of small molecules and most large molecules. To overcome this, nanotechnology has made it possible to implement non-invasive drug delivery strategies for designing novel and improved formulated therapeutic agents with enhanced delivery potentials across the blood-brain barrier [152]. Several studies reviewed here have adapted this approach using a nano-encapsulated phytochemical formulation [153, 118]. Considering the diversity and heterogeneity of astrogliosis functionality in various CNS pathologies, using only one marker for determining astrogliosis, such as GFAP, does not represent a sufficient understanding of how astrogliosis affects the pathophysiology of

neurodegenerative disease model and also how astrogliosis is affected by phytochemicals. This problem is needed to be addressed in future studies of phytochemicals in neurodegenerative disorders. Furthermore, whether polyphenols or other phytochemicals have receptors or transporters in the brain tissues has yet to be determined. While these factors are present, phytochemicals with various targets are emerging as promising therapeutic classes for treating neurodegenerative disorders. Future studies can address the effects of phytochemicals on astrocytes' function in areas such as mitochondrial dynamics of astrocytes and metabolic profiles in different neurodegenerative disorders. As discussed in this review, many phytochemical compounds act as neuroprotectants by mitigating astrogliosis, which is a key mechanism of their protective effects (**Figure 1**). Finally, there is no evidence that brain tissue possesses phytochemical receptors or transporters. Still, compounds with multiple targets seem promising therapeutic strategies for treating neurodegenerative diseases.

LIST OF ABBREVIATION

central nervous system (CNS)

glia fibrillary acidic protein (GFAP)

extracellular matrix (ECM)

Alzheimer's disease (AD)

Huntington's disease (HD)

amyotrophic lateral sclerosis (ALS)

Parkinson's disease (PD)

tyrosine hydroxylase-immunoreactive (TH-IR)

small interfering RNA (siRNA)

reactive oxygen species (ROS)

mossy fiber sprouting (MFS)

Table 1. The effectiveness of phytochemicals for the management of neurodegenerative disorders.

Phytochemical	Diseases	Dose, duration	Main findings	References
Curcumin	PD	(40 mg/kg bw (i.p.)) daily for a period of 21 days	↓GFAP; ↓protein activity of NF-κB, TNF-α, IL-1β, IL-1α, and iNOS; ↓apoptotic markers (Bax, Bcl-2, Caspase 3 and Caspase 9); ↓expression of α-synuclein; ↓iron deposition in dopaminergic neurons	[47]
		Curcumin, 1 week, start at lesion induction	↑nigral TH-IR neurons; ↑striatal TH-IR fibers; ↑microglial and astroglial reaction in the SNpc and striatum	[48]
	AD	Curcumin, 0.8 g/kg, orally via food, for 12 weeks	↓p25-mediated astrocyte activation; ↓ pro-inflammatory chemokines/cytokines production in p25Tg mice. ↓progression of p25-induced tau/amyloid pathology; ↓p25-induced cognitive deficits	[49]
Thymoquinone	Epilepsy	10 g/kg, orally	↓nitrite, MDA, and nitrate; ↑SOD. ↓neuronal loss in CA1, CA3 and the hilar regions. ↓mossy fiber sprouting (MFS). ↓number of reactive astrocytes.	[66]
Rosmarinic acid	AD	50 mg/kg, daily, orally, 14 days	↑GSH-Px, CAT, SOD, and glutathione levels; ↑acetylcholine content and acetylcholine esterase activity; ↓Aβ staining and astrocyte activation; ↑MMN response and theta power/coherence of AERPs	[71].
Sesamin	PD	10 or 20mg/kg/day for one week	↓motor imbalance in narrow beam test; ↓striatal MDA level and ROS; ↑SOD activity; ↓striatal caspase 3 activity and α-synuclein expression; ↓GFAP immunoreactivity; ↓nigral neuronal apoptosis; ↓damage of dopaminergic neurons	[79].
Genistein	AD	10 mg/kg, orally	↓formation of Aβ1–40 positive aggregates; ↑nNOS+ cells in the hippocampus; ↓astrogliosis	[83].
		10 mg/kg, orally	-reduced the GFAP intensity and mean cell body volume and area of astrocytes - inhibited the enlargement of astrocytes in the hippocampus	[84]
	ALS	16 mg/kg, twice a day	↓COX-2, TLR2, TLR4 and NF-kB p65 in spinal cords; ↑gliosis in the spinal cord of SOD1-G93A mice; ↑autophagic processes; ↑viability of spinal motor neurons. ↑ALS-related symptoms; ↑lifespan in SOD1-G93A transgenic mouse	[88].
Troxerutin	PD	150mg/kg/day, 7 days	↓apomorphine-induced motor asymmetry; ↓latency to initiate and the total time in the narrow beam task. ↓striatal MDA, GFAP, reactive oxygen species, and DNA fragmentation. ↓ loss of nigral (TH)-positive neurons	[93].

Apigenin and luteolin	PD	Apigenin: 5, 10 and 20 mg/kg; luteolin:10 and 20 mg/kg; both orally, 26 days	↑locomotor and muscular activities; ↑TH-positive cells and BDNF levels; ↓GFAP in the SN of the brain	[98].
Berberine	AD	25 mg/kg or 100 mg/kg, orally, for 4 months	↓learning deficits; ↑long-term spatial memory retention. ↓detergent-soluble and -insoluble β-amyloid levels; ↓Glycogen synthase kinase 3	[105].
Baicalein	PD	1 and 10 mg/kg, i.p., 7 days	↑motor ability; ↓dopaminergic neuron loss; ↓microglial and astrocyte activations; ↓MPTP-induced nuclear translocation of NF-κB; ↓JNK and ERK activations of primary astrocytes	[111].
		200 mg/kg, i.g.,15 days	↓muscle tremor of 6-OHDA-lesioned rats; ↑TH-positive neurons; ↓astroglial response within the substantia nigra	[112].
		200 mg/kg i.g., 7days	↓abnormal behavior; ↑DA and 5-HT levels; ↑dopaminergic neurons in the striatum; ↓oxidative stress; ↓astroglia response in MPTP-treated mice	[113].
Quercetin	AD	25 mg/kg i.p. injection every 48 h for 3 months	↓extracellular β-amyloidosis; ↓tauopathy; ↓astrogliosis and microgliosis in hippocampus and amygdala. ↓paired helical filament (PHF); ↓β-amyloid (βA) 1–40 and βA 1–42 levels; ↓BACE1-mediated cleavage of APP (into CTFβ); ↑performance on learning and spatial memory tasks; ↑risk assessment behavior	[117].
		Nano-encapsulated in in zein nanoparticles, 25mg/kg, every 2 days	↑cognition; ↓memory impairments; ↓reduced hippocampal GFAP expression	[118].
	HD	25mg/kg, orally, 21days	↓mitochondrial dysfunctions; ↓oxidative stress; ↓pyknotic nuclei and astrogliosis in striatum and neurobehavioral deficits	[119].
		20 mg/kg, i.p., daily, 4 days	↓anxiety; ↓motor coordination deficits and gait despair. ↓3-NP mediated metabolism of serotonin. Failed to affect 3-NP-induced striatal neuronal lesion. ↓microglial proliferation; ↑astrocyte numbers in the lesion core	[153].
Quercetin	AD	In diet, 2 mg/g diet, 8 days	↓cognitive dysfunction; ↑Aβ clearance; ↓astrogliosis in APP/PS1 mice	[120].
Rutin	HD	Rutin, 50mg/kg + selenium nitrate, 0.2mg/kg, orally, daily for 30 days	↓body weight loss; ↓oxidative stress, neuroinflammation, and the apoptotic cascade; ↓astrocytes activation; ↑BDNF and cholinergic and monoaminergic transmission	[129]
Resveratrol	AD	Free form or resveratrol-loaded lipid-core nano	↓cognitive deficits; ↓levels of phosphorylated tau; ↓TNF-α and IL-1β; ↓gliosis and synapse loss in the brain	[137].

		capsules, 5 mg/kg, i.p., 14 days		
Capsaicin	PD	0.01, 0.1, 0.5, 1 and 2.5 mg/ kg, i.p., once, 30 min before MPTP injection.	↑nigrostriatal dopamine neurons, ↑striatal dopamine functions, ↑behavioral recovery by restoring striatal dopamine depletion. ↓microglial activation; ↓proinflammatory mediators expression in the substantia nigra; ↓microglial NADPH oxidase-derived oxidative stress in the substantia nigra; ↓expression of astroglial MPO in the substantia nigra	[148].

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CONFLICT OF INTEREST

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Figure legend

Figure 1. Neuroprotective activities of phytochemicals against neurodegenerative disorders through modulation of astrogliosis.

In AD, the accumulation of Aβ proteins activates astrogliosis in the peripheral astrocytes. The reactive astrocytes secrete various chemicals and affect several pathways, producing neurotoxicity in the neurons with Aβ protein accumulations. The neurotoxicity of these neurons leads to neuronal dysfunction, which gradually advances to the development of AD.

Similarly, ALS-associated mutant proteins in ALS disease cause astrogliosis and neurotoxicity after that, which is inhibited by the phytochemical. In HD, the reactive astrocytes cause the release of pro-inflammatory cytokines (NF-κb and TNF-α) and down-regulation of protective factors

(BDNF), which can cause neurotoxicity and development of HD. The phytochemical can inhibit the neurotoxicity and possibly the development of HD. In PD, α-synuclein accumulation results in astrocytes entering the reactive state, which causes the secretion of pro-inflammatory cytokines (IFN-γ and TNF-α). Also, decreased or mutated DJ-1 and Parkin genes can cause astrogliosis. These changes result in neurotoxicity, which can ultimately result in neuronal dysfunction and the development of neurodegenerative disorders. Therefore, phytochemicals can protect against PD development by suppressing neurotoxicity and protecting neurons against inflammation and oxidative stress by stimulating astrocytes to release anti-inflammatory and antioxidant chemicals and factors.

Abbreviations: AD: Alzheimer's disease; Aβ: Amyloid beta; ALS: Amyotrophic Lateral Sclerosis; Aβ; NF-κb: Nuclear factor kappa B; TNF-α: Tumor necrosis factor α; BDNF: Brain-Derived Neurotrophic Factor; ARE: Antioxidant response element; Nrf2: The nuclear factor erythroid 2–related factor 2; IFN-γ: Interferon-gamma.