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REVIEW ARTICLE

Fisetin and Neurodegeneration: From Preclinical Studies to Potential Clinical Applications

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Abstract: Neurodegenerative diseases (NDs), like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis, pose significant challenges due to their gradual deterioration and limited available treatments. Fisetin, a naturally occurring flavonoid, has gained attention for its neuroprotective properties. This review explores the therapeutic potential of fisetin in NDs, focusing on its molecular processes and signaling pathways. Additionally, fisetin exhibits significant protective properties, particularly in reducing oxidative stress, neuroinflammation, and apoptosis. It enhances neuronal survival and reduces neuroinflammation by regulating key pathways, such as Nrf2/ARE, PI3K/Akt, and NF-κB. It also has anti-inflammatory, anti-apoptotic, and antioxidant actions. It stimulates autophagic processes, aiding in the removal of harmful protein aggregates, like tau tangles and amyloid plaques, which are hallmarks of NDs. Fisetin, as demonstrated through behavioral evaluations in animal models, has been found to improve motor coordination, synaptic plasticity, and cognitive function. Furthermore, fisetin's potential as a neuroprotective drug is emphasized by its role in enhancing autophagy and reducing tau and amyloid pathology. Research has shown its efficacy in enhancing neural resilience, synaptic plasticity, and cognitive function in both preclinical and *in vitro* settings. However, clinical translation remains limited due to challenges in pharmacokinetics and bioavailability, despite robust experimental evidence. Further clinical trials are needed to evaluate the safety and efficacy of fisetin, especially in early-stage NDs, explore potential synergistic effects, and understand the molecular interactions. The review demonstrates fisetin's therapeutic potential, recent research, and future strategies for NDs, highlighting bioavailability limitations and the need for new formulations or delivery systems.

Keywords: Fisetin, neuroprotection, neurodegenerative diseases, oxidative stress, signaling pathways, clinical studies.

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1. INTRODUCTION

The World Health Organization predicts a global increase in the percentage of individuals aged 60 and older from 11% to 22% by 2050, leading to a rise in age-related disease morbidity and mortality [1]. Neurodegenerative diseases (NDs) permanently cause a specific neuron to die, leading to progressive loss of brain function, primarily affecting the subcortical region, particularly the basal ganglia, and can affect older adults [2, 3]. There is no known cure or treatment for the most prevalent NDs, which include amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD). Common signs of these disorders include memory and cognitive impairments, and speech and movement difficulties [4, 5]. Neurodegeneration is triggered by protein accumulation, including huntingtin in HD, α-synuclein in PD, β-amyloid plaque and tau in AD, and FUS, SOD1, and TDP-43 in ALS. Neuronal dysfunctions and death during NDs are influenced by factors, such as proteotoxic stress, decreased system activity, mitochondrial dysfunction, glutamate toxicity, calcium load, neuroinflammation, and aging [6-8]. A study investigating fifteen NDs revealed stroke and other dementias as leading causes of death and disability-adjusted life years (DALYs). As people age, the prevalence of non-communicable brain diseases increases, posing challenges for global healthcare systems. NDs, complex and aging brain diseases, have no proven cures, making targeting a single pathophysiological alteration unlikely to prevent nerve cell damage and death. Clinical trials attempting to cure AD using single-target therapy candidates against the amyloid pathway have failed [9, 10]. Furthermore, individuals are likely to have varying contributions from various pathophysiological alterations. Modifications interact with genetic, environmental, and lifestyle risk factors, making medication combinations targeting multiple disease targets a strategic approach. However, this strategy faces potential issues, like pharmacokinetics and bioavailability issues, particularly in central nervous system (CNS) diseases, due to the BBB's inability to transport substances. Identifying small compounds with diverse biological activities that can impact brain pathophysiological changes leading to ND onset and progression is a superior strategy [11]. NDs are primarily caused by oxidative stress (OS) and mitochondrial dysfunction, where the electron transport chain is the primary site for metabolic reactions. When mitochondrial function is compromised, reactive oxygen species (ROS), like superoxide anion radicals, are produced in higher quantities [12]. Glutathione peroxidase (GPx) breaks down hydrogen peroxide, causing overproduction of ROS, leading to apoptosis, ATP loss, mitochondrial membrane potential drop, and cell death [13, 14]. ROS causes DNA damage, lipid peroxidation, and protein carbonyl molecule production, accelerating AD, PD, HD, and ALS, directly or indirectly [15]. Neuronal apoptosis and ferroptosis are key features of NDs, while DNA fragmentation in PD, AD, HD, and ALS was observed in human postmortem brain samples. Additionally, BclXL and caspases are implicated in AD pathophysiology, with caspase-6 being crucial in AD and HD pathophysiology, while caspase-7 is active in ALS mouse models. Apoptosis leads to neurodegeneration, and NDs cause cell cycle regulator protein aberrant expression and elevated p53 levels in motor neurons of the spinal cord and motor cortex [16]. Plants produce secondary metabolites, which are non-essential substances made from a few fundamental chemical scaffolds that have undergone specific substitutions. Theories suggest that substances, receptors, enzymes, and regulatory proteins may have co-evolved from a small number of ancestral molecules to interact [17]. Fisetin, a potent flavonoid found in various fruits and vegetables, like apples, grapes, kiwis, strawberries, onions, persimmons, and cucumbers, is a well-known and powerful antioxidant. It has strong pharmacological activities against various diseases, including cancer, OS, inflammatory bowel disease, and cognitive/synaptic dysfunctions [18-20]. Ahmad *et al*. found the neuroprotective impact of fisetin on AD using the Aβ1-42 mouse model. It reduces neurodegeneration, neuroinflammation, and memory/synaptic impairments caused by Aβ1-42 injections. It also reverses synaptic dysfunction by raising protein levels and improving memory. It increases the expression of p-PI3K, p-Akt, and p-GSK3β in mice treated with Aβ1-42, inhibiting gliosis and neuroinflammatory mediators [21]. Moreover, Ahmad *et al*. investigated the neuroprotective and antioxidant properties of fisetin in adult mice. They found that fisetin-activated phosphorylated c-JUN N-terminal kinase reversed enhanced ROS/OS caused by LPS, reduced activated gliosis, reduced inflammatory mediators, and enhanced hippocampus-dependent synaptic and memory functions. It also reversed LPS-induced apoptotic neurodegeneration [22]. Furthermore, fisetin can reduce neurodegeneration and inflammation in rats induced by aluminium chloride, thereby reducing the expression of GFAP and IBA1 markers and lipid peroxidation [23]. To ensure the inclusion of the most appropriate articles in this review, an in-depth search was carried out on prominent medical, biological, and chemical databases, including Scopus, PubMed, and Web of Science. The search used the primary keywords listed below: "Fiscetin, neuroprotection, neurodegeneration." Furthermore, the secondary keywords used were "Oxidative stress, clinical studies. Research reports, review articles, and original research articles in English published up to October 2025 were selected and evaluated. This review demonstrates the therapeutic potential of fisetin in NDs, highlighting its protective properties, particularly in reducing oxidative stress, neuroinflammation, and apoptosis through molecular processes and signaling pathways.

2. METABOLISM OF FISETIN

The earliest documentation of fisetin as an isolated compound from Venetian sumach (*Rhus cotinus* L.) dates back to 1833. Schmidt [24] provided fundamental chemical properties of the molecule many years later, while S. Kostanecki explained its structure and ultimately validated it through synthesis. In the 1890s, Kostanecki *et al*. initiated an extensive investigation of yellow pigments from plants and introduced new nomenclature for their subcategories, now recognized as “flavones”, “chromones”, “chalcones”, and others [25]. Fisetin has been identified as a secondary metabolite present in various plants, found in their green tissues, barks, hardwood, and fruits [26-29]. Roux studied oligomeric tannins, including flavon-3-olic structures linked to fisetin, fisetidinol, fustin, and similar structures in African arboreal species before spectral structural analysis tools emerged

[30-33]. Flavonoids undergo substantial metabolism after oral ingestion, yielding glucuronidated, sulfated, and methylated metabolites [34, 35]. The metabolic processes of fisetin were initially described in rats after oral and intravenous treatment [36]. A study found that after both injection methods, unbound fisetin concentrations decreased, while glucuronidated/sulfated fisetin concentrations increased. Oral treatment of 50 mg/kg body weight sustained fisetin sulfates and glucuronides levels for over 24 hours. These findings contrast with those for 5 OH and 7 OH flavones [36] and baicalein [37], where the concentrations of unconstrained and attached flavonoids have never surpassed 1 μM after oral delivery. In an analysis evaluating antioxidant effectiveness, the fisetin sulfates/glucuronides exhibited moderately reduced yet still notable activity relative to free fisetin [36]. A study found that glucuronidation affects flavonoids' ability to protect lymphoid and neuronal cells from OS-related apoptosis [38]. Flavonoid glucuronides show high EC50 values, but demonstrate remarkable efficacy. Systemic flavonoid sulfates and glucuronides can be converted to tissue-specific forms through enzymatic conversion [35]. Moreover, sulfated flavonoids exhibit biological action [39]. In mice, after intravenous treatment of fisetin at 223 mg/kg body weight, free fisetin was observed in the serum for multiple hours (t1/2=3.12 hours). A study on fisetin, a drug used in treating lung cancer, found that it had a peak concentration of 2.5 μg/ml at 15 minutes after an effective dose of 223 mg/kg. The plasma concentration decreased biphasically, with a quick half-life of 0.09 hours and a terminal half-life of 3.1 hours. Three metabolites were identified: one glucuronide of fisetin, another glucuronide, and a previously unidentified fisetin metabolite. Fisetin metabolite was identified as a methoxylated metabolite of fisetin, which was found to be more potent than fisetin in Lewis's lung cancers. Geraldol, a metabolite of fisetin, showed greater cytotoxicity toward tumor cells and inhibited endothelial cell migration and proliferation [40]. Jo *et al*. quantified geraldol and fisetin levels in mouse plasma using LC-MS/MS after protein precipitation. The concentrations were established after administering fisetin at intravenous doses of 2 mg/kg and oral doses of 100 and 200 mg/kg, respectively. The pharmacokinetic characteristics of fisetin and geraldol were assessed utilizing an approved procedure in mice. Fisetin was quickly methylated to geraldol *in vivo*, with geraldol exceeding fisetin's C_{max} and AUC values. The absolute bioavailability of fisetin was 7.8% and 31.7% following oral dosing [41].

3. FISETIN AND ITS PHARMACOLOGICAL PROPERTIES

The FDA has approved certain cholinesterase inhibitors and memantine as therapeutic drugs to improve cognitive symptoms of AD without affecting its progression, while research continues to identify effective pharmaceuticals [42]. A multitude of natural compounds have preventive or curative benefits on NDs through pharmaceutical effects, including neurofunctional modulation, antioxidant properties, anti-apoptotic effects, anti-inflammatory actions, and calcium antagonism [43-45]. Fisetin is classified as a flavonoid under the category of polyphenolic chemicals. Flavonoids are plant pigments with a wide pharmacological range, serving as anti-inflammatory substances, antiviral agents, antioxidants, anticarcinogens, antibacterial compounds, neurotrophic factors, neuroprotective agents, and immunological stimulants [3]. Numerous fruits, such as cucumbers, lotus root, apples, grapes, kiwis, peaches, strawberries, and persimmons, contain fisetin [46, 47]. Fisetin, an anti-inflammatory and antioxidant substance, has demonstrated the ability to be beneficial in treating neurological health issues and NDs [48]. A study [49] demonstrated that fisetin reduced inflammation, OS, and senescent cells in SAMP 8 mice with accelerated aging. Fisetin plays a role in nerve cell differentiation [50], activating the Ras-ERK pathway in rat embryonic origin NGF-expressing PC-12 cells, despite OS reducing antioxidant reduced-glutathione levels [51]. This syndrome is prevalent in the aging brain [52]. A substantial body of evidence substantiates fisetin's role as a defensive agent as opposed to NDs [53]. Reduction of GSH exacerbates mitochondrial dysfunction, enhances ROS generation, activates lipoxygenase, promotes lipid peroxidation, and increases calcium influx, culminating in cell death [51, 54]. Fisetin (Fig. **1**) recovers mitochondrial activity, enhances metabolic processes, mitigates OS, and scavenges ROS. It demonstrates immediate antioxidative action while also enhancing intracellular antioxidants, like glutathione [55]. Furthermore, fisetin modulates essential neurotrophic factor-mediated signaling pathways, inhibiting cellular death induced by oxytosis/ferroptosis [48, 54, 56]. Furthermore, fisetin inhibits lipid peroxidation and enhances the antiapoptotic protein Bcl2 [3]. Fisetin inhibits neuronal apoptosis induced by OS. It protects HT-22 cells (derived from CNS neurons) and rat primary neurons from hypoglycemia and glutamate neurotoxicity. It also elevates reduced GSH levels and scavenges ROS, hence preventing hydrogen peroxide (H_2O_2)-induced neuronal death [56]. Chronic inflammation exacerbates the chance of neural injury. Fisetin enhances TrkB, ERK, and PI3K-Akt signaling pathways in depression treatment, while inhibiting inflammatory agent production [57, 58]. Fisetin reinstates proteasome activity in NDs [59]. Additionally, fisetin enhances dementia related to NDs, cognitive processes, and behavioral disorders with advancing age [3, 48, 60, 61]. NF-κB stimulates pro-inflammatory mediators, like COXs, while fisetin has anti-inflammatory properties and inhibits chronic inflammation [62]. Fisetin suppresses the production of cyclooxygenase enzymes, 12-lipoxygenase (12-LOX), and obstructs the production of prostaglandins and leukotrienes [63]. Moreover, fisetin inhibits D-galactose-induced OS neurological inflammation and neuronal degeneration. It enhances PSD-95, SNAP-25, and SIRT1/Nrf2 levels. Conversely, it also reduces Bax levels, activation of caspase-3, and p-JNK/NF-κB action [64]. Fisetin inhibits the functions of TAK1, RIP, IKK, NF-κB, IκBα, Syk, and Src [65]. Furthermore, fisetin enhances the synthesis of cytokine IL-10, which is anti-inflammatory. A study [66] indicated that fisetin enhanced the activity of the Nrf2-ARE for neuroprotection. It stimulated the production of Nrf2 *via* the activation of the transcription factor 4 gene, leading to an increase in GSH levels [67]. NF-κB disrupts the function of Nrf2. Under typical physiological circumstances, an equilibrium is preserved among the activities of Nrf2 and NF-κB. This equilibrium is broken with advancing age. Fisetin suppresses activation of NF-κB and enhances Nrf2 function to avert the degeneration

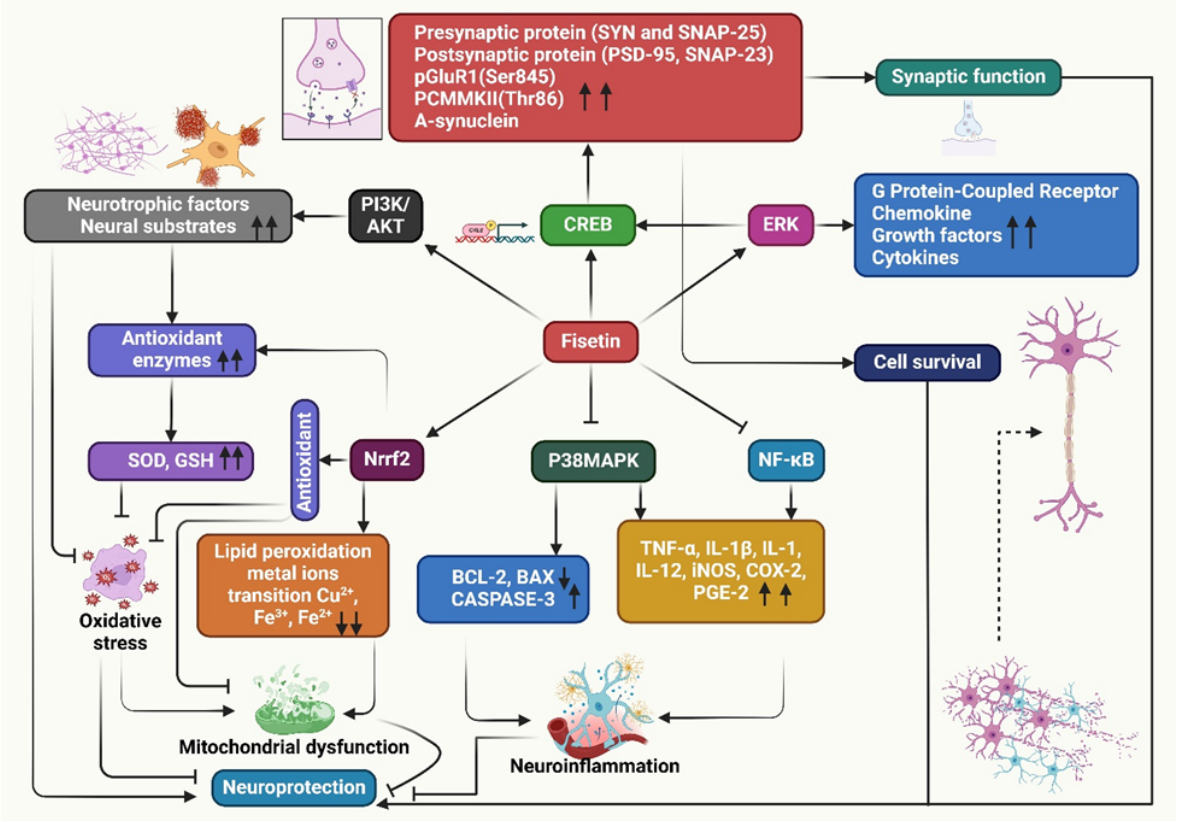

Fig. (1). Fisetin targets neuroinflammation and mitochondrial dysfunction, improving neuron energy generation and controlling OS. The figure was designed by Biorender.com program (https://biorender.com). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

of neurons [68]. The Keap 1-Nrf2-ARE pathway regulates redox signaling by regulating the production of cytoprotective proteins and antioxidative enzymes to maintain redox equilibrium [69, 70]. Under typical circumstances, Keap1-facilitated proteasomal degradation of Nrf2 inhibits the excessive production of antioxidative enzymes. OS, however, releases Nrf2 from the Keap1 complex, allowing its translocation to the nucleus where it attaches to ARE to promote the production of antioxidative enzymes [69, 71]. Fisetin inhibits Nrf2 degradation and elevates its levels, hence enhancing antioxidant gene transcription regulated by ARE [3, 72, 73].

4. IMPACT OF FISETIN IN NEURODEGENERATION

Fisetin has demonstrated advantageous results in preclinical studies of various NDs, including ALS, HD, AD, PD, schizophrenia, stroke, vascular dementia, traumatic brain injury (TBI), diabetic neuropathy, and depression. Fisetin's medicinal actions stem from its influence on various ND pathways, and its recognized anti-inflammatory and antioxidant properties [48]. The intricacy of NDs and the importance of fisetin in their treatment are shown *via* AD as a prime example. AD is characterized by progressive cognitive impairment, particularly memory decline (dementia), accompanied by alterations in behavior and personality. The defining characteristic of AD is the accumulation and excessive synthesis of Aβ peptides in neurons, leading to neuroinflammation and synaptic impairment. The study links the malfunctioning of multiple cellular pathways to the pathology of AD, despite the conventional belief that Aβ plaques and tau tangles are the main cause. The development of drug molecules that can address multiple aberrations and modulate biological pathways is crucial for superior health effects compared to single-path or specific protein-targeted medicinal products [74]. Golde *et al*. found that clinical studies for single-target medications to treat AD have shown disappointing outcomes [75]. Research focuses on specific target proteins, leading to the development of a substituting method using therapeutic molecules to target multiple molecular pathways linked to AD [76]. Fisetin is more effective in performing its function, as it can target multiple proteins and pathways [60, 61]. The anti-inflammatory attributes of fisetin have been demonstrated in both *in vivo* and *in vitro* studies [77] by the suppression of Aβ fibril aggregation [78]. Age is a substantial warning sign for multiple NDs, and the prevalence of behavioral and cognitive impairments often correlates with advancing age. Age-associated degenerative alterations in the brain are very intricate, necessitating the simultaneous treatment of various disorders. Fisetin is a suitable treatment for various age-related anomalies due to its targeting of various pathways. Its significance lies in the treatment of age-related diseases, including dementia and cognitive impairments [48, 60, 61]. An experimental study indicated decreased inflammation, OS, and senescent cells in the premature, rapidly aging SAMP8 mouse treated with fisetin [49, 79]. Fisetin possesses neuroprotective and cognitive-improving attributes, with the capacity to mitigate age-associated impairments and cognitive decline [58, 60, 62,

77, 78]. Chronic inflammation, resulting from a dysregulated immune response, is the fundamental cause of many brain injuries and NDs. Fisetin's potent anti-inflammatory properties make it a significant tool in treating multiple chronic diseases and preventing chronic inflammation [62]. Fisetin is utilized in treating depression induced by LPS *via* enhancing TrkB/BDNF, PI3K-Akt, and ERK signaling pathways, while simultaneously suppressing inflammatory mediator production [57, 58, 80]. Fisetin plays a crucial role in reducing age-related ailments by regulating redox homeostasis, activating neurotrophic factor signaling pathways, reducing inflammation, enhancing cognition, and modulating proteasome activity. Nutraceutical firms in the US are promoting fisetin in capsule form or alongside other natural substances to enhance its benefits. Fisetin enhances cognitive function, maintains brain health, and facilitates appropriate aging [81].

5. NEUROPROTECTIVE EFFECT OF FISETIN

5.1. Fisetin and Antioxidative Stress

OS is characterized by an imbalance among the levels of oxidants and their removal by defensive processes, like antioxidants. A disparity between ROS and antioxidants leads to a mismatch between antioxidant defense and OS [82]. When the production of oxidants surpasses the capability of antioxidants, damage to vital biomolecules, including nucleotides, proteins, carbohydrates, and organs, may occur, potentially affecting the whole organism. ROS, as primary oxidant molecular derivatives, encompass hydroxyl radicals, superoxide, and hydrogen peroxide [55]. ROS may originate from several external or endogenous sources. The external generation of ROS may result from chemicals, UV light, and environmental pollutants [83]. The CNS is particularly susceptible to OS due to its limited redox homeostatic range. The normal level of ROS is crucial for maintaining cellular redox equilibrium and regulating cell growth and certain signaling pathways. Overproduction of ROS can lead to various cellular malfunctions, harmful inflammatory responses, and ultimately, cell death. Occasionally, neurotransmitters and excitatory amino acids function as generators of ROS, notably in the brain, resulting in damage [84]. ROS can lead to protein oxidation and lipid peroxidation, ultimately causing neuronal death [85]. Hydroperoxides and lipid peroxides exacerbate the oxidative cascade by producing more persistent and permeable harmful byproducts, including malondialdehyde [86]. Consequently, this sequence of oxidative damage intensifies the effects on the body and its tissues. Similarly, ROS and lipid peroxides have been linked to the gradual development of numerous brain injuries, including epilepsy and NDs [86]. Glutathione (GSH) and its related metabolism are the primary defense against OS. GSH may neutralize electrophilic chemicals and free radicals [67]. Moreover, GSH is essential for preserving redox equilibrium, modulating certain enzyme functions, facilitating cysteine transport and storage, and mediating cellular communication [87]. OS is a significant pathogenic mechanism in NDs. Disease situations culminate in heightened production of ROS and ensuing oxidative injury. Research signifies that fisetin (Fig. **2**) has immediate antioxidant properties, shown by a substantial decrease in ROS generation in cells and elevated intracellular concentrations of GSH. The anti-oxidant properties of fisetin are associated with its composition, pH level, and interaction with the cell membranes [55]. GSH production relies on the activity of glutamate-cysteine ligase (GCL) and the availability of cysteine [88]. GCL comprises a modifier subunit (GCLM) and a catalytic subunit (GCLC) [68]. Fisetin is known to stimulate GCLM and GCLC expression [89]. Additionally, fisetin (10 μM) inhibited the reduction of two GCL subunits in primary rat neurons caused by SIN-1 peroxynitrite donor [90]. Liu *et al*. found that fisetin's antioxidative activity arises from the augmentation of GSH synthesis, hence suppressing oxidative formation. The xCT, a cystine/glutamate antiporter, is a member of the solute carrier family 7 that aids in cystine absorption and glutathione production, thus protecting OS [91]. Moreover, Yen *et al*. demonstrated that fisetin (5-20 μM) may alleviate PC12 cell death induced by tunicamycin *via* scavenging ROS by the excessive expression of xCT [89]. Another study on the management of NDs revealed that in an iron-induced epilepsy model, a 12-week preliminary therapy with fisetin (20 mg/kg) reduced MDA production, indicative of lipid peroxide formation, and preserved Na^+, K^+-ATPase activity within the hippocampus and cerebral cortex of rats [86]. Fisetin administration significantly attenuated GSH depletion and restored SOD and GPx activities in the cortex and hippocampus of amnesic animals and scopolamine-treated mice [92]. Similarly, fisetin (10 and 50 mg/kg bw) reduced levels of lipid peroxidation and protein carbonyls while maintaining NO and GSH levels in the brain areas of pups from mothers exposed to MeHg [93]. Meanwhile, fisetin may enhance the activity of SOD, catalase, GPx, and glutathione-S-transferase, reduce glutathione reductase activity, and maintain protein thiol and total thiol levels in brain areas [93], demonstrating fisetin's antioxidative properties in the management of NDs. A further intriguing investigation on TBI revealed that fisetin treatment significantly decreased MDA levels and restored the oxidation-antioxidation equilibrium [66], thus reducing the progression of neurotrauma. Fisetin's antioxidative properties were demonstrated in a rat model induced by D-galactose, reducing ROS, lipid hydroperoxidation, protein carbonyls, intracellular calcium ions, nitric oxide, and advanced oxidation protein products [94]. Fisetin protects against oxidation-induced brain degeneration and inhibits 6-OHDA-induced upregulation of OS-related genes [95], suggesting that fisetin's antioxidant properties may be essential for neuroprotection.

5.2. Fisetin and Neuroinflammation

A multitude of NDs, like AD, PD, and HD, are well recognized as complex and varied in their pathophysiology [96]. Neuroinflammation is often the cause of many NDs across various brain areas, despite their unique clinical traits and varied etiologies. It is a significant factor contributing to the progression of the aforementioned diseases. It is also triggered by various stressors, including trauma, cancer, hyperphosphorylated tau, Aβ protein, and degeneration, and may also be a response to initial CNS injuries [85, 97]. Most NDs are primarily linked to neuroinflammation, regardless of whether they are chronic or acute. The neuroinflammatory process can lead to the elimination of necrotic cells and tissues caused by infections [98]. Inflammation of neurons

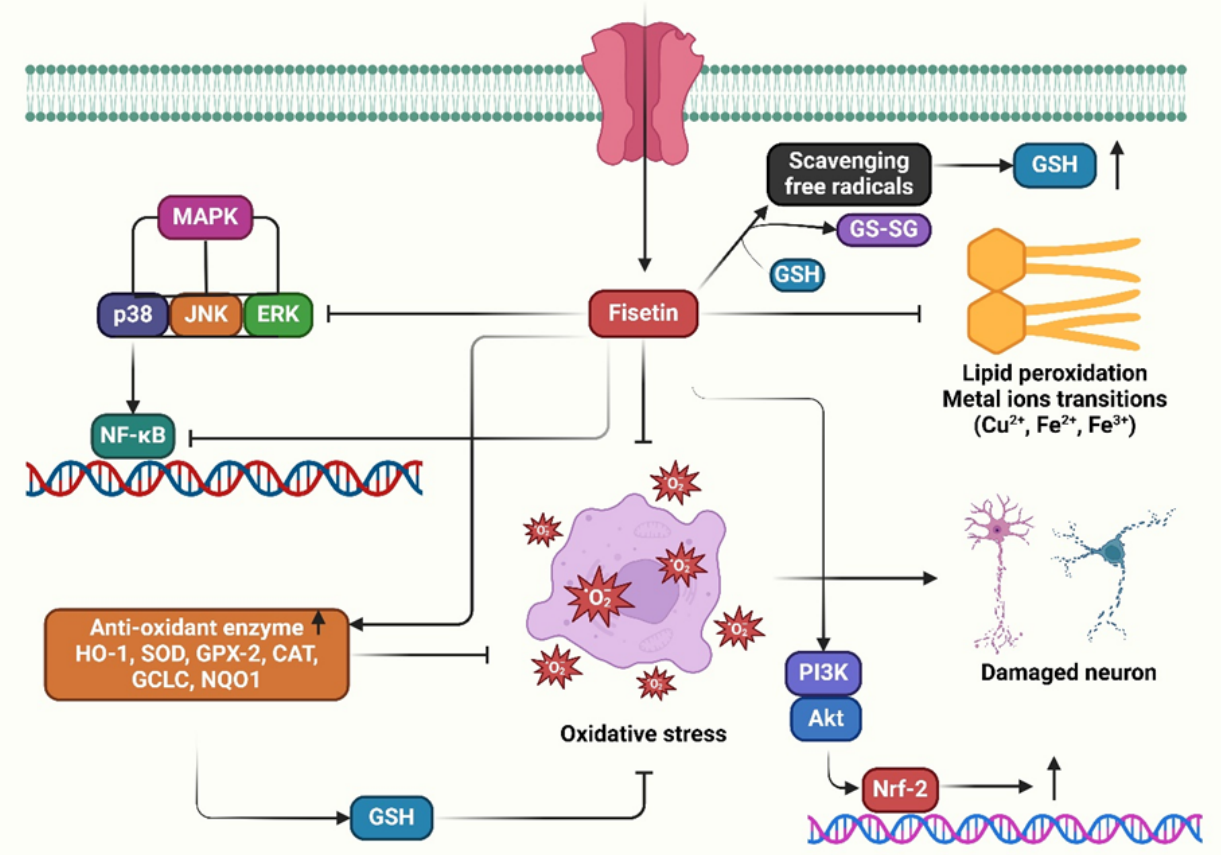

Fig. (2). Fisetin neutralizes ROS, reducing OS and contributing to reduced damage associated with aging and NDs. The figure was designed by Biorender.com program (https://biorender.com). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

is a dual-faceted phenomenon, essential for healing from several disorders but also contributing to disease progression [96]. CNS inflammation is likely triggered by the interaction of microglial cells, oligodendrocytes, astrocytes, myeloid cells, the BBB, and signaling molecules from both peripheral and central systems [99]. Ahmad *et al*. investigated the preventive properties of fisetin against OS produced by D-galactose, neurological inflammation, and cognitive deficits in mice. D-gal increases OS, neuroinflammation, synaptic dysfunction, and cognitive dysfunction. Fisetin inhibits D-gal-induced ROS buildup by modulating endogenous antioxidant mechanisms, including Sirt1/Nrf2 signaling, and suppressing the activated p-JNK/NF-κB pathway and its downstream targets [64].

5.3. Fisetin and Cyclin-dependent Kinase 5 (Cdk5)

Cyclin-dependent kinase-5 (CDK5) is a key player in the nervous system, essential for neuronal development [100]. Cdk5 is a useful serine/threonine protein kinase that regulates several physiological mechanisms, encompassing neuronal viability, migration, synaptic plasticity, synaptogenesis, differentiation, and neural transmission [101]. Cdk5 is crucial in several prevalent NDs [102], epilepsy, pathological pain, anxiety, depression, and stroke [103]. Cdk5 may be inappropriately activated in diseased states, like neurotoxic injury and NDs, contributing to the onset and progression of various NDs [104]. Normal Cdk5 activity is primarily given by its interaction with the principal activator, p35 [105]. In neurotoxic situations, p35 is cleaved proteolytically to p25, which is associated with many NDs. Subsequently, p25 emerges as a powerful and Cdk5 mislocalized hyperactivator, leading to a dysregulation of Cdk5 functionality [105]. The p25 accumulation is a pathogenic component in AD, leading to phosphorylated tau, neurofibrillary tangles, and cognitive impairments, all hallmarks of AD [105]. Fisetin reduces the concentration of Cdk5, specifically the p35 cleavage product p25, in the brains of APPswe/PS1dE9 transgenic AD mice [61, 106, 107], therefore resulting in the suppression of neurodegeneration [61].

5.4. Fisetin and Apoptosis

Apoptosis, commonly known as programmed cell death, is an extensively conserved biological process. It is essential in several pathological and physiological processes, including homeostasis, tissue and organ growth, degeneration of cells, and immunological response [108]. Apoptosis is a complex process triggered by microenvironment disturbances, involving initiator and executioner caspases, which are activated through various routes [109]. Furthermore, the antiapoptotic Bcl-family regulatory proteins, together with the proapoptotic modulators Bax and p53, are crucial in the initiation of apoptotic processes. Consequently, modulating the intrinsic endogenous protective signaling pathways may be beneficial for the avoidance and management of NDs.

Fisetin reduces the proportion of the pro-apoptotic Bax protein to the anti-apoptotic Bcl-2 protein in SH-SY5Y cells [95]. Furthermore, fisetin substantially inhibited the 6-OHDA-induced initiation of caspase-3 and -9, leading to cellular apoptosis. Simultaneously, the activity of caspase-3/7, increased by 6-OHDA, was diminished [95], demonstrating the neurologically protective effects of fisetin against 6-OHDA-induced apoptosis. Fisetin reversed the elevation of caspase-3 and Bax expression and the decreased expression of Bcl-2 induced by Pb in the mouse cerebrum [110]. Fisetin significantly elevated Bcl-2 expression while decreasing expression of caspase-3 and Bax after traumatic brain injury, therefore inhibiting neural cell demise and apoptosis [66]. Furthermore, fisetin reduced Aβ accumulation, ASK-1, phosphorylated JNK, p53, cytochrome C, and the protein expressions of caspase-9 and caspase-3, while also modulating the Bax/Bcl-2 ratio in rats induced with AlCl3 [111]. In glioma, fisetin enhances the production of caspase-3, -9, -8, and Bax at dosages of 25 and 50 μM, while decreasing the levels of Bcl-2 and survivin in T98G cells [112]. A study investigated the biological actions of seven structurally comparable flavonoids on the human leukemia cell line HL-60. Wogonin and fisetin were found to be the most potent inducers of cell death, with cytotoxic effects linked to apoptotic features, like apoptotic bodies and DNA fragmentation. These activate caspase 3/CPP32 activity, cleave PARP, reduce pro-caspase 3 protein levels, elevate pro-apoptotic protein bax, and decrease anti-apoptotic protein Mcl-1. However, Bcl-2, Bcl-XL, and Bad showed no alterations in HL-60 cells treated with wogonin and fisetin. Wogonin and fisetin significantly increased endonuclease activity in HL-60 cells, while EDTA and EGTA inhibited activation. Ac-DEVD-CHO mitigated DNA ladders, endonuclease activation, and PARP cleavage. Pretreatment with N-acetyl-cysteine or catalase suppressed apoptosis [113].

5.5. Abnormal Protein Accumulation and Fisetin and Proteasome Function

Neuronal death in NDs is often associated with misfolded proteins that accumulate in the brain due to genetic mutations or disrupted protein homeostasis. Aging often leads to metabolic changes, including reduced proteasome degradation and autophagy, increased neurotoxic protein aggregates, like Aβ and tau α, and loss of synaptic nucleoproteins [114]. The ubiquitin-proteasome system and the autophagy-lysosome route are the primary degradation mechanisms that remove undesired or misfolded proteins from cells, therefore preventing buildup and preserving cellular health [114]. A prior investigation indicated that cells expressing mutant huntingtin exhibited a significant reduction in caspase and chymotrypsin-like activity [115]. The activity of trypsin-like enzymes was similarly decreased in the gray and white matter of people with MS, alongside the activities of chymotrypsin and caspase-like enzymes [116]. Fisetin enhances the proteasome's chymotrypsin-like function in primary cortical neurons [117]. Subsequent research with the HT22 nerve cell line showed that fisetin enhancef proteasome activity in a manner dependent on time and dosage [60]. Aβ accumulation and elevated amounts of hyperphosphorylated tau protein are prevalent characteristics of AD [118]. Neprilysin, a major endogenous catabolic enzyme responsible for Aβ degradation, enhances Aβ clearance and mitigates Alzheimer's disease pathology [119]. Fisetin reduces the accumulation of phosphorylated tau and Aβ while enhancing the production of neprilysin in the brain [110]. The biochemical function of fisetin is achieved by inhibiting the production of β-strands and its interaction with the tau K18 protein [120]. The deterioration of AchE and BACE1 and the interrelation between Aβ and ABAD are critical elements that intensify the degenerative progression of AD [121]. Fisetin, a drug that disrupts the binding capacity of certain proteins, is expected to be effective in treating AD [121]. Additionally, fisetin reduces cytotoxicity and cell mortality caused by MPTP/MPP+ by decreasing α-Syn expression [122]. Furthermore, fisetin significantly reduced the number and size of α-Syn inclusions in an α-Syn accumulation yeast model [123]. Fisetin's hydrophobic interactions with α-Syn can enhance its stability, increasing its inhibitory efficacy against fibrillation of α-Syn [124]. The mutated huntingtin protein disrupts crucial cellular functions, like mitochondrial activity, transcription, and protein synthesis, leading to cell death [125]. Fisetin administration significantly reduced the production of mutated huntingtin protein in PC12 cells, leading to improved cell survival (Table **1**) [126].

5.6. Fisetin and Mitochondrial Function

Mitochondria are essential for cellular survival and apoptosis. Mitochondrial dysfunction is a significant pathogenic factor in the development of various NDs. The preservation of mitochondrial activity in response to various stressors has been recognized as the most efficacious treatment approach to mitigate the progression of NDs. A decrease in mitochondrial membrane potential, a key regulator of mitochondrial permeability, leads to the loss of membrane integrity and subsequently activates apoptotic pathways. Fisetin reduces depolarization in brain cells of aging rats, helping to mitigate the decline in mitochondrial membrane potential [94]. Fisetin enhances the action of mitochondrial enzymes [127], demonstrating the protective effects of fisetin on mitochondrial activity. Fisetin, when administered orally, can restore brain NADH-dehydrogenase, mitochondrial succinate dehydrogenase, mitochondrial MTT (complex-III), and mitochondrial cytochrome oxidase levels in rats with chronic moderate hyperhomocysteinemia [128]. Jacob and Thangarajan demonstrated that oral treatment of fisetin (30 mg/kg) substantially reduced mitochondrial swelling induced by MeHg and decreased mitochondrial electron transport chain activity in the rat hippocampus [129]. Moreover, Ding *et al*. investigated the anticancer effects of fisetin and its impact on pancreatic ductal adenocarcinoma (PDAC). They used various methodologies, including proteomics, transcriptomics, and metabolomics investigations. It also impaired mitochondrial homeostasis and triggered SOD2 acetylation in PDAC. It suppressed SIRT2 expression, obstructing SOD2 deacetylation. Overexpression of SIRT2 may obstruct fisetin's SOD2 production. Furthermore, fisetin enhances folate metabolism, suggesting that it may be a potential therapy for PDAC [130].

6. FISETIN AND NEURODEGENERATIVE DISEASES

NDs are costly and impact patients' quality of life. Each disease has unique clinical features and molecular mechanisms, making it difficult to treat them using a single method. Therefore, multitherapeutic targeting is crucial to address brain dysfunction. Fisetin has been identified as a promising neuroprotective agent for treating NDs. It promotes brain protection and reverses cognitive impairments due to its biological functions and treatment processes linked to different NDs. Thus, a multitherapeutic approach is essential for effective neurological treatment [131]. Fisetin has been discovered as a neuroprotective and cognition-enhancing chemical. It can raise glutathione levels, activate neurotrophic factor signaling pathways, inhibit lipoxygenases, and have anti-inflammatory properties against microglial cells. Fisetin's diverse effects may help reduce the negative effects of age-related NDs on brain function [81].

6.1. Fisetin and Parkinson's Disease

PD is an ND caused by the deterioration of dopaminergic neurons in the midbrain. It initially manifests as a mobility disorder, but cognitive and behavioral issues emerge later. Current treatments only delay or alleviate motor symptoms, and no medications exist to inhibit nerve cell degeneration or cure the condition. NDs are increasingly recognized as multifactorial, involving disturbances in various cellular systems. Flavonoids have various biological functions that may help treat PD. The study explores the potential benefits of flavonoids and fisetin in PD models, suggesting they could potentially reduce the disease's impact on cognitive function [132]. The essential symptoms of PD involve bradykinesia, resting tremors, stiffness, and postural instability. PD is also linked to other non-motor symptoms that exacerbate impairment. Most incidences of PD are sporadic, with only around 10% of individuals indicating a familial history of the condition [133]. Similar to AD, age is the primary risk determinant for the onset of the condition. The pathogenic characteristic of PD is that dopaminergic neurons in the SNc are degenerated [134]. Animal models of PD often involve exposure to a toxin, such as a pesticide or other hazardous substance linked to the disease *in vivo*. A prevalent model uses the toxin MPTP, whereas chronic, low-dose injections of the herbicide rotenone are increasingly favored [135, 136]. Fisetin was recently evaluated in a chronic, low-dose rotenone model in rats, administered orally at 10 and 20 mg/kg bw/day, initiated 10 days after rotenone therapy, and maintained through the end of the treatment [127].

6.2. Fisetin and Amyotrophic Lateral Sclerosis

ALS is a terminal ND distinguished by the degradation of motor neurons responsible for the volitional movement of the muscles, leading to immobility and mortality, often within five years following discovery [137]. About 10% of ALS cases are caused by hereditary gene mutations, but other mutations are increasingly identified in patients without a familial history [138]. The predominant animal model for ALS is derived from mutations in the Cu/Zn SOD1 gene, the initially recognized genetic alteration linked to the disease [138]. The SOD1-G93A transgenic mouse model revealed SOD1 mutations in 20% of ALS patients, characterized by motor neuron degradation, progressive paralysis, and decreased longevity [138]. The oral dose of fisetin (9 mg/kg/day) commencing at the age of two months markedly postponed the onset of motor impairments, decreased their progression rate, and extended longevity [139] in the SOD1-G93A mouse model. This corresponded with a substantial rise in the motor neuron population inside the spinal cord. Fisetin significantly increased ERK phosphorylation and antioxidant protein heme oxygenase 1 levels in a transgenic AD model, enhancing ERK activation at the molecular level [61] and in HD flies [126], indicating that this mechanism may partially underlie its advantageous benefits in these several ND models. A study exploring the potential effects of fisetin on ALS is linked to a mutation in the copper/zinc SOD1 gene. Fisetin prevents cells from damage by ROS and ameliorates the pathogenic effects induced by OS in disease models associated with SOD1 gene mutations, likely through the activation of ERK, thus providing a potential therapy for ALS (Table **1**) [139].

6.3. Fisetin and Alzheimer's Disease and Dementia

AD is a progressive ND distinguished by cognitive deterioration due to the aggregation of Aβ plaques and tau neurofibrillary tangles. Fisetin can inhibit Aβ aggregation, enhance peptide clearance, and reduce tau hyperphosphorylation. It improves synaptic plasticity and cognitive function by regulating critical signaling pathways. Preclinical studies show fisetin's effectiveness in reducing pathology, improving cognitive performance, and reducing OS and neuroinflammation. However, extensive clinical trials, molecular investigations, combination treatment assessments, and personalized medicine strategies are needed to fully utilize fisetin's therapeutic potential [140]. AD is the predominant form of dementia. Pathologically, it is defined by the existence of extracellular neuritic plaques composed of Aβ peptide and intracellular neurofibrillary tangles containing tau [141]. AD leads to a gradual decline in cognitive function and ultimately impairs everyday activities [142, 143]. Current treatments are symptomatic, providing mild memory enhancements without altering the pathology of the disease [144, 145]. Recent clinical studies have focused on therapeutic candidates to reduce amyloid plaque accumulation through direct or indirect means [9, 10]. Three distinct model types have been used to investigate the possible therapeutic advantages of fisetin in AD: sporadic, transgenic, and interventional. In interventional research, Aβ is administered straight into the cerebral ventricles of the mice's brains by intracerebroventricular (icv) injection. Transgenic models of AD are based on mutations linked to the rare hereditary variant, familial Alzheimer's disease (FAD). The models exhibit varying levels of cognitive dysfunction, plaque and tangle accumulation, synapse loss, gliosis, and neuronal mortality based on the kind and quantity of mutations present [9-11, 146, 147]. Despite the predominant emphasis on FAD models in AD medication research, this variant constitutes just around 1% of all cases [148] and may significantly differ from the more common, age-related sporadic type of AD. Despite several amyloid pathway treatments showing efficacy in FAD transgenic mice, none have successfully transitioned to clinical use yet [9]. Given that advanced age is the predominant risk determinant for AD [148, 149], ani-

mal models that integrate aging into the progression of the disease may be more beneficial for therapeutic development. The SAMP8 mouse, a model of aging with AD features, was formed in Japan through selective breeding of a rapidly aging phenotype. These mice demonstrated a gradual, age-related deterioration in cognitive performance like that seen in individuals with human sporadic AD [79, 150, 151]. In all three AD models (SAMP8, 2×FAD mice, icv Aβ injection), fisetin reliably inhibited cognitive decline [21, 49, 61]. Both oral delivery *via* food (500 mg/kg meal; about 45 mg/kg body weight per day) [49, 61] and intraperitoneal injection (20 mg/kg body weight per day) [21] demonstrated efficacy. In every model, fisetin preserved synaptic protein levels and decreased inflammatory indicators. It reduced many indicators of OS and stimulated the ERK pathway, which is implicated in memory [152] and neurotrophic factor synthesis and signaling [50]. Vascular dementia, caused by vascular endothelium malfunction, results in cognitive decline similar to conventional AD and often coexists with it [153]. The administration of L-methionine to rats has been found to mimic the neurological changes observed in vascular dementia. Fisetin, orally administered at doses ranging from 5-25 mg/kg body weight per day, effectively reduced the effects of L-methionine on cognitive performance, vascular functionality, and neurodegenerative markers in rats [154].

Table 1. The use of fisetin to prevent and treat NDs.

Neurodegenerative Disorders	Study model	Dose/Concentration	Findings	References
Parkinson's disease	Male C57BL/6 mice	100 ng/kg	Reduced dopaminergic neurodegeneration caused by MPTP in mice.	[155]
	Rat	10 and 20 mg/kg	Improved behavioral impairments, oxidative alterations, and mitochondrial dysfunctions in a rat model of PD.	[127]
	Female Sprague Dawley rats	10 and 20 mg/kg	Improved fisetin bioavailability, provided neuroprotection against rotenone-induced neurotoxicity, and significantly reduced alpha-synuclein aggregation.	[156]
	Adult Sprague-Dawley male rat	20 mg/kg	Permeated the BBB, reducing TH-positive cells and dopamine levels in the SN.	[157]
	Sprague-Dawley rat	5, 10, and 25 mg/kg	Enhanced striatal mitochondrial dysfunction and monoamine turnover, preventing the progression of abnormal involuntary movements and dyskinesia.	[158]
Alzheimer's disease	Adult mice	20 mg/kg	Reduced Aβ-induced buildup, BACE-1 expression, and tau hyperphosphorylation.	[21]
	Rat	100, 50, and 25 mg/kg	Improved learning and memory deficits in rats treated with Ab1-42.	[159]
	APPswe/PS1dE9 double transgenic AD mice	25 mg kg-1	Inhibited learning and memory impairments, reduced OS, and decreased cyclin-dependent kinase 5 activator p35 cleavage product levels.	[61]
	C57BL/6J AD mice	25 and 20 mg/kg	Impact of aerobic training and resveratrol and fisetin combination on neurogenesis signaling pathways in mice with AD.	[160]
	C57BL/6 mice	20 mg/kg	Enhanced neurogenesis in Alzheimer's patients by increasing BDNF and Fn1 expression, and decreasing Aβ levels.	[161]
	Male albino Wistar rats	40 mg/kg	Fisetin-encapsulated pluronic nanogel was used to treat neurocognitive deficits in a rat AD model.	[162]
Huntington's disease	R6/2 mice	5 and 10 mM	Activated the Ras-ERK cascade, which was found to mitigate the effects of mutant huntingtin in HD models.	[126]
Spinal cord injury	Adult male Sprague-Dawley rat	10, 20, and 40 mg/kg	Downregulated inflammatory mediators and B-cell inhibitor-alpha protein levels.	[163]
Brain injury	Adult male Sprague-Dawley rat	25 and 50 mg/kg	Prevented early brain injury in rats following subarachnoid hemorrhage by inhibiting the TLR 4/NF-κB signaling pathway.	[164]
	C57BL/6J mice	25 and 50 mg/kg	Exhibited neuroprotective properties and reduced ferroptosis and OS in the brain after TBI.	[165]
	Adult male ICR mice	25 and 50 mg/kg	Reduced OS in the brain following TBI through the Nrf2ARE pathway.	[66]
	Mice	25, 50, and 75 mg/kg	Decreased NF-κB activity and TLR 4 expression.	[166]

(Table 1) Contd….

Neurodegenerative Disorders	Study model	Dose/Concentration	Findings	References
Amyotrophic lateral sclerosis	Transgenic hSOD1G93A mice	9 mg/kg	Exhibited antioxidant and neuroprotective properties in various mutant hSOD1 models of ALS.	[139]
Dementia	Wistar rats	5, 10, and 25 mg/kg	Reduced these changes, indicating its endothelial and neuroprotective benefits against hyperhomocysteinemia-induced VaD and ED.	[154]
	Sprague Dawley rats	40 mg/kg	Prevented cognitive impairments by inhibiting ROS-induced NF-κB/NLRP3 inflammasome activation and activating antioxidant Nrf2/HO-1.	[167]
	Male BALB/c mice	10 and 20 mg/kg	Inhibited monoamine oxidase A and B enzymes, reducing anxiety-like behavior and enhancing locomotor activity in mice.	[168]

6.4. Fisetin and Huntington's Disease

HD is an ND defined by mental, cognitive, and motor symptoms. The Ras-extracellular signal-regulated kinase (ERK) cascade is linked to HD. Research suggests that ERK activation could be a potential therapeutic target. Fisetin, a polyphenol activating the Ras-ERK pathway, mitigated mutant huntingtin's effects in HD models, while resveratrol also activated ERK, highlighting the limited number of small-molecule activators of ERK signaling. Therefore, fisetin, resveratrol, and similar substances may be beneficial for HD treatment due to their unique capacity to activate ERK [126]. HD is a late-onset, growing, and lethal neurodegenerative condition marked by motor and mental abnormalities, along with cognitive decline. HD is an autosomal dominant disorder attributed to an unstable CAG repeat, causing an excessively long polyglutamine sequence in the huntingtin protein. The discovery has led to various models for understanding its onset and progression [169-172]. Fisetin was evaluated in the R6/2 mouse model of HD, a transgenic strain characterized by a severe disease pattern and reduced longevity [126].

6.5. Multiple Sclerosis

MS is a neuroinflammatory disorder impacting the brain and spinal cord, resulting in irreversible damage to the myelin sheath of neurons. The main symptom is immobility. Fisetin can inhibit *in vitro* myelin phagocytosis by reducing macrophage activity, potentially influencing the release of inflammatory mediators, chronic inflammation in the CNS, and neurological impairments. It decreases ROS generation without compromising macrophage cell survival and inhibits ROS-generating enzymes. It also selectively reduces NF-κB-induced proinflammatory mediators. The study investigates the impact of flavonoids on myelin phagocytosis induced by macrophages in MS. Flavonoids, like luteolin, quercetin, and fisetin, reduced myelin phagocytosis while preserving its viability. The flavonoid structure was found to be crucial for their effectiveness. Flavonoids with hydroxyl groups at B-3 and B-4 positions and a C-2,3 double bond exhibited the highest efficacy. Fisetin may inhibit demyelination in MS [173].

6.6. Age-related Changes

Rats and mice show greater interest in novel objects than in familiar ones, aiding behavioral pharmacologists and neuroscientists in studying memory and learning. A study examined mutant mice, age-related impairments, early developmental impacts, nootropic interventions, teratogenic drug exposure, and novelty-seeking behavior [174]. He *et al*. investigated the memory-enhancing properties of the flavonoid fisetin in rats. It significantly enhanced the induction of long-term potentiation in the hippocampus at CA1 synapses. The oral fisetin's effect was weakened by intracerebroventricular administration of U0126, a compound that hindered its effect in hippocampus slices. It improved synaptic functioning in the hippocampus [175]. The free radical hypothesis suggests that reducing cellular OS can modulate the aging process. Fisetin decreased cellular ROS levels and enhanced tolerance to OS. It increased lifespans, but at the cost of reduced fertility. It also postponed age-related loss in motility, reduced Aβ-induced toxicity, and restored impaired motility from a high-glucose diet. In a PD model, fisetin therapy slowed the degradation of dopaminergic neurons. The lifetime extension induced by fisetin was facilitated by the DAF-16-mediated stress response and autophagy. These outcomes corroborate the free radical hypothesis of aging and suggest fisetin as a potential anti-aging antioxidant nutraceutical [176].

6.7. Hyperhomocysteinemia

Hyperhomocysteinemia is a hereditary disease marked by high homocysteine levels in the blood. A study was intended to assess the neuroprotective effects of hesperidin and fisetin in Wistar rats with chronic moderate hyperhomocysteinemia. The rats were administered DL-homocysteine, which led to persistent moderate hyperhomocysteinemia. Fisetin and hesperidin treatment improved neuroprotection against chronic mild hyperhomocysteinemia, reducing behavioral deficits, enhancing brain antioxidant and nitrite levels, and reducing pro-inflammatory biomarkers [128].

6.8. Cognitive Dysfunction

Fisetin has antioxidant, anti-inflammatory, and antitumor activities. The free radical hypothesis of the process of aging indicates that decreasing cellular OS can modulate senescence. The research analyzes the impact of fisetin dietary supplementation on stress response, aging, and age-associated diseases. It has been reported to reduce cellular ROS levels and enhance tolerance to OS, increase lifespans,

reduce Aβ-induced toxicity, and restore impaired motility in PD models. These results support the free radical hypothesis of aging and suggest fisetin as a potential anti-aging antioxidant nutraceutical [177].

6.9. Vascular Dementia

Vascular dementia is the second predominant factor in dementia, causing cognitive impairments due to ischemia brought on by OS, neuroinflammation, endothelial dysfunction, and cerebral hypoperfusion (Fig. **3**). Fisetin was reported to exert protective effects in a mouse model of vascular dementia caused by recurrent ischemia-reperfusion. Vascular dementia leads to cerebral damage, lipid peroxidation, and neuronal apoptosis in the hippocampus, activating astrocytes and microglia, reducing BDNF neurotrophic factor production, and behavioral changes. Fisetin's protective effects may be due to its ability to suppress ROS-induced activation of the NF-κB/NLRP3 inflammasome and activate the antioxidant Nrf2/HO-1 [167]. Hemanth Kumar *et al*. found that fisetin could mitigate hyperhomocysteinemia-induced endothelial dysfunction and vascular dementia in rats. Fisetin, when administered at dose-dependent levels, effectively mitigated behavioral deficits, reduced brain lipid peroxidation, and increased serum homocysteine and cholesterol levels, demonstrating its endothelial and neuroprotective benefits [154].

6.10. Brain Stroke

Brain ischemic stroke is a major global health issue, causing sensory and neurological impairments and disrupting the BBB. Currently, rt-PA is used as an intervention for acute cerebral ischemia [178]. However, delayed treatment has been linked to suboptimal outcomes and increased risk of adverse effects, such as intracerebral hemorrhage and hyperperfusion. Therefore, the wider clinical application of rt-PA therapy is limited [179, 180]. Fisetin significantly improved cell viability in PC12 cells after exposure to hydrogen peroxide as a model for permanent localized ischemia [181]. Furthermore, in murine stroke models, fisetin decreased infarct size, activation, and infiltration of postischemic immune cells [77], and alleviated the abnormalities after a stroke [182]. Wang *et al*. evaluated fisetin's efficacy in extending the therapeutic window of rt-PA treatment in stroke patients. Stroke patients were randomized to rt-PA treatment with fisetin or a placebo, with fisetin showing improved treatment results in the delayed OTT stratum, possibly due to reduced serum MMP-2, MMP-9, and CRP levels [183].

7. PHARMACOKINETICS AND BIOAVAILABILITY

Fisetin has been studied for its potential health benefits in diabetes, inflammation, OS, neuroprotection, cardioprotection, and chemoprevention. However, its low oral bioavailability may limit its clinical efficacy. A food-grade fisetin formulation (FF-20) was created using hybrid-FENUMAT, encapsulating fisetin micelles into a fenugreek galactomannan hydrogel scaffold. The study found that FF-20 increased plasma fisetin concentration by 26.9-fold compared to UF and decreased fisetin-to-geranylgeranyl conversion [184]. Despite its broad therapeutic potential, fisetin

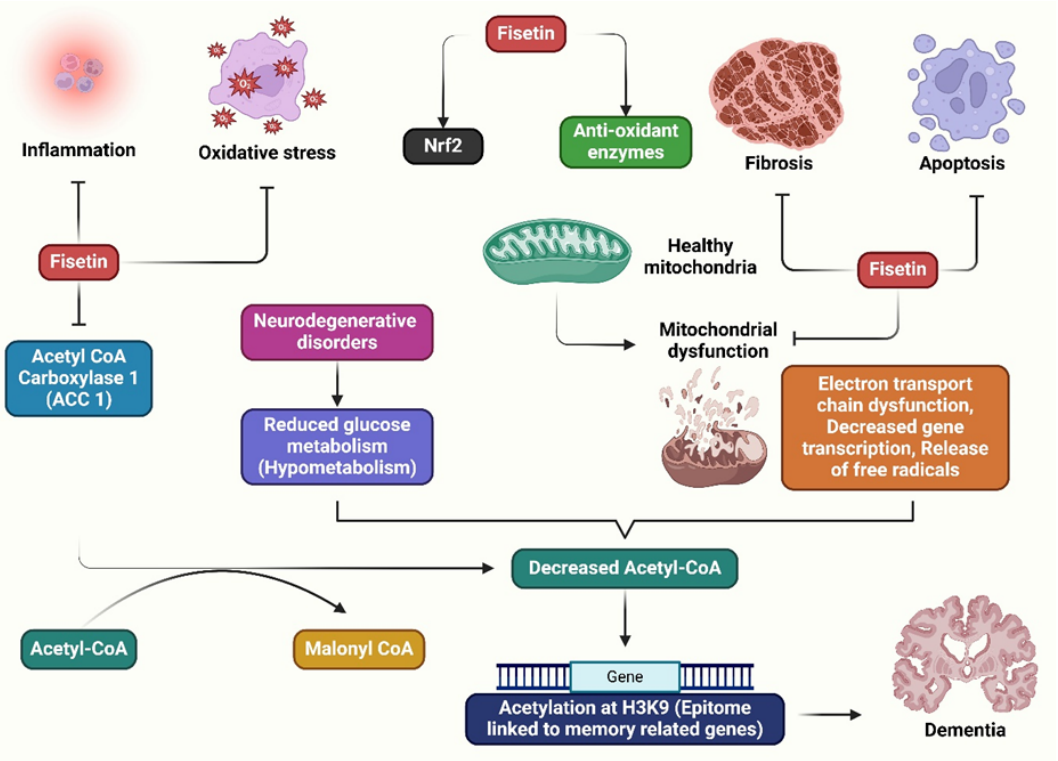

Fig. (3). Fisetin's neuroprotective properties make it a promising treatment for dementia. It enhances antioxidant defense, lowers OS, and improves brain health. The figure was designed by Biorender.com program (https://biorender.com). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

has drawbacks, including high lipophilicity (logP 3.2), poor water solubility (10.45 g/mL), and low bioavailability (44.1%) [185]. Pharmacokinetic research indicates that fisetin is rapidly absorbed and transforms into glucuronides and sulfates through phase II biotransformation. After 15 minutes of intraperitoneal administration, the highest concentration of fisetin (2.53 g/mL) was reached [36]. Regular dosage administration is crucial for ensuring therapeutic efficacy. The improvement in bioavailability may allow for a lower dosage and delay the onset of undesirable side effects. In a mouse model, fisetin was rapidly dispersed in brain vesicles and parenchyma after oral and intraperitoneal injection [186]. When compared to free fisetin, liposomal fisetin permitted a 47-fold increase in relative bioavailability *in vivo*. Compared to free fisetin at the same dose (1.6 days), the effect of liposomal fisetin on LLC tumor growth in mice at a modest dose (21 mg/kg) permitted a greater tumor growth delay (3.3 days). When liposomal fisetin therapy was optimized by co-treating it with cyclophosphamide, the tumor growth delay was significantly improved (7.2 days) as compared to 4.2 days when cyclophosphamide was used with control liposomes. Fisetin liposomes significantly enhanced the bioavailability and anticancer effectiveness of fisetin in mice, potentially simplifying its clinical administration [187]. Fisetin and its phase II conjugated derivatives may be excreted partially by the biliary system. Male Sprague-Dawley rats were used to test this theory. The pharmacokinetic findings showed that fisetin, its glucuronides, and sulfates had AUC ratios of 1:6:21 in plasma and 1:4:75 in bile. P-glycoprotein mediates fisetin biliary excretion [188]. Additionally, fisetin has anticancer effects but is difficult to administer *in vivo* due to its *in vivo* metabolism and limited solubility. To improve its therapeutic effectiveness, researchers developed nanocochleates, a lipid-based supramolecular assembly. These nanocochleates showed stable layers, an elongated shape, and an increase *in vitro* anticancer activity against human breast cancer cells. They also showed a 141-fold increase in bioavailability when administered intraperitoneally. The nanocochleates could make fisetin administration easier in therapeutic settings [189]. A study investigated the metabolism and distribution of fisetin in mice, finding its plasma level peaking at 2.53 mg/ml 15 minutes after injection. The kidneys had the highest levels, followed by the liver and intestine. The study identified a new cytotoxic metabolite, geraldol, which accumulates at higher levels in lung tumors [40].

8. SAFETY AND TOXICITY

Flavonoids are generally considered harmless and have minimal toxicity due to their widespread presence [190]. In several research studies, an oral dosage of 20 mg/kg/day is predominantly utilized for two successive days and/or two successive months [191]. The acute toxicity trial of fisetin revealed no indications or symptoms of toxicity, such as agitation, respiratory distress, diarrhea, reduced body weight, contractions, or coma [40, 192]. Moreover, it exhibited no symptoms of toxicity at dosages up to 2 g/kg in an acute toxicity trial, with no toxic effects seen in the histological examination of the reproductive organs, stomach, intestines, spleen, kidneys, liver, lungs, and heart [61]. The LD50 values of fisetin in mice were documented at various dosages, including subcutaneous, intravenous, oral, and intraperitoneal, across various administration methods [193]. Seal *et al*. used various analytical techniques to synthesize and analyze the fisetin ruthenium-p-cymene complex. The complex's toxicological profile was assessed using acute and sub-acute toxicity tests. Swiss albino mice were tested for mutagenic and genotoxic properties. Sub-acute doses were chosen after the complex's LD50 of 500 mg/kg was revealed. The 400 mg/kg group showed significant toxicological incidences, while the 50, 100, and 200 mg/kg groups did not [194]. Moreover, Rahimian *et al*. explored the effects of fisetin on hepatotoxicity, liver damage, and liver fibrosis. It lowered OS, stopped lipid peroxidation, boosted antioxidant levels, and neutralized free radicals. It also inhibited various inflammatory processes, suppressed detoxification enzymes, and reduced collagen formation. It reduced liver function tests and fat buildup. In both *in vitro* and *in vivo* tests, it improved detoxification, reduced fibrosis, and attenuated liver injury, contributing to liver health [195].

9. CLINICAL TRIALS

Fisetin is used in clinical trials to examine its effects on conditions, like mild cognitive impairment, Gulf War disease, diabetes, chronic kidney disease, osteoarthritis, and diabetic nephropathies. GlaucoCetin, the first regulated vision-specific medicinal food containing fisetin, supports and safeguards the mitochondrial function of optic nerve cells in glaucoma patients. Fisetin has numerous health advantages and is available as a medication ingredient, oral dietary supplement, and medical food [196]. A study aimed to evaluate fisetin's potential to prolong the therapeutic window of recombinant tissue plasminogen activator (rt-PA) treatment in stroke patients. Stroke patients were divided into placebo and rt-PA therapy combination groups. Fisetin significantly improved treatment results for stroke patients with delayed OTT. It may enhance conventional rt-PA therapy, especially for those with delayed OTT, extending the therapeutic window [183]. Fisetin can interact with various redox-related signaling pathways when it passes through cellular membranes. It effectively exerts its antioxidant activity through various mechanisms, including chelating transition metal ions, supporting intracellular antioxidants, and serving as a substrate for oxidoreductase activity. Fisetin's antioxidant properties extend beyond scavenging free radicals, involving pathways, like NF-κB, Nrf2, MAPK, and PI3K/Akt. Future research should explore additional pathways and conduct clinical trials [55].

CONCLUSION AND FUTURE PERSPECTIVE

Fisetin has shown significant potential in treating NDs. The therapeutic option is promising due to its ability to target various molecular pathways linked to OS, neuroinflammation, apoptosis, and autophagy. Fisetin has shown promising potential in preclinical models of NDs, like AD, PD, ALS, MS, and HD. Additionally, it enhances cognitive function, protects neurons, and mitigates NDs, like AD, PD, and others. Its clinical use remains significantly inhibited by its pharmacokinetic and bioavailability issues. Furthermore,

it is involved in various pathways linked to neuronal dysfunction and degeneration, including antioxidant, anti-inflammatory, anti-apoptotic, and autophagic actions. Fisetin also exhibits anti-inflammatory, anti-apoptotic, antioxidant, and autophagy-modulating properties, affecting key signaling pathways, like Nrf2/ARE, PI3K/Akt, and NF-κB. Fisetin, despite promising preclinical findings, faces challenges, like low brain penetration, fast metabolism, and poor oral bioavailability. Techniques, like liposomal administration, need validation in translational models, and the lack of solid human clinical data is a significant gap. Future research should prioritize clinical trials to determine fisetin's effectiveness, ideal dosage, and long-term safety in NDs. The focus should be on improving delivery methods and exploring fisetin's use in combination therapy. Moreover, future research should focus on developing advanced drug delivery methods, like liposomal formulations or nanoparticles, to enhance fisetin's therapeutic reach and bioavailability. Clinical trials are also required to confirm its safety and effectiveness in human populations. The review suggests that investigating the interaction between fisetin and other neuroprotective substances or pharmaceutical treatments could provide a novel approach to improving the prognosis of NDs. Further understanding of fisetin's molecular processes can enhance its neuroprotective properties and facilitate the development of personalized treatment strategies. Further clinical trials are needed to assess the safety, efficacy, and long-term effects of fisetin, particularly in early-stage NDs, explore potential synergistic effects, and understand its molecular interactions. Fisetin's multitarget activities and advantageous preclinical profile make it a top choice for neuroprotection. To translate advantages into clinical application, pharmacokinetic constraints must be addressed, clinical trials conducted thoroughly, and safety ensured across diverse patient demographics. Fisetin may progress from an experimental substance to a neurotherapeutic drug that is therapeutically feasible with these developments.

STUDY LIMITATIONS

This review identifies several limitations regarding fisetin's neuroprotective effects, primarily stemming from reliance on in vitro and animal studies, which may not accurately reflect human neurodegenerative conditions. Variability in experimental designs and potential publication bias could distort the perceived therapeutic benefits. Additionally, the absence of standardized clinical data complicates translational insights, influenced by pharmacokinetic variability and formulation differences. Previous mechanistic studies may oversimplify complex disease pathways. Lastly, a lack of data on long-term safety and interactions with current therapies is noted. Future research should focus on robust clinical trials and consistent methodologies to bridge these gaps.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: MAA contributed to conceptualization, data curation, formal analysis, investigation, methodology, resource allocation, software curation, visualization, writing of the original draft, and writing, review, and editing. MZ contributed to data curation, investigation, methodology, resource allocation, software curation, writing of the original draft, writing, review, and editing, and supervision. SHS contributed to data curation, investigation, methodology, resource allocation, software curation, writing of the original draft, and writing, review, and editing. RD took part in formal analysis, investigation, validation, visualization, and writing, review, and editing. JKG, EB, GD, VVK, AAR, MS, TP, and TBE performed project administration, supervision, validation, visualization, and writing, review, and editing.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
ALS	=	Amyotrophic Lateral Sclerosis
CNS	=	Central Nervous System
DALYs	=	Disability-adjusted Life Years
FAD	=	Familial Alzheimer's Disease
GPx	=	Glutathione Peroxidase
GSH	=	Glutathione
H_2O_2	=	Hydrogen Peroxide
HD	=	Huntington's Disease
LTP	=	Long-term Potentiation
NDs	=	Neurodegenerative Diseases
OS	=	Oxidative Stress
PD	=	Parkinson's Disease
ROS	=	Reactive Oxygen Species
TBI	=	Traumatic Brain Injury

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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