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Neuropharmacology of *Fisetin* as a Senotherapeutic Agent: Investigating Its Role in Neurodegeneration and Brain Aging

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ABSTRACT

Fisetin, a flavonoid in various fruits and vegetables, has emerged as a promising chemotherapeutic agent with potential neuroprotective effects, particularly in neurodegeneration and brain aging. **Objective:** To explore the role of *fisetin* in mitigating age-related neuronal damage by targeting oxidative stress, inflammation, and cellular senescence, common contributors to neurodegenerative diseases such as Alzheimer's and Parkinson's. **Methods:** Following PRISMA guidelines, relevant studies were sourced from ScienceDirect, Google Scholar, and PubMed, spanning publications between April 2014 and August 2024. One website was also used to retrieve studies, i.e., Frontiers. *Fisetin*'s mechanism of action includes modulating key pathways, such as the inhibition of inflammatory markers, reduction of Reactive Oxygen Species (ROS), and protection against neuronal apoptosis. **Results:** Studies conducted on various animal models and human-derived neurodegenerative cell lines reveal its potential to improve cognitive function and reduce the progression of age-related brain disorders. **Conclusions:** *Fisetin*'s ability to selectively target senescent cells, reduce neuroinflammation, and enhance synaptic function positions it as a potential therapeutic for brain aging. Future research focusing on clinical trials and dosing optimization was crucial to establishing *fisetin* as a viable treatment for neurodegenerative conditions and cognitive decline associated with aging.

INTRODUCTION

Neurodegenerative disorders are diseases that affect the neurons, resulting in the loss of various mental and motor mechanisms. They are frequently found in patients of old age; this showed their connection to the aging of the brain. They are considered to be a significant threat to global health since they are set to worsen given the emerging aging population. In Asia, especially China, the prevalence of neurodegenerative diseases is rapidly rising along with life expectancy [1]. Likewise, North America has been on the rise; however, there are more efforts in the early detection and control of such diseases [2]. These variations may be attributed to environmental, genetic, or healthcare factors [3]. However, the neurodegenerative ailment burden persists to rise globally, notwithstanding advancements in treatment and innovation, widening the social, economic, and humanistic burden of these diseases. Several factors involving oxidative stress, chronic inflammation, and genetic predisposition, as well as exposure to environmental factors, have been cited for the development of neurodegenerative diseases [4]. Cellular senescence, where cells grow dysfunctional and are unable to divide, is a critical factor in brain aging [5]. Aging, Alzheimer's disease, and other diseases that affect the flow of blood to the brain and the proper functioning of a

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person's cerebral cortex are caused by this dysfunction [6]. In neuronal damage, the importance of oxidative stress raises it specifically as a viable therapeutic target. Among the interventions, one that has aroused the interest of researchers is *fisetin*, which belongs to the group of flavonoids that possess anti-inflammatory and antioxidant effects that may alleviate some of these undesirable conditions [7].*Fisetin* has been identified as a neuroprotective compound and a potential candidate to combat neurodegenerative diseases and brain aging because of its action on certain molecular targets associated with neurodegeneration and aging [8]. Studies showed that *fisetin* can enhance cognitive function, protect neurons, and kill senescent cells, which highlights its potential against brain aging and overall neurological health [9]. The neuroprotective effects of this flavonoid are significant because it opposes processes such as cellular ageing, reduces inflammation in the brain, and helps to maintain synaptic connections which are all vital for the deceleration of brain aging [10]. Due to such an interesting profile, there are ongoing efforts to understand the potential of *fisetin* as an anti-neurodegenerative disease drug in general, regardless of the type of disease that a patient has [11]. The prospects of using *fisetin* in the neurotherapeutic market in the future are relatively promising.Future research with clinical trials might strengthen the position of *fisetin* as a potential medicine for neurodegenerative diseases and the prevention of brain aging [12]. Future work should pinpoint the methods by which it would be delivered and the dose administered, understanding how it would impact the other molecular processes connected to aging and neurodegeneration [13]. In cooperation with innovation in the pharmacological industry, the choice of *fisetin* can be a natural supplemental therapy that could help in stabilizing or reversing the decline of neurodegenerative diseases and increasing the standards of living for the elderly [14].

METHODS

The methodology involved the collection and filtration of studies taken for this study. PRISMA guidelines were taken into consideration throughout the process of filtering for precise results. The studies taken for this study were in the range of 10 years, i.e., 2014 to 2024. Initially, it included 96 articles in English from the last 10 years (2014-2024). Additionally, 10 studies were taken from a website. The inclusion criteria depended upon the essential features, such as mechanism pathways of disease that can relate to fisetin, brain ageing, and neurodegeneration, particularly among elder patients, to study the process of senescence. To assess the potential and potency of fisetin in the neurodegenerative and brain aging models, and in vitro experiments showing variable-induced cytotoxicity and inhibition through fisetin in specific concentrations. Several search engines were used for the study: Science Direct, Google Scholar, and PubMed. The website from which three studies were retrieved includes Frontiers. 65% of the articles were taken from Science Direct, 25% from Google Scholar, and 10% from other search engines, including PubMed. A search was conducted using phrases such as fisetin, neurodegeneration, neurological signalling pathways, brain ageing, etc. Article searches were done using keywords: fisetin, neurological disorders, neurodegeneration, the role of natural compounds in brain-related disorders, etc. The articles that did not contain fisetin or neurodegeneration as keywords and did not come under the range of years selected for the study did not meet the inclusion criteria and were eliminated in the filtering process. Inclusion criteria focused on the pharmacological effect of fisetin on neurodegenerative disorders by slowing the process of ageing. 96 articles in total were downloaded from databases; 3 duplicates were removed, and 93 were left for further study analysis. 16 out of 93 were excluded as they were just abstracts and complete articles could not be reached, so 77 were left. Out of 77, 10 were not retrievable and 67 were assessed for eligibility, out of which again 27 studies were excluded as they were older studies (not from the last 10 years) and 27 contained insufficient data, e.g., study population, sample size was not mentioned, and in some even variables. Finally, 16 were selected, which were sorted and used. 13 out of 16 studies were taken from databases, and 3 were retrieved from websites. The total number of places where these studies were reported as published was also 16. The selected papers were used to extract the following elements, which were arranged systematically according to the inclusion criteria of PRISMA: author name followed by year, demographics, key outcomes, mechanisms, factors, study type, and references. PRISMA work flow for filtering out articles focusing on inclusion and exclusion method. Initially, 96 studies were taken from databases and 10 from a website according to relevancy. All duplicates were eliminated. Only full-text articles that can be downloaded and read were screened. Finally, 16 studies of which 13 were rooted from databases and 3 from a website were taken, each study was reported once (Figure 1).

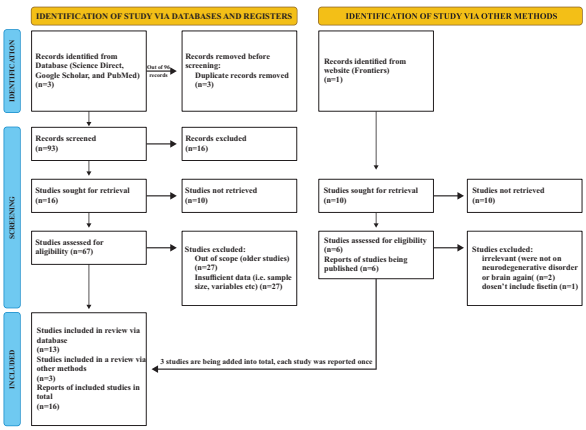

Figure 1: PRISMA Flowchart for Article Selection Based on Inclusion and Exclusion Criteria

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RESULTS

All reviewed studies were based on neurodegenerative disorders, of which 60% articles were from Asia, 20% from America, and the rest 20% equally from Europe and Africa. Out of 16 studies, 6 were taken from Science Direct; others were from various sources, including Semantic Scholar, Frontiers, and Google Scholar. 7 studies focused on in vitro identification of the role of fisetin as a therapeutic drug; 2 were focused on the same subject but were both in vitro and in vivo combined; 1 was a longitudinal study and contained a population under observation; the rest were in vivo. The results of these studies [15-30] were shown in table 1.

Table 1: Systemic Scheme of Studies Most Relevant To Fisetin's Therapeutic Role In Neurodegenerative Disorders And Brain Aging

Author and Year, Reference (Region)	Study Population (Mean ± SD) Age (Years)	Study Methodology (Sample Size, N)	Study Variables	Key Findings
Zhong *et al.*, 2022 [15] (China)	RAW264.7 Macrophage Cell line of Mouse	In Vitro Study	*Fisetin*, myricetin, quercetin	Fisetin showed strongest inhibition of nitric oxide, Reactive oxygen species ROS, IL-6 and Tumor Necrosis Factor Alpha TNF-α in dose dependent manner. Flavanols also prevented nuclear translocation of Nuclear Factor Kappa NF-kb p65.
Lee E *et al.*, 2023 [16] (USA)	USA Residents with neurodegeneration Problems (range 43.0 - 86.6)	Longitudinal Study (n=19)	Dasatinib, quercetin, *fisetin*	*Fisetin* had a mitigating effect on DQ (Dasatinib and quercetin impact on epigenetic aging.
Maher, P *et al.*, 2020 [17] (USA)	Ht22 Hippocampal Nerve Cells of Mouse	In Vitro Study	*Fisetin*, iron, copper, glutathione GSH, glutamate, Nrf2, ATF4 (transcription factors), RSL3 (a small molecule)	*Fisetin* reduced oxidative stress and inflammation. This provides neuroprotective and anti-inflammatory effects of *fisetin.*
Wang Y *et al.*, 2023 [18] (China)	Sprauge-Dawley Rats (six weeks old)	In Vivo Study	(72 rats) *Fisetin*, Amyloid Beta Aβ1-42	In Aβ1-42 treated rats, *Fisetin* had a healing effect on memory and learning impairments. *Fisetin* reduced apoptosis, inflammation and oxidative stress.
Zhang S *et al.*, 2020 [19] (China)	Murine HT22 Hippocampal Nerve Cells	In Vitro Study	*Fisetin*, glucose	Fisetin effectively reduced the toxicity cause by self-induced high glucose levels in cells. It reduced neurotoxicity and apoptosis. It upregulated neurotrophic factors like BDNF and GDNF (Brain-derived and Ganglia-derived neurotropic factors).
Chen TJ, *et al.*, 2020 [20] (China)	Male C57BL/6 Mice (12 weeks old)	In Vivo Study (24 mice)	*Fisetin*, MPTP (neurotoxin)	Impairments in behavior caused by MPTP were effectively improved by *Fisetin. Fisetin* showed neuroprotective ability through mediation of gut microbiota.
Ahmad S *et al.*, 2021 [21] (South Korea)	C57BL/6N Mice (9 weeks old)	In Vivo Study (60 mice)	D-galactose, *Fisetin*	By upregulation of SIRT1/Nrf2 pathway *Fisetin* effectively reduced oxidative stress and neuroinflammation in intoxicated mice. It suppressed pro inflammatory markers and apoptosis-related protein.
Li X *et al.*, 2022 [22] (China)	Transgenic APP/PS1 Mice (4 months old)	In Vivo Study (50 mice)	*Fisetin*, Amyloid-β (Aβ) oligomers, synaptic proteins	The combination of *Fisetin* and other compounds used improved curiosity and movement in AD (Alzheimer Disease) mice. *Fisetin* reduced Aβ proteins which were harmful.
Ay M *et al.*, 2023 [23] (Turkey)	SH-SY5Y Neuronal Cells	In Vitro Study	*Fisetin*, mitochondrial biogenesis indicators, genes related to Parkinson.	Fisetin increased the mitochondrial biogenesis. Increased levels of anti-Parkinson genes and reduced apoptotic genes.
Rosado-Ramos R *et al.*, 2021 [24] (Portugal)	Yeast model, SH-SY5Y and LUHMES Neuronal Cells.	In Vitro Study	*Fisetin*, TH (tyrosine hydrolase), DAT (dopamine transporter), t-BHP (organic peroxide), MPP+ (neurotoxin)	*Fisetin* protected neuronal cells from oxidative stress. Increased cell viability. Improved the survival of LUHMES cells exposed to toxicity.
Elsallabi O, *et al.*, 2022 [25] (Italy and Sweden)	Human Hs 683 Cell Line, ICH Mice and SAMP8 Mice (few weeks old vs aged Mice)	In vitro and in Vivo Study	ROS, interleukin IL-1β, TNF-α, IL-6, *Fisetin*	*Fisetin* showed a promise as a senolytic drug. Improved mitochondrial function and decreased inflammation in aging models. Reduces oxidative stress.

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Renault-Mahieux M, *et al.*, 2021 [26] (France)	Glioblastoma Cells	In Vitro Study (Co-encapsulated *fisetin* and cisplatin containing liposomal formulations.)	*Fisetin*, cisplatin	Co encapsulation of fisetin and cisplatin into liposomes showed success.The co-loaded drugs were effective against glioblastoma (GBM)
Mbara K.C *et al.*, 2022 [27](South Africa)	Human Senescent Cells, Senescent Murine	In Vitro, In Vivo (aged Mice)	*Fisetin*	*Fisetin* showed reduction in senescent cells and improved age relating diseases. Increased apoptosis and reduced aged relating factors in cells. *Fisetin* improved life span of progeroid mice.
Akpa A.R *et al.*, 2020 [28](Nigeria)	Adult Albino Male Mice. (10 weeks old)	In Vivo (32 Mice)	*Fisetin*, chlorpyrifos, oxidative stress biomarkers.	*Fisetin* reduced the CPF (neurotoxin) induced oxidative stress. *Fisetin* improved antioxidant defense. *Fisetin* has neuroprotective potential again CPF-induced stress.
Xiao S *et al.*, 2021 [29](USA)	tau K18 filaments in Alzheimer's disease	In Vitro	*Fisetin*, tau protein	*Fisetin* inhibits gathering of tau protein by interacting with k18 fragment and beta strand formation. *Fisetin* proves to be an important candidate as an Alzheimer's treatment.
Yang W et al., 2019 [30](China)	ICR Mice	In Vivo (40 Mice)	*Fisetin*, p-tau, lead	Neurodegradation and neuroinflammation in mice was explored. *Fisetin* improved learning behaviors in lead exposed mice. It reduced inflammatory markers and increased neprilysin that remove A-beta.

DISCUSSION

In this review, we discuss the potential of *fisetin* in mitigating neuronal damage that was associated with age and attributed to factors such as oxidative stress, inflammation, and cellular senescence, which were usually implicated with neurodegenerative diseases such as Alzheimer's or Parkinsonian disorders. Oxidative stress, inflammation, and cellular aging were frequently associated with aging and were increasingly prevalent in both Asia as well as North America, leading to neurodegeneration associated with aging [31, 32]. For example, in China, the current proportion of neurodegenerative diseases was lower but was predicted to increase steadily with time due to the country's aging population, based on high-quality data. On the contrary, the prevalence of neurodegenerative diseases in North America was already a substantial challenge, given the existing high elderly population and rising incidence rates of these conditions [33]. Focusing on the existing literature, the present study demonstrates that *fisetin* may play a complex role in combating neurodegeneration. Some current discoveries represent that this *fisetin* can shield neurons from toxic proteins' impact, decrease inflammation, and improve cognitive abilities [34, 35]. Due to its capabilities of influencing pathways involved in oxidative stress and inflammation, the flavonoid could be considered a therapeutic target for neurodegenerative diseases [36]. About its neuroprotective effect, *fisetin* has been shown to engage several signalling pathways that are particularly important to neuroprotection against neurodegenerative diseases. According to research, fisetin has the potential to downregulate ROS generation and reduce inflammatory biomarkers like IL-6 and TNF-α, which are toxic to neurons [37]. In addition, *fisetin's* properly coordinated anti-inflammatory effects have assisted in the up-regulation of neurotrophic factors, including the BDNF to boost neuronal survival and synaptic plasticity, which were crucial for cognitive function in aging and neurodegenerative diseases [38]. In addition to its antioxidant actions, *fisetin* has been demonstrated to modulate a variety of signalling processes that are involved in neurological disorders. For instance, it stimulates the PI3K/Akt signalling pathway, which is involved in cell survival; the Nrf2 signalling is involved in stress responses [39]. *Fisetin* modulates the Nrf2 pathway, increases the levels of antioxidant-protecting genes, and thus shields neurons from oxidative lesions [40]. Moreover, the fact that *fisetin* alters neuronal signalling pathways to reverse the detrimental effects of oxidative stress in aging and neurodegenerative diseases means that it may be a useful drug candidate to treat or attenuate cognitive function in these conditions. Several in vitro and in vivo tests support the regulatory neuroprotective properties of fisetin in different models of neurodegenerative diseases. Several in vitro experiments have also shown that fisetin inhibits oxidative stress and enhances neuronal cell viability under conditions of neurodegeneration in neuronal cell lines [41]. Experimental animal models have demonstrated that a *fisetin*-supplemented diet enhances learning ability and mitigates inflammation and neuronal die-off in Alzheimer's and other age-related diseases [42]. These results indicate that *fisetin* exhibits neuroprotective action and also improves brain function where neurodegenerative diseases are present. The use of *fisetin* together with other therapeutic agents may extend the effectiveness of the drug on neurodegenerative diseases. Studies have shown that *fisetin* when combined with other flavonoids like

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quercetin or curcumin, boosts their overall antioxidant and neurogenic properties [43]. The given combination therapies may act on several pathophysiologic processes of neurodegeneration and, therefore, may be less prone to secondary disease progression [44]. Additional studies of these combination therapies will be necessary to define formulations that can be useful for treatment. The therapeutic potentials of *fisetin* indicate the need to perform more studies to establish the efficacy, safety, and dosing of *fisetin* for treating neurodegenerative diseases. Solving these issues will become the key to achieving maximum therapeutic efficacy of *fisetin* as a potentially effective treatment for neurodegenerative diseases and brain ageing. Moreover, the neuroprotective function of *fisetin* was not only valid for these fundamental profiles but also expanded beyond the neuroprotective effects of the existing drugs, making it fit for responding to the multifaceted therapy needs of neurodegenerative diseases for potential distinctive candidacy [45]. There was a well-known difficulty for many therapeutic agents in crossing the blood-brain barrier, which was crucial for the treatment of CNS conditions; this lies in the fact that fisetin has been recognized to possess the capability to cross this barrier. Studies show that the main properties of *fisetin*, such as its small molecular weight and lipophilicity, enable it to cross the BBB and act positively on neuronal cells [46]. This characteristic was especially relevant for compounds designed for the therapy of neurodegenerative diseases that require their delivery to the brain. However, the ability of *fisetin* to positively or negatively influence mitochondrial homeostasis only serves as an extra dimension to its activity. This type of cellular respiration has been implicated in many neurodegenerative disorders due to energy failure and enhancement of oxidative stress on neuronal cells [47]. *Fisetin* has been found to improve the process and efficiency of mitochondrial generation, and its normal functioning neutralizes these effects [48]. This property becomes significant given that mitochondrial integrity was strongly associated with neuronal and cognitive integrity. Yet another viable area of research has to do with how *fisetin* acts within the context of the gut-brain axis. Recent animal and human studies have shown that the gut microbiota dramatically affects the brain and its diseases; it may underlie the development of neurodegenerative diseases. The neuroprotective effect of *fisetin* could benefit from the changes in the gut microbiota, as a healthy composition of the microbiota leads to a decrease in neuro-inflammation status and improved cognitive performance [49]. Furthermore, because inflammation was seen as a common feature in aging populations, *fisetin* also works to decrease systemic inflammation that typically occurs in aging individuals, thus improving brain health. Despite the promising literature reviews that demonstrated the antineoplastic, antioxidant, and anti-inflammatory effects of *fisetin,* the further steps of its introduction to clinical practice require investigations of its tolerance and dosing. Randomized control trials were required to evaluate the bioavailability and safety of *fisetin* in humans and its application in the prevention or treatment of neurodegenerative diseases in an aging population. These studies should also establish whether the use of *fisetin* can be complementary with other well-known treatments or other forms of nutrition that could amplify the neuroprotective effect of *fisetin* with minimal toxic effect. In light of the current focus on complementary compounds to conventional therapies, *fisetin* could be another candidate that will enhance the standard treatment regimens, making positive changes in neurodegenerative diseases.

CONCLUSIONS

The present review indicates that *fisetin* has therapeutic potential for neurodegenerative disorders because of its strong neuroprotection activity in terms of antioxidant, anti-inflammatory, and anti-apoptotic properties. *Fisetin* being able to modulate oxidative stress as well as neuroinflammation has shown to rescue the neurons and enhance learning abilities in models of neurodegenerative diseases. Adding to these benefits, its capacity to improve synaptic plasticity and mitochondrial function makes it a drug candidate. However, the given reports suggest that there were more clinical trials to define the appropriate dosing regimen, pharmacokinetics, toxicity, and therapeutic effects on a larger patient population. Dietary manipulations especially with *fisetin*-supplemented products, have the potential to influence patient outcomes, especially with increasing incidences of neurodegenerative diseases, especially in the elderly.

Authors Contribution

Conceptualization: SJ, AM, BA
Methodology: AM, BA, AA, EUH
Formal analysis: AM, FP, EUH
Writing, review and editing: AM, BA, ZB, AA, FP, EUH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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