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REVIEW

A Review on Potential Footprints of Ferulic Acid for Treatment of Neurological Disorders

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Abstract

Ferulic acid is being screened in preclinical settings to combat various neurological disorders. It is a naturally occurring dietary flavonoid commonly found in grains, fruits, and vegetables such as rice, wheat, oats, tomatoes, sweet corn etc., which exhibits protective effects against a number of neurological diseases such as epilepsy, depression, ischemia-reperfusion injury, Alzheimer's disease, and Parkinson's disease. Ferulic acid prevents and treats different neurological diseases pertaining to its potent anti-oxidative and anti-inflammatory effects, beside modulating unique neuro-signaling pathways. It stays in the bloodstream for longer periods than other dietary polyphenols and antioxidants and easily crosses blood brain barrier. The use of novel drug delivery systems such as solid-lipid nanoparticles (SLNs) or its salt forms (sodium ferulate, ethyl ferulate, and isopentyl ferulate) further enhance its bioavailability and cerebral penetration. Based on reported studies, ferulic acid appears to be a promising molecule for treatment of neurological disorders; however, more preclinical (in vitro and in vivo) mechanism-based studies should be planned and conceived followed by its testing in clinical settings.

Keywords Ferulic acid · Epilepsy · Depression · Ischemia-reperfusion injury · Parkinson's disease · Alzheimer's disease

Introduction

Plant-based drugs are being explored for treatment of neurological disorders. In the last five decades, preclinical studies have shown numerous evidences indicating the beneficial role of phytochemicals in prophylaxis and treatment of neurological diseases [1–5]. Polyphenols and carotenoids are two important categories of phytochemicals, contributing maximally towards the medicinal value of plants [6]. In recent years, various studies have reported the neuroprotective action of polyphenols and phenolic acids such as ferulic acid, caffeic acid, syringic acid, ellagic acid, sinapic acid, p-coumaric acid, tannic acid, rosmarinic acid, and chlorogenic acid [7]. Among these, ferulic acid is of great interest for neuroscientists because it has good bioavailability, stays in blood for longer period of time, permeable to blood-brain barrier (BBB) and exhibits multiple neurotherapeutic effects [8]. Beside its antioxidant and anti-inflammatory effects, ferulic acid modulates various neuro-signaling pathways via interaction with multiple receptors or enzymes [9, 10]. It also modulates the expression of various proinflammatory cytokines, and pro-apoptotic signals which explains its neurotherapeutic effects [11, 12].

Ferulic acid belongs to the class of hydroxycinnamic acid, and have broad spectrum of pharmacotherapeutic effects [13, 14] (Fig. 1). An animal study showed that ferulic acid (521 µmol/kg p.o) administered to rats was detectable in the brain in the concentration range of 2.6 µg/g of tissue, ≈13.39 nmol/ml. Sixty minutes following administration, brain concentration decreased only by 50 % [15]. Ferulic acid has been used and approved in traditional Chinese system of medicine for treatment of cardiovascular diseases

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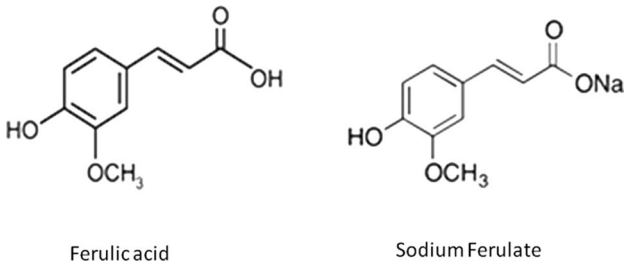

Fig. 1 Structure of ferulic acid and sodium ferulate

such as coronary heart disease (CHD), atherosclerosis, pulmonary heart disease, and hypertension for decades [16–32]. Sodium ferulate (0.08 g/day i.v.) administered for 3 to 7 days in CHD patients (n = 94) decreased symptoms of angina pectoris [17]. Sodium ferulate as an adjuvant therapy improved therapeutic effects of various cardiovascular drugs such as nitrates, β receptor antagonists, and calcium channel blockers (improved heart functions, normalized myocardial enzyme levels, reduced the incidence of other cardiovascular disease such as heart failure or arrhythmias) [25–30]. Ferulic acid showed cardioprotective effects pertaining to its modulatory effects on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and NF-E2-related factor 2 (Nrf2)/Heme oxygenase (HO)-1 system pathway [33, 34]. These inflammatory signaling pathways are also reported in progression and development of neurological disorders [35–41]. Therefore, due to its potent anti-inflammatory effects as well as modulatory effects on multiple signaling pathways, various studies elucidated the neuroprotective effects of ferulic acid in different animal models of neurodegenerative diseases [42–44]. As a common pathological mechanism in multiple neurodegenerative diseases, ferulic acid mitigates cascades of oxidative stress and neuroinflammation. Phenolic and hydroxyl groups in its structure donates electrons to quench the free radicals and imbibe it with antioxidant potential. Recently, a study reported modulatory effects of ethyl ferulate (15 μM) to HO-1 expression in neurons and astrocytes [45]. Although, the study did not identify the specific cascade of events that triggers HO-1 up-regulation, it speculated the involvement of the Nrf2 pathway. However, ethyl ferulate at high concentration (50 μM) gave contrasting results (cytotoxic effects) [46], which could partially be explained by possible HO-1 gene repression [47].

Patients with major depressive disorder (MDD) and animal studies have shown decreased monoamine (serotonin, dopamine, norepinephrine) and brain derived neurotrophic factor (BDNF) levels in the hippocampus [48–52]. Ferulic acid treatment restored monoamine levels, BDNF levels, and decreased depression-like phenotypes in corticosterone treated mice (an animal model of depression) [53]. Ferulic acid was also neuroprotective against monosodium glutamate (MSG) induced excitotoxic damage on developing fetal mouse brain through its N-methyl-D-aspartate (NMDA) receptor inhibition properties [54]. Studies have also reported a key role of ferulic acid in epileptogenesis and development of seizures [55]. Ferulic acid also attenuated the cyclooxygenase-2 (COX-2) enzyme levels, inducible nitric oxide synthase (iNOS), proinflammatory cytokines (Interleukin 1β [IL-1β], Tumor Necrosis Factor-α [TNF-α]) and myeloid differentiation primary response 88 (MyD88) expression, and has shown neuroprotective potential in various experimental models of Parkinson's disease (PD) [56–58]. Similarly, in Alzheimer's disease (AD), in vitro and in vivo studies showed that tacrine-6-ferulic acid (T6FA), a multifunctional semi-synthetic dimer exhibits acetylcholinesterase (AChE) inhibitor activity and prevented deposition of Aβ- peptide and other pathological changes. These semi-synthetic molecules are result of an interesting approach to increase bioavailability as well as to combat adverse effects associated with available drugs for treatment of AD [59]. Thus, based on these studies, we reviewed the therapeutic potential of ferulic acid and elaborated its pleiotropic neuroprotective mechanisms in major neurological disorders such as epilepsy, depression, cerebral ischemia, AD, and PD in more detail.

Methodology

The scientific literature was collected using online search engines and databases such as Science Direct, Scopus, PubMed, and Google Scholar until November 2020. The search was conducted using keywords "Ferulic acid", "Neurodegenerative disorders", "Depression", "Parkinson's disease", "Alzheimer's disease", "Epilepsy", "Ischemia-reperfusion injury" in combination with ferulic acid or alone.

Ferulic Acid and Epilepsy

Epilepsy is a neurological disorder characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition [60]. Epileptogenic events such as traumatic brain injury or status epilepticus triggers neuroinflammatory and apoptotic pathways, which subserves multiple neuroplastic changes leading to development of seizures [61–63]. Phytoconstituents such as ferulic acid, which have antioxidant and anti-inflammatory potential showed putative antiepileptic and antiepileptogenic effects [64, 65].

In line with this, ferulic acid attenuated epileptogenesis and showed neuroprotective effects in the pentylenetetrazole (PTZ) kindling induced model of chronic epilepsy.

Treatment decreased gap junction alpha-1 (GJA1) or connexin 43 protein expression in the brain [66]. Connexins are a family of 21 protein isoforms, 11 of which are expressed in the central nervous system (CNS). These proteins form hemichannels, also known as connexons and channels (gap junctions/electric synapses) that enables smooth functional and metabolic coupling between neurons and astrocytes. Epileptogenic events increase opening of hemichannels in astrocytes, enable gliotransmitter release and increase synchronization between coupled neurons involved in seizure initiation and propagation. Pharmacological blockade of these channels and hemichannels using GJA-1 antagonists have shown anti-epileptic effects [67, 68].

In another study, isopentyl ferulate (25, 50 and 75 mg/kg, i.p.) also showed anti-epileptic effect in two acute models of seizures induced by pilocarpine and PTZ. Flumazenil blocked its antiepileptic potential, suggesting GABA-A modulatory effects of ferulic acid [69]. Ferulic acid has also been reported to inhibit monoamine oxidase-A (MAO-A) activity, increasing synaptic levels of monoamines, which may also explain its potent anti-epileptic effect reported in PTZ post kindled epileptic animals [70]. Monoamines are neuroactive substances in CNS that are capable of regulating the seizure initiation and propagation [71, 72]. Elevated levels of monoamines in the brain have been speculated to exert an anticonvulsant action [73, 74] and deficiencies in monoamines are also implicated in different types of seizures [75–78] possibly via lowering seizure threshold [79]. Ferulic acid (60 mg/kg) has also been reported to modulate apoptotic pathways, another possible pathway explaing its antiepileptic effect observed in PTZ kindling induced epilepsy model [80].

Methanolic extract of *Ipomoea reniformis* (MEIR) with principle constituents (sinapic and ferulic acid) have also demonstrated potent anti-epileptic effect against isonicotinyl hydrazine (INH) and PTZ-induced acute seizures in mice. MEIR (400 mg/kg) significantly increased mean latency time to myoclonic jerks and generalized tonic-clonic seizures (GTCS) observed post-PTZ injection, which was comparable to diazepam, a standard antiepilptic drug (AED). However, MEIR pretreatment did not stop animals predisposition towards GTCS [81]. Thus, all available reports consistently showcase the antiepileptic and anti-epileptogenic potential of ferulic acid. This molecule may have significant advantage over available marketed anti-epileptic drugs, which are associated with various adverse effects such as depression, cognitive deficit, anxiety, gingival hyperplasia, osteomalacia, megaloblastic anemia, hirsutism, leucopenia, thrombocytopenia, pancytopenia, teratogenic and liver cells toxicity [82].

In another interesting study, ferulic acid was reported as a safe adjuvant therapy for management of epilepsy associated depression. Epilepsy itself and use of AEDs is associated with comorbid psychiatric disorders such as depression [83]. Antidepressants prescribed for treatment of depression decrease seizure threshold in epileptic patients [84, 85]. Thus, there is an unmet need to discover novel and safe therapies having antidepressant action with no effect on seizure threshold. Ferulic acid (40, 80 mg/kg. p.o.) as an adjuvant therapy ameliorated depression-like phenotypes in PTZ kindling induced chronic epileptic animals without affecting anti-epileptic potential of the levetiracetam (an AED). The study showed that ferulic acid decreased the levels of pro-inflammatory cytokines (IL-1β, TNF-α), restored monoamine levels, and HPA axis dysregulation (marked by normal serum corticosterone levels) [86]. In another study, ferulic acid (75 and 100 mg/kg, i.p.) showed potent antiepileptogenic effects and improved cognitive impairment possibly due to its potent anti-inflammatory effects [70]. Various studies implicated neuroinflammation observed in epilepsy as one of the major causes of epilepsy associated comorbid conditions such as depression and cognitive impairment [87–89]. Thus, due to its anti-inflammatory actvity and potential to modulate various neuro-signaling pathways, ferulic acid could serve as a safe adjuvant therapy with available AEDs for treatment of comorbid depression. However, streamlined pharmacokinetic and pharmacodynamic studies are necessary in a battery of acute or chronic epilepsy models to develop this molecule as a next generation AED or safer alternative to antidepressants in epileptic patients. The ameliorative effect of ferulic acid on major pathways involved in progression of epilepsy have been shown in Table 1; Fig. 2.

Ferulic Acid and Depression

Depression is characterized by persistent sadness and a lack of interest or pleasure in previously rewarding or enjoyable activities. It is a common neurological disorder affecting more than 264 million people worldwide [90, 91]. Recent findings in animal studies suggested decreased monoamine and BDNF levels, with elevated neuroinflammation as major determinants of behavioral depression [92]. Elevated corticosterone levels due to HPA axis dysregulation is another important circulating peripheral biomarker of depression [93]. Anti-depressants (ADs) primarily increase the synaptic levels of monoamines and increase BDNF levels, which ameliorated depression-like symptoms [94, 95]. However, they are associated with serious side-effects such as tachycardia, blurred vision, weight gain, hemorrhage, perioperative headache, and seizures [96, 97]. Furthermore, 50% patients with depression show resistant towards available ADs [98, 99]. Thus, there is unmet need to develop ADs with novel mechanisms, which could be useful for safe

Table 1 Effect of ferulic acid on various mediators altered during neurological disorders

Ferulic acid influence on mediators	*Epilepsy*	*Depression*	*Cerebral ischemia*	*Alzheimer's disease*	*Parkinson's disease*
Antioxidant					
SOD		↑ [188]	↑ [46]	↓ [189]	↑ [180]
MDA	↓ [74]		↓ [46]	↓ [190]	↓ [180]
CAT		↑ [188]		↓ [189]	↑ [180]
Pro-inflammatory cytokines					
TNF-α	↓ [11]	↓ [191]		↓ [189]	↓ [192]
IL-1β	↓ [11]	↓ [191]	↓ [125]	↓ [189]	↓ [192]
Prostaglandins					
COX-2	↓ [11]			↓ [190]	↓ [180]
iNOS	↓ [11]		↓ [193]		↓ [180]
Transduction signaling					
NF-κB	↓ [194]	↓ [191]	↓ [109]	↓ [190]	↓ [192]
TLR/MyD88			↓ [46]		
Apoptotic					
Bax	↓ [11]		↓ [46]		↓ [195]
Bcl-2			↑ [46]		
Miscellaneous (hallmarks)		↓ [98] , [196] MAO	↑ [197], [198] PI3/K/Akt/ mTOR signaling pathway	↓ [189], [190] Aβ, BACE1, AChE, β secretase modulator	↓ [192] , [199] α-synuclein, TH

↓ Inhibition/decrease ↑ Stimulate/increase

SOD, Superoxide dismutase; MDA, Malondialdehyde; CAT, Catalase; TNF-α, Tumor Necrosis Factor Alpha; IL-1β, Interleukin-1β; COX-2, Cyclooxygenase-2; iNOS, inducible Nitric oxide synthase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; TLR-4, Toll-like receptors-4; MyD88, Myeloid differentiation primary response 88; BAX, Bcl2-Associated X Protein; Bcl-2, B-cell lymphoma 2; MAO, Monoamine oxidase; PI3K, Phosphatidylinositol 3-kinase; Akt, Protein Kinase B; mTOR, Mammalian target of rapamycin; Aβ, Amyloid β peptide; BACE1, β-site amyloid precursor protein (APP) cleaving enzyme 1; AChE, Acetylcholinesterase; TH, Tyrosine hydroxylase

management of depression as well as effective in treatment resistant depression.

Phytoconstituents such as ferulic acid have been explored and reported for their AD like effects [100, 101]. A diverse range of mechanisms contribute to the AD like effects of this molecule [102, 103]. In animal studies, chronic treatment restored monoamine and BDNF levels in the brain, which improved depression like phenotypes manifested as decreased immobility time in tail suspension test [104, 105]. Ferulic acid was also reported to upregulate intracellular adenosine triphosphate (ATP) levels suggesting a novel pathway for its antidepressant effects [106–108]. In addition, ferulic acid treatment also decreased oxidative stress as observed with decreased thiobarbituric acid reactive substances (TBARS) as well as increased catalase (CAT) and superoxide dismutase (SOD) levels [109].

Various studies have also demonstrated that ferulic acid showed AD like effects pertaining to its anti-inflammatory effects [110–112]. Chronic ferulic acid treatment reduced the expression of pro-inflammatory cytokines (NF- κB, IL-6, IL-1β, and TNF-α) and nitric oxide synthase (NOS) enzyme in the hippocampus of prenatally stressed offspring rats indicating its AD like effects [111, 112]. Ferulic acid also decreased glucocorticoid receptor protein expression, restored HPA axis reactivity, and circulating corticosterone levels. The hippocampus is particularly vulnerable to elevated glucocorticoids because it expresses the highest density of glucocorticoid receptors in the brain. Elevated corticosterone levels over-activate glucocorticoid receptors, impairs hippocampal plasticity by suppressing BDNF expression and neurogenesis, intrinsically linked to both behavior as well as learning and memory [111, 112]. Ferulic acid (40, 80) mg/kg; p.o. treatment also inhibited the MAO-A activity in the hippocampus, enhanced monoamine levels and showed AD like effects [113, 114]. Thus, these findings suggest the potential of ferulic acid as an AD. Nonetheless, further studies are necessary to report its safety and efficacy to translate this molecule into clinical settings. Ferulic acid should also be screened as an adjuvant therapy with available ADs in animal models of treatment resistant depression as elevated neuroinflammation has been reported to be one of the major reasons in developing resistance to available ADs [115]. Pathological pathways responsible

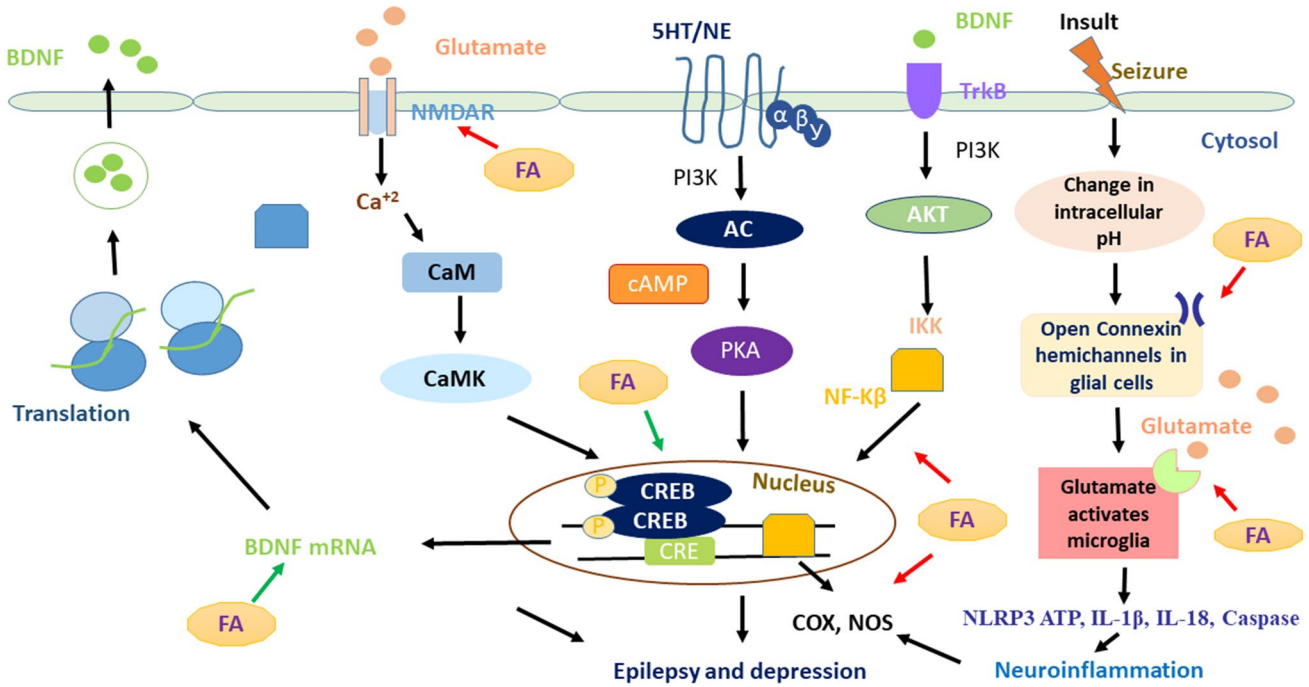

Fig. 2 Insights into the multi-target action of ferulic acid in epilepsy and depression. Abbreviations: BDNF, Brain-derived neurotrophic factor; FA, Ferulic acid; NMDAR, N-methyl-D-aspartate receptor; CaM, calmodulin; CaMK, Ca2+/calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; CRE, cAMP response elements; PI3K, Phosphoinositide 3-kinases; AC, Adenylate cyclase; cAMP, cyclic adenosine monophosphate; PKA, Protein kinase cAMP-dependent; TrKB, tyrosine kinase receptor type 2; AKT, Protein kinase B; IKK, IκB kinase; TNF-α, Tumor Necrosis Factor Alpha; ATP, Adenosine triphosphate; IL-1β, Interleukin-1β; COX-2, Cyclooxygenase-2; NOS, Nitric oxide synthase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; Glu, Glutamate; NLRP3, NLR family pyrin domain containing 3; ATP, Adenosine triphosphate; IL-1β, Interleukin-1β; IL-18, Interleukin-18. Green arrow indicates stimulate/increase, red arrow indicates inhibition/decrease

for depression and ameliorative effect of ferulic acid on these pathways are shown in Table 1; Fig. 2.

Ferulic Acid and Cerebral Ischemia

Ischemia-reperfusion injury (IRI) is defined as the paradoxical exacerbation of cellular dysfunction and death, following restoration of blood flow to previously ischemic tissues [116]. Numerous studies have demonstrated the neuroprotective effect of ferulic acid following IRI primarily due to its neuro-signaling modulatory and anti-apoptotic effects.

Ferulic acid (100 mg/kg) treatment 30 min before middle cerebral artery occlusion (MCAO) significantly reduced cerebral infarct and neurological deficit-score in rats. The neuroprotective effect of ferulic acid was mainly attributed to the inhibition of superoxide radicals, intercellular adhesion molecule 1 (ICAM-1) and NF-κB expression [117–119]. During neuronal stress such as ischemia, NF-κB translocate into the nucleus through nuclear pore complexes, regulates synthesis of proinflammatory cytokines and adhesion factors such as ICAM-1 and endothelial-leukocyte adhesion molecule 1 (ELAM-1), which further promotes leukocytes infiltration through the endothelium layer [120, 121]. Pharmacological blockade of leukocytes infiltration and migration with anti-ICAM-1 antibody or activated leukocyte inhibitors reduced infarct volume following MCAO [122–126]. Ferulic acid also enhanced GABA-B1 receptor expression and reduced IRI derived nitric oxide-induced apoptosis following MCAO in rats [43].

Another study investigated the neuroprotective effect of ferulic acid in cerebral ischemia induced nerve injury. In this study, focal cerebral ischemia was induced by MCAO for 90 min followed by reperfusion for 24 h in rats. Ferulic acid (100 mg/kg) treatment for 7 days following MCAO attenuated nerve injury, neurological deficits, and secured normal brain histology, assessed using hematoxylin and eosin staining [127]. Ferulic acid has also been reported to increase erythropoietin levels in brain and blood following MCAO. Elevated erythropoietin levels increased red blood cell production, which increased the oxygen carrying capacity of blood. It also stimulated production of nitric oxide, modulated blood flow, and provided neuroprotection against IRI [128, 129].

Ferulic acid administration has also been reported to restore peroxiredoxin-2 and thioredoxin levels following

MCAO in rats [130]. Peroxiredoxin-2 and thioredoxin are endogenous antioxidant enzymes abundantly expressed in the brain, which exhibit neuroprotective effects against ROS and prevent neuronal insult during brain ischemia by reducing infarct size and neuronal cell death. Following MCAO, peroxiredoxin-2 and thioredoxin levels decreased, which predisposed neurons to neuronal cell injury. Peroxiredoxin-2 reduced neuronal injury by modulating thioredoxin levels, thereby preventing activation of apoptosis signal-regulating kinase 1 (ASK1), which decreased apoptotic cell death following transient brain ischemia [131].

In another study it is reported that ferulic acid inhibits nerve damage following IRI by attenuating reactive astrocytosis and by activating p38 Mitogen-activated protein (MAP) kinase signaling. Activation of p38 MAP kinase signaling activates BAX-induced apoptotic pathways and contributes to inhibition of the cytochrome c-mediated caspase-3-dependent apoptotic pathways in cortex and provides neuroprotection [132]. Ferulic acid as an adjuvant therapy with puerarin and astragaloside provided synergistic neurotherapeutic effects and decreased the infarct volume following MCAO. The neuroprotective effects were observed by markedly decreased pro-inflammatory cytokines (IL-1β) and neuropeptide Y (NPY) levels in the brain [133].

It has also been reported that ferulic acid treatment (100 mg/kg), 24 h after the onset of MCAO protected against neuronal damage and decreased terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positive cells. Treatment attenuated the downregulation of MEK/ERK/p90RSK signaling pathway [134]. MAP kinase belongs to family of serine/threonine protein kinases reported to modulate cell proliferation, differentiation, and death [135]. The p44/42 MAP kinase, also known as ERK1/2 signaling pathway, interacts with extracellular stimuli such as mitogens and growth factors [136–138]. Raf, an important upstream activator of MAP kinase, phosphorylate MEK1/2 under stress conditions, which activates ERK1/2. Following activation, ERK1/2 further regulates the down-stream targets of MAP kinase such as 90 kDa ribosomalS6 kinase (p90RSK) [139–142]. Activated p90RSK further phosphorylates pro-apoptotic protein BCL2 associated agonist of cell death (Bad), which results in the inhibition of the apoptosis [143–145]. Multiple studies reported neuroprotective effects of ferulic acid by modulating ERK kinase signaling [146–149]. These studies suggested the potential of kinase inhibitors such as MAP kinase inhibitors or ERK inhibitors in serving neuroprotection following MCAO.

It has also been reported that treatment with ferulic acid protected against MCAO induced cell death by regulating expression levels of γ-enolase [150, 151], a neuron-specific enolase, which increases neuron survival and enhances neurotrophic activity [152]. It also activates phosphatidylinositol 3-kinase (PI3K) and MAP kinase signaling pathways and promotes cell survival and neurite outgrowth and protects against IRI [153].

Ferulic acid treatment following MCAO has also been reported to restore protein phosphatase 2A (PP2A) levels. PP2A is an essential serine and threonine phosphatase protein involved in the regulation of several cellular functions such as cell differentiation, apoptosis, and signal transduction [154]. Additionally, ferulic acid regulates PI3K/AKT/GSK-3β/CRMP-2 signaling pathway in focal cerebral ischemic injury, thereby protecting against cerebral injury [155]. PI3K/AKT activation suppresses neuronal death following cerebral ischemia and enhances cell survival [156–158]. Stress-induced AKT phosphorylation results in activation of several pro-apoptotic proteins, such as Bad and glycogen synthase kinase-3β (GSK-3β) [159]. Although GSK-3β has been reported to elevate caspase-3 activity and induce apoptotic cell death following transient global ischemia, its pro-apoptotic potential is inhibited by activation of AKT phosphorylation [159, 160]. GSK-3β has also been reported to phosphorylate collapsin response mediator protein 2 (CRMP-2), and inhibit the polymerization and stabilization of microtubules, which in turn inhibits axonal elongation [161, 162]. CRMP-2 abundantly exists in the growing axons of hippocampal neurons and mediates neuronal differentiation and growth [163–165]. *In silico* studies also demonstrated that ferulic acid can attenuate stress induced CRMP-2 increase during IRI [166, 167]. Thus, based on all these studies, ferulic acid can be seen as a potential candidate for novel and safe management of IRI pertaining to its modulatory effects on multiple neurosignaling pathways (Table 1) (Fig. 3).

Ferulic Acid and Alzheimer's Disease

Alzheimer's disease (AD) is a progressive brain disorder which causes dementia and slowly deteriorates cognitive skills primarily in the older population [168]. The abnormal accumulation of extracellular amyloid-beta (Aβ) and intracellular neurofibrillary tangles (NFTs) impairs neural transmission [169]. There are reports showing positive correlation between reactive oxygen species (ROS) and reactive nitrogen species (RNS) levels and Aβ-deposition in transgenic APP mice [170–172]. These studies provided the first quantitative analysis of oxidative stress and lipid peroxidation (LPO) in a transgenic model of AD amyloidosis (Tg2576). Isoprostanes (iPs) formed by a free radical peroxidation of polyunsaturated fatty acids was used as specific markers of LPO. Urine, plasma, and brain tissues were collected at different ages, starting at 4-months, and continuing until 18 months. Elevated levels of 8,12-iso-iPF2a-VI in urine, plasma, cerebral cortex, and hippocampus were observed at the age of 8 months.

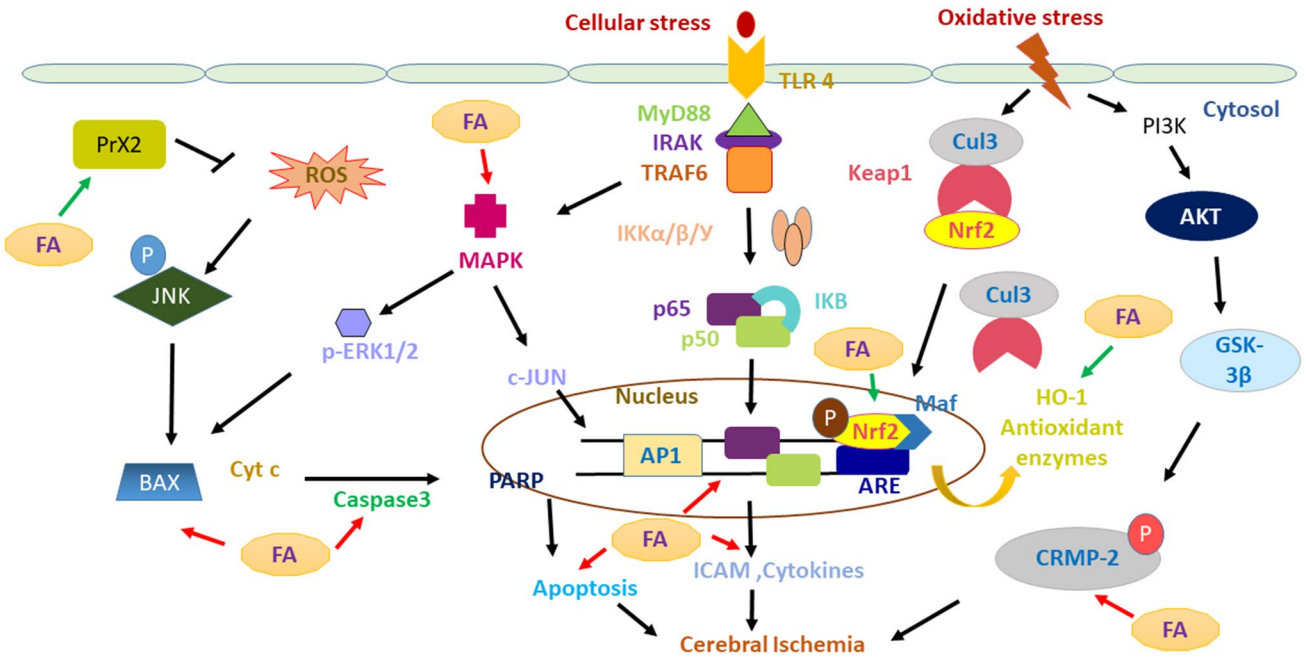

Fig. 3 Insights into the multi-target action of ferulic acid in cerebral ischemia. Abbreviations: FA, ferulic acid; PrX2, Peroxiredoxin 2; ROS, Reactive oxygen species; JNK, c-Jun N-terminal kinase; TLR-4, Toll-like receptor-4; MAPK, mitogen-activated protein kinase; ERK1, Extracellular signal-regulated kinase 1 ; BAX, bcl-2-like protein 4; Cyt c, cytochrome c; c-JUN, c-Jun N-terminal kinases ; AP1, Activator protein 1; MyD88, Myeloid differentiation primary response gene 88; IRAK, IL-1 Receptor-Associated Kinases ; TRAF6, TNF Receptor-Associated Factor 6; IKK, IκB Kinase; ICAM, Intercellular adhesion molecule-1; Keap1, Kelch ECH associating protein 1; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; ARE, antioxidant response element; HO-1, Heme oxygenase; PI3K, Phosphoinositide 3-kinases; AKT, Protein kinase B; GSK-3β, Glycogen synthase kinase 3; CRMP2, Collapsin response mediator protein 2; PARP, poly-ADP ribose polymerase; Cul3, Cullin 3; Maf, Musculoaponeurotic fibrosarcoma. Green arrow indicates stimulate/increase, red arrow indicates inhibition/decrease

However, Aβ $_{1-40}$ and $A\beta_{1-42}$ surge as well as Aβ deposits in Tg2576 mouse brains started at 12 months. Thus, these studies provided the direct evidence that oxidative stress precedes Aβ deposits and development of AD like symptoms [170–172].

In-silico studies have shown interaction of ferulic acid with Aβ deposits through hydrogen bonding, which causes hindrance in amyloid aggregation via interfering with the β sheets formation [173]. The structure-activity relationship studies demonstrated that ligands with particular orientation of the phenolic group towards aromatic residues of the Aβ peptide sequence would halt Aβ aggregation, which ferulic acid possesses [174]. These *in-silico* studies were further corroborated by in vitro studies where ferulic acid showed potent anti-amyloidogenic and fibril-destabilizing properties when exposed to $A\beta_{1-40}$ and $A\beta_{1-42}$ in neuronal cell culture [175]. Ferulic acid interacts with $A\beta_{1-40}$ in the initial phase of aggregation and intervenes with an Aβ assembly which results in the production of non-fibril amorphous deposits [176]. Another in vitro study also confirms the neuroprotective effect of ferulic acid on the neurons damaged due to oxidative stress and neurotoxicity triggered by abnormal accumulation of Aβ plaques [177].

Animal studies have also showed that ferulic acid treatment following $A\beta_{1-42}$ i.c.v injection significantly decreased oxidative stress, neuroinflammation and improved cognitive impairment [178, 179]. In another study, cognitive improvement with sodium ferulate (100, 200 mg/kg/daily) treatment was correlated with its antiapoptotic effects following $A\beta_{1-42}$ i.c.v injection. $A\beta_{1-42}$ increased pro-inflammatory cytokine (IL-1β) receptor protein levels and its mRNA expression in hippocampal tissue. The elevation of IL-1β in combination with enhanced activation of p38 MAP kinase and reduced activation of ERK1/2 and AKT/PKB, activates caspase-3 which executes apoptosis and cell death [180]. Sodium ferulate has also been reported to prevent Aβ-induced activation of apoptotic pathways by activating caspase-3 and inhibiting MKK3/MKK6-p38/MAPK-Hsp27 signal pathways [147]. Ferulic acid as an adjuvant therapy with epigallocatechin-3-gallate (EGCG) has also been found to ameliorate AD like symptoms [181].

The neurotherapeutic potential of ferulic acid to combat neurological disorders also captured considerable interest of pharmaceutical technologists and to further improve its cerebral delivery, scientists developed novel drug delivery systems such as nanoparticles. These novel drug delivery

formulations of ferulic acid showed enhanced efficacy tested in in vitro (neuronal culture) models of AD [182]. One such approach was to entrap ferulic acid into solid lipid nanoparticles (SLN) using microemulsion technique. The SLNs obtained employing this technique used lipid matrix Compritol 888 ATO which showed high loading capacity of ferulic acid and best characteristics in terms of size, polydispersity index, and drug release profile with no cytotoxic potential. Another study also used a similar approach and entrapped ferulic acid into SLNs. These studies showed that entrapped ferulic acid decreased ROS generation, restored mitochondrial membrane potential, reduced cytochrome c release and intrinsic pathway apoptosis activation more effectively than ferulic acid [183, 184]. Therefore, based on *in silico*, in vitro, and in vivo studies, it is suggestive that ferulic acid may develop as a novel therapy for treatment of AD. Pathological pathways responsible for AD and ameliorative effect of ferulic acid on these pathways are shown in Table 1; Fig. 4.

Ferulic Acid and Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder that leads to shaking, stiffness, and difficulty with walking, balance and coordination [185]. The major pathological hallmarks of PD are diminution of dopaminergic neurons in substantia nigra accompanied by the appearance of Lewy body [186]. PD is a multifactorial disease that also involves oxidative stress, neuroinflammation, and mitochondrial impairment [187].

Ferulic acid (50 mg/kg, i.p) has been reported to exhibit neuroprotection in the rotenone induced PD model through its antioxidant and anti-inflammatory properties [188]. Another study also showed antiparkinsonian effects of ferulic acid whereby its administration (40 mg/kg) significantly inhibited the microglial cell activation, altered the bax/bcl2 ratio (indicators of apoptosis and neuroinflammation), and prevented the cell death of dopaminergic neurons induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in C57BL/6J mice [189]. Lithospermum officinale (active constituent ferulic acid) (10 and 50 mg/kg) administered

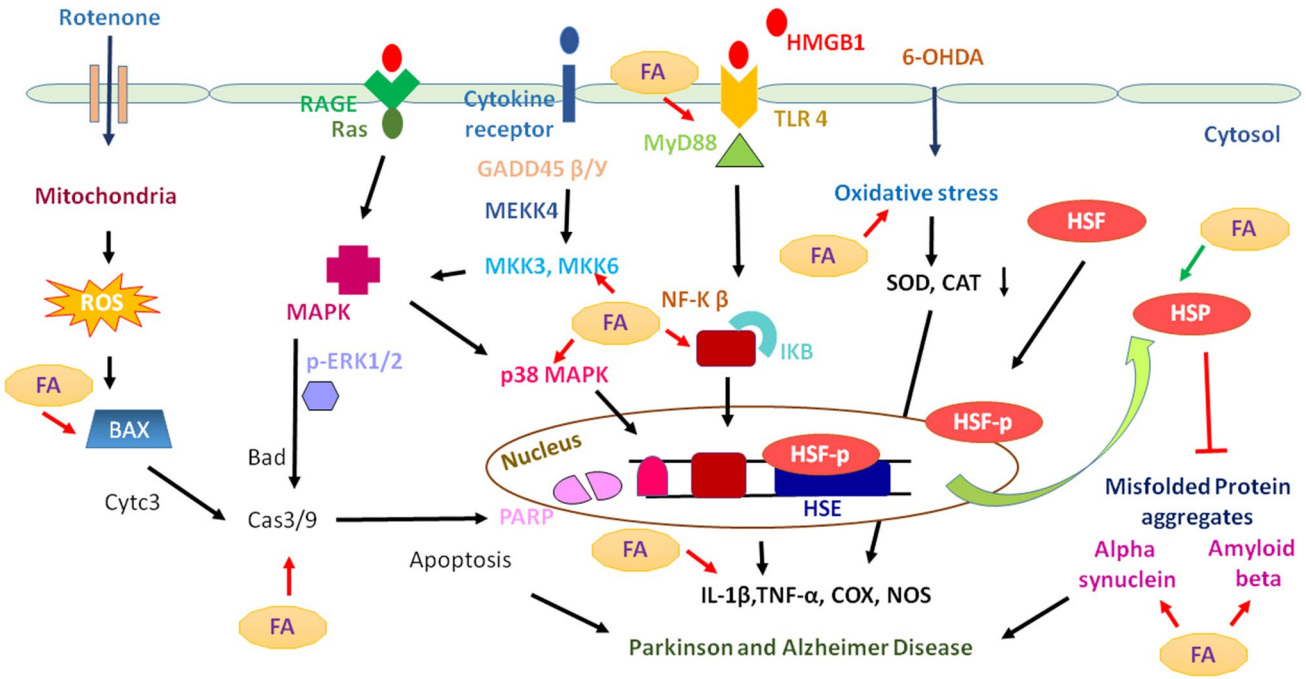

Fig. 4 Insights into the multi-target action of ferulic acid in in Alzheimer and Parkinson's disease. Abbreviations: FA, ferulic acid; ROS, Reactive oxygen species; BAX, Bcl-2-Associated X protein ; Cyt c, cytochrome c; Cas3/9, Caspase 3/9; PARP, Poly (ADP-ribose) polymerase; RAGE, Receptor for advanced glycation end-products; MAPK, mitogen-activated protein kinase; ERK1, Extracellular signal-regulated kinase 1; Bad, BCL2 associated agonist of cell death; MEKK4, Mitogen-activated protein kinase 4; MKK3/MKK6, Mitogen-activated protein kinase 3/6; GADD45, Growth arrest and DNA-damage-inducible protein; IL-1β, Interleukin-1β; COX-2, Cyclooxygenase-2; NOS, Nitric oxide synthase; TNF-α, Tumor Necrosis Factor Alpha; HMGB1, High mobility group box 1; TLR-4, Toll-like receptor 4; MyD88, Myeloid Differentiation Primary Response Gene 88; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; 6-OHDA, 6-hydroxydopamine; SOD, superoxide dismutase; CAT, catalase; HSF, Heat shock factors; HSE Heat Shock sequence Elements; MAPK, mitogen-activated protein kinase; ERK1, Extracellular signal-regulated kinase. Green arrow indicates stimulate/increase, red arrow indicates inhibition/decrease.

for 14 days, p.o. improved behavior deficits and reduced neuroinflammatory responses in the MPTP induced PD in mice [190]. Ferulic acid has also been reported to prevent α-synuclein aggregation in substantia nigra which is also a major neuropathological hallmark in PD [191].

Ferulic acid also showed antiparkinsonian effects by modulating levels of heat shock proteins (HSPs) in the rotenone induced PD rat model. It provided neuroprotection by significantly increasing tyrosine hydroxylase (rate limiting enzyme for dopamine synthesis) levels and heat shock protein (HSP70) expression in corpus striatum area of the brain. It is postulated that HSPs have an important role as protein folding machinery, which work with the ubiquitin-proteasome system (UPS) to decompose aberrant proteins. HSPs also possess anti-apoptotic effects and maintain the homeostasis of dopaminergic neurons against stress conditions [192–194].

Another interesting study has also reported anti-parkinsonian effect of γ-oryzanol (steryl triterpenyl esters of ferulic acid) in rotenone induced PD model in *Drosophila melanogaster*. In this study, flies (aged 1–5 days, both genders) exposed to rotenone for 7 days showed impaired motor function seen as elevated geotaxic response and decreased crossing numbers, mitochondrial dysfunction (decreased MTT reduction), decreased AChE activity, dopamine, SOD, CAT, and glutathione-S-transferase levels. Treatment with γ-oryzanol improved motor function as well as restored AChE, dopamine and other oxidative stress parameters [195]. This study suggested that γ-oryzanol due to presence of antioxidant constituents such as ferulic acid, was effective in reducing the rotenone induced toxicity in *D. melanogaster*. Thus, these studies strongly suggest the neurotherapeutic potentials of ferulic acid in management of PD. Nonetheless, cellular studies should be envisioned to unfold multiple neuroprotective mechanisms of ferulic acid before its development as anti-parkinsonian drug in clinics. The ameliorative effect of ferulic acid on major pathways involved in development of PD have been shown in Table 1; Fig. 4.

Conclusions

The present review provided evidence of neuroprotective effects of ferulic acid in a range of neurological disorders. The results cogently highlighted the pleiotropic modulatory effects of ferulic acid on multiple neuro-signaling pathways which may explain its neuroprotective actions. However, many questions need to be addressed before ferulic acid becomes a potential candidate for treatment of neurological disorders in clinical settings. Therefore, multiple preclinical, mechanism-based studies are to be conceived and performed to provide more detailed answers and clarify mechanisms through which ferulic acid would act for the management and treatment of various neurological disorders.

Compliance with Ethical Standards

Conflict of Interest No conflict of interest.

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