Fisetin as a Neuroprotective Flavonoid in Alzheimer's Disease; Targeting Bdnf and TAU Pathways

Ananya A.Rahangdale, Shankar S. Bisen, Dr. Pankaj M. Pimpalshende, Prajwali V. Shende*

Hi-tech college of pharmacy, Chandrapur-442406

Corresponding author Email: prajwalishende25@gmail.com

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes cognitive decline, synaptic dysfunction, neuronal loss, and characteristic pathologies such as Tau hyperphosphorylation and neurofibrillary tangle formation. In addition to amyloid and Tau pathology, impaired brain-derived neurotrophic factor (BDNF) signaling, oxidative stress, and chronic neuroinflammation all play important roles in disease development. Current therapeutic approaches only provide symptomatic alleviation, emphasizing the critical need for disease-modifying medicines capable of addressing numerous pathogenic pathways. Fisetin, a naturally occurring dietary flavonoid, has received increased interest due to its extensive neuroprotective potential in AD. Preclinical investigations show that fisetin has antioxidant and anti-inflammatory properties while also improving neuronal survival and synaptic plasticity. Fisetin regulates BDNF signaling by increasing BDNF expression and activating downstream pathways such as Trk-B, CREB, PI3K/Akt, and MAPK, so promoting learning and memory processes. Fisetin reduces Tau pathology by suppressing hyperphosphorylation and aggregation. It does this by regulating important kinases such glycogen synthase kinase-3β (GSK-3β), which helps stabilize microtubules and maintain neuronal integrity. Despite convincing preclinical evidence, the clinical translation of fisetin is hampered by issues such as inadequate bioavailability, insufficient human research, and a lack of knowledge of its pharmacokinetics. Future research should focus on enhancing fisetin delivery using innovative formulations, verifying its efficacy in clinical trials, and investigating synergistic effects with existing AD medications. Fisetin stands out as a promising multitarget option for Alzheimer's disease prevention and treatment since it targets both BDNF-mediated neurotrophic support and Tau-associated neurodegenerative pathways.

Keywords: Alzheimer’s disease, Amyloid-β, Tau hyperphosphorylation, BDNF, Fisetin.

1. Introduction

AD is recognized as the most common neurodegenerative disorder and stands as the primary cause of dementia in the elderly population globally. This condition is marked by a gradual deterioration in memory, cognitive abilities, and behavioural skills, ultimately leading to total dependence and death. Recent epidemiological data indicates that over 55 million individuals worldwide are currently affected by dementia, with AD representing roughly 60–80% of these instances. The incidence of AD is projected to increase significantly due to rising life expectancy, creating a considerable socio-economic and healthcare challenge, especially in low- and middle-income nations [1]. The risk factors associated with AD are categorized into two groups: modifiable and non-modifiable. Non-modifiable factors include age, genetic predispositions (notably the APOE ε4 allele and rarer mutations in APP, PSEN1, and PSEN2), and family history. Modifiable factors encompass cardiovascular conditions such as obesity, diabetes, and hypertension, along with lifestyle choices like smoking, lack of physical activity, poor dietary habits, and limited social engagement [2]. Despite significant research initiatives, AD remains without a cure, with existing treatments primarily providing symptomatic relief rather than altering the disease's progression. Approved therapies, such as acetylcholinesterase inhibitors and the NMDA receptor antagonist, yield only modest and temporary cognitive improvements and do not prevent neuronal degeneration or address the fundamental pathological processes. While monoclonal antibodies targeting amyloid-β have shown some degree of plaque reduction, their clinical effectiveness is restricted and frequently associated with side

effects, including amyloid-related imaging abnormalities. Furthermore, strategies focused on amyloid do not adequately address tau pathology, synaptic loss, and neurotrophic dysfunction, which are more closely linked to cognitive decline [3] Considering the complex nature of AD pathogenesis, which includes amyloid-β accumulation, tau hyperphosphorylation, and oxidative stress, it is essential to explore comprehensive approaches for treatment. In this context, phytochemicals, particularly flavonoids, have emerged as intriguing neuroprotective agents due to their pleiotropic properties, which include antioxidant, anti-inflammatory, and neurotrophic signalling regulation. Flavonoids are promising prospects for AD treatment because they influence critical pathways such as PI3K/Akt, MAPK/ERK, and CREB-mediated transcription, as well as enhance brain-derived neurotrophic factor (BDNF) expression [4].

Fisetin (3,3′,4′,7-tetrahydroxyflavone) is a flavonoid that has received a lot of attention because of its strong neuroprotective effects and potential to alter critical signalling pathways in AD. Fisetin is a naturally occurring flavonoid found in strawberries, apples, onions, and cucumbers. Unlike many polyphenols, fisetin has good pharmacokinetic properties, including enough lipophilicity, which allows it to pass the blood-brain barrier. Preclinical investigations have shown that fisetin accumulates in brain tissue and has long-term neuroprotective benefits without causing severe harm. Its safety profile and low likelihood of adverse effects make it ideal for long-term treatment, which is critical for controlling progressive neurodegenerative illnesses like AD. Fisetin exhibits pleiotropic effects relevant to AD. It acts as a powerful antioxidant, boosting endogenous antioxidant defence and lowering lipid peroxidation. Fisetin also reduces neuroinflammation by decreasing microglial activation and proinflammatory cytokine release [5]. Fisetin inhibits tau hyperphosphorylation by modulating important kinases such as glycogen synthase kinase-3β (GSK-3β), leading to reduced tau pathology. Crucially, fisetin has been demonstrated to increase BDNF expression and activate Trk-B dependent signalling pathways, resulting in improved synaptic plasticity, neuronal survival, and cognitive function. Fisetin's capacity to target both BDNF signalling and tau pathology distinguishes it as a novel and intriguing multi-target therapy option for AD. The convergence of fisetin-mediated BDNF increase and reduction of tau hyperphosphorylation implies that fisetin may exert its neuroprotective effects via modulating the BDNF-tau signalling axis. By restoring neurotrophic support and inhibiting tau-mediated synaptic dysfunction, fisetin offers a mechanistically integrated approach to counteract cognitive decline in AD [6].

2. Pathophysiology of AD

2.1 Amyloid-β cascade

The amyloid cascade hypothesis suggests that the abnormal processing of amyloid precursor protein (APP) by β- and γ-secretases results in the excessive generation of neurotoxic amyloid-β peptides, especially $A\beta_{1-42}$.These peptides form aggregates that manifest as soluble oligomers and insoluble plaques, with the soluble Aβ oligomers having the strongest synaptotoxic impact. Aβ oligomers interfere with synaptic transmission by disrupting glutamatergic signalling, diminishing the functionality of NMDA and AMPA receptors, and causing calcium dyshomeostasis [7]. Crucially, the accumulation of Aβ inhibits BDNF expression and disrupts TrkB receptor signalling, which leads to a decline in synaptic plasticity and memory formation. Experimental findings demonstrate that the Aβ-mediated suppression of CREB phosphorylation reduces BDNF transcription, thereby compromising the neurotrophic support that is vital for neuronal survival. Moreover, oxidative stress and mitochondrial dysfunction induced by Aβ worsen synaptic vulnerability, leading to early synaptic loss that occurs prior to noticeable neuronal death. Consequently, Aβ pathology not only triggers synaptic toxicity but also contributes to the depletion of BDNF, thereby intensifying neurodegenerative processes in AD [8].

2.2 Tau Pathology and Neurofibrillary Tangles

Tau is a microtubule-associated protein that is crucial for maintaining axonal stability and facilitating intracellular transport. In the context of AD, the disruption of the normal balance between phosphorylation and dephosphorylation results in tau hyperphosphorylation and the development of neurofibrillary tangles (NFTs), which are closely linked to cognitive decline. The pathological modification of tau is caused by the abnormal activation of kinases, especially glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase-5 (CDK5), along with a decrease in the activity of protein phosphatase-2A (PP2A). When tau becomes hyperphosphorylated, it detaches from microtubules, leading to microtubule destabilization and hindering the axonal transport of mitochondria, synaptic vesicles, and neurotrophic factors such as BDNF [9]. The detached tau then aggregates into paired helical filaments and NFTs, while soluble tau oligomers have significant synaptotoxic effects by disrupting calcium homeostasis and synaptic plasticity, particularly in the hippocampal and cortical areas. Tau

pathology is more strongly associated with cognitive impairment than the burden of amyloid-β and serves as a vital downstream mediator of the neurotoxicity induced by amyloid-β [10].

2.3 Synaptic Loss, Neuroinflammation, and Oxidative Stress

Synaptic loss represents the most significant pathological indicator of cognitive decline in AD and occurs prior to noticeable neuronal death. Both amyloid-β (Aβ) oligomers and hyperphosphorylated tau directly interfere with synaptic structure and function by disrupting neurotransmitter release, modifying postsynaptic receptor signalling, and destabilizing dendritic spines, especially in the hippocampus and cerebral cortex. Soluble Aβ oligomers cause synaptic toxicity through the dysregulation of NMDA and AMPA receptor activity, calcium imbalance, and the inhibition of long-term potentiation, while pathological tau further worsens synaptic failure by hindering axonal transport and the trafficking of synaptic proteins. The progressive degeneration of synapses is accompanied by chronic neuroinflammation, which is driven by the persistent activation of microglia and astrocytes in response to Aβ plaques and neurofibrillary tangles [11] Activated glial cells secrete pro-inflammatory cytokines, such as tumour necrosis factor-α, interleukin-1β, and interleukin-6, along with chemokines and reactive nitrogen species, which exacerbate synaptic dysfunction and neuronal damage. Neuroinflammation also disrupts the mechanisms of synaptic pruning, resulting in the excessive removal of functional synapses. Concurrently, oxidative stress plays a crucial role in the pathogenesis of AD, stemming from mitochondrial dysfunction, weakened antioxidant defences, and the overproduction of reactive oxygen species [12] Oxidative damage to lipids, proteins, and nucleic acids undermines synaptic membrane integrity, disrupts mitochondrial energy metabolism, and encourages neuronal apoptosis. Crucially, oxidative stress and neuroinflammatory signalling intersect to diminish neurotrophic support by inhibiting the expression of BDNF and Trk-B receptor signalling, thereby impairing synaptic plasticity and pathways that promote neuronal survival. In summary, synaptic loss, chronic neuroinflammation, and oxidative stress create a self-reinforcing pathological triad that accelerates neuronal degeneration.

2.4 Neurotransmitter Imbalance

Neurotransmitter imbalance represents a fundamental neurochemical characteristic of AD, which is responsible for cognitive and behavioural impairments. In the later stages of AD, there is a significant reduction in the number of cholinergic neurons in certain brain regions; acetylcholine levels have diminished by over 75%, leading to memory impairment and cognitive deterioration. The degeneration of basal forebrain cholinergic neurons results in decreased acetylcholine concentrations in the hippocampus and cortex, which hinders learning and memory, forming the foundation for existing symptomatic treatments. Additionally, glutamatergic dysfunction, caused by amyloid-β–induced overactivation of NMDA receptors, results in excitotoxicity, calcium dysregulation, and synaptic failure [12]. Concurrently, impaired GABAergic inhibition leads to an excitatory–inhibitory imbalance and increased network hyperexcitability. Deficits in monoaminergic systems, including noradrenergic, serotonergic, and dopaminergic dysfunction, further exacerbate difficulties in attention, mood, sleep, and executive functioning. These changes are intricately associated with amyloid-β and tau pathology, oxidative stress, neuroinflammation, and diminished BDNF signalling, collectively indicating extensive synaptic dysfunction in AD [13].

2.5 Impairment of Neurotrophic Signaling

Among neurotrophic factors, BDNF is crucial for neuronal survival, synaptic plasticity, and the processes of learning and memory. BDNF primarily exerts its influence through the activation of the TrkB receptor, which initiates downstream signaling pathways such as PI3K/Akt, MAPK/ERK, and PLCγ, all of which are vital for synaptic maintenance and neuroprotection. Postmortem examinations of brains affected by AD have consistently revealed diminished levels of BDNF in critical cognitive areas, including the hippocampus and cerebral cortex [14]. This reduction is linked to impaired Trk-B signaling, decreased CREB phosphorylation, and compromised synaptic plasticity. Both amyloid-beta (Aβ) and tau pathology directly lead to the downregulation of BDNF by interfering with transcriptional regulation and the axonal transport of BDNF. The absence of BDNF-mediated neurotrophic support makes neurons increasingly susceptible to amyloid toxicity, tau-related synaptic dysfunction, oxidative stress, and inflammatory damage. As a result, the disruption of BDNF signaling constitutes a unifying pathological mechanism that connects various aspects of AD [15].

3. Fisetin Modulates Tau Pathology and Neurofibrillary Tangles

Tau pathology represents a fundamental characteristic AD, marked by the intracellular buildup of hyperphosphorylated tau protein and its aggregation into neurofibrillary tangles (NFTs). This process results in the destabilization of microtubules, neuronal dysfunction, and cognitive decline. Recent studies indicate that fisetin, a naturally occurring flavonoid, provides substantial neuroprotective benefits by influencing various facets of tau pathology [16] One of the key ways in which fisetin alleviates tau pathology is by inhibiting tau hyperphosphorylation. Hyperphosphorylation diminishes tau's binding affinity for microtubules, which encourages their disassembly and aids in the formation of NFTs. In both cellular and transgenic animal models of AD, fisetin has been demonstrated to significantly lower levels of hyperphosphorylated tau. This effect is partially mediated by the inhibition of glycogen synthase kinase-3β (GSK-3β), a crucial kinase involved in the pathological phosphorylation of tau. The overactivation of GSK-3β is closely associated with AD, and the suppression of this kinase by fisetin results in decreased tau phosphorylation and aggregation [17]

In addition to inhibiting kinases, fisetin promotes tau dephosphorylation by modulating protein phosphatase 2A (PP2A), the primary phosphatase responsible for tau regulation. The activation of PP2A facilitates the removal of excess phosphate groups from tau, thereby restoring its normal physiological state and curtailing NFT formation. By regulating tau-related kinases and phosphatases, fisetin effectively sustains tau phosphorylation homeostasis. Beyond its role in phosphorylation regulation, fisetin directly disrupts tau aggregation and encourages the disassembly of pre-existing tau filaments. Experimental research shows that fisetin interacts with tau protein, inhibiting its self-assembly into harmful oligomers and fibrils. This anti-aggregation characteristic is vital for maintaining tau in a soluble, non-toxic state and safeguarding neuronal integrity [18].

Fisetin's antioxidant and anti-inflammatory capabilities enhance its protective benefits against tau disease. Oxidative stress and persistent neuroinflammation are the primary causes of tau hyperphosphorylation and aggregation. Fisetin scavenges reactive oxygen species (ROS), lowers oxidative damage, and inhibits microglial and astrocytic activation, reducing the release of pro-inflammatory cytokines that worsen tau toxicity. Fisetin promotes the Nrf2 pathway, increasing antioxidant defences, while suppressing the NF-κB pathway, which regulates neuroinflammation linked to tau disease. Preclinical research in AD transgenic mouse models indicate fisetin's therapeutic potential by demonstrating reduced tau pathology, improved synaptic integrity, and improved cognitive performance after therapy. Overall, our findings suggest that fisetin modulates tau pathogenesis in multiple ways, including suppressing hyperphosphorylation, preventing aggregation, boosting tau clearance, and reducing oxidative stress and neuroinflammation [18].

4. Fisetin-mediated BDNF Modulation

BDNF serves as a crucial regulator of neuronal survival, synaptic plasticity, and cognitive function. Extensive clinical and experimental evidence indicates a significant decrease in BDNF expression and signaling in AD, especially in the hippocampus and cerebral cortex. This reduction contributes to synaptic degeneration, impaired long-term potentiation (LTP), neuronal loss, and progressive cognitive decline. As a result, the restoration of BDNF signaling has emerged as a promising strategy for modifying the disease in AD. Fisetin, a naturally occurring flavonoid known for its favourable permeability across the blood–brain barrier, has attracted significant interest due to its capacity to modulate various neuroprotective pathways, including the BDNF axis [19].

4.1 Regulation of BDNF Transcription via the ERK–CREB Pathway

A key mechanism through which fisetin boosts BDNF expression is the activation of the extracellular signal-regulated kinase (ERK)–cAMP response element-binding protein (CREB) signaling pathway. CREB serves as an essential transcription factor that regulates activity-dependent BDNF gene expression, and its phosphorylation is markedly diminished in the brains of individuals with AD. Fisetin facilitates the phosphorylation of ERK1/2, which in turn activates CREB and enhances the binding of phospho-CREB to cAMP response elements located within the promoters of BDNF genes. This process leads to an increase in both BDNF mRNA and protein levels in neuronal cells as well as in vivo models of cognitive impairment. Importantly, fisetin maintains CREB activation even in the presence of oxidative stress and amyloid-β (Aβ) toxicity, conditions that usually inhibit CREB signaling in AD, thus supporting both basal and activity-dependent transcription of BDNF in neurodegenerative contexts [20].

4.2 Enhancement of TrkB-Dependent Neuroprotective Signaling

In addition to enhancing the availability of BDNF, fisetin also strengthens downstream signaling via the BDNF high-affinity receptor, known as tropomyosin receptor kinase B (Trk-B). The activation of Trk-B triggers

neuroprotective cascades, notably the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, which is essential for neuronal survival, synaptic maintenance, and the ability to withstand apoptotic stimuli [21]. Fisetin promotes the phosphorylation of Akt and stabilizes PI3K/Akt signaling in pathological conditions, thereby enhancing the neuroprotective effects of endogenous BDNF. This dual mechanism—boosting BDNF expression while simultaneously enhancing Trk-B signaling—sets fisetin apart from other agents that focus solely on specific components of the neurotrophins [4].

4.3 Epigenetic Regulation of BDNF Expression

Recent studies indicate that fisetin may also influence BDNF transcription via epigenetic mechanism. AD is characterized by heightened histone deacetylase (HDAC) activity and diminished histone acetylation at BDNF promoters, resulting in transcriptional suppression. Fisetin has been shown to inhibit HDAC activity and increase histone acetylation, thus facilitating a chromatin structure that is conducive to BDNF gene transcription. This type of epigenetic modification may hold particular significance in the later stages of AD, where neuronal activity alone fails to adequately stimulate BDNF expression [22].

5. Additional neurodegenerative mechanism of Fisetin

5.1 Antioxidant Activity

Oxidative stress contributes significantly to the etiology of neurodegenerative diseases by causing neuronal damage, mitochondrial malfunction, and protein misfolding. Fisetin, a bioactive flavanol, has significant antioxidant activity, which contributes to its neuroprotective properties. It works as a direct scavenger of reactive oxygen species (ROS), decreasing lipid peroxidation, DNA damage, and neuronal protein oxidation. In addition to its free radical-scavenging capabilities, fisetin boosts endogenous antioxidant defences by increasing enzymes including superoxide dismutase, catalase, and glutathione peroxidase while preserving intracellular glutathione levels [23]. Fisetin also activates the Nrf2-ARE signaling pathway, which promotes the expression of cytoprotective genes involved in redox homeostasis. Furthermore, fisetin conserves mitochondrial function by lowering mitochondrial ROS production and maintaining membrane potential. Collectively, these antioxidant systems allow fisetin to reduce oxidative stress-induced neuronal degeneration and promote neuronal survival in neurodegenerative disorders [24].

5.2 Anti-Inflammatory Modulation

Fisetin is a natural flavonoid that has neuroprotective properties, primarily via decreasing neuroinflammation, which is a major contributor to neurodegenerative illnesses like Alzheimer's. It inhibits microglial activation, lowering the release of pro-inflammatory mediators like TNF-α, IL-1β, IL-6, NO, iNOS, and COX-2. Fisetin inhibits the NF-kB signaling pathway, a key regulator of inflammatory gene expression in the brain [25]. Furthermore, it inhibits TLR4-mediated inflammatory signaling and MAPK pathways, decreasing cytokine synthesis. Fisetin's antioxidant function lowers oxidative stress-induced inflammatory reactions. Overall, fisetin protects neurons by stopping the loop of inflammation and oxidative stress, which slows neuronal damage and disease progression in neurodegenerative illnesses [26].

5.3 Mitochondrial Protection

Mitochondrial malfunction is a significant cause of dementia, resulting in energy loss, oxidative stress, and neuronal death. Fisetin enhances cellular antioxidant defences and preserves mitochondrial membrane potential ($\Delta\Psi m$), hence protecting mitochondrial function. It decreases the overproduction of mitochondrial reactive oxygen species (ROS), reducing oxidative damage to mitochondrial DNA and respiratory chain enzymes. Fisetin also modulates apoptotic signaling by increasing anti-apoptotic proteins (Bcl-2) while decreasing pro-apoptotic factors (Bax, cytochrome-c release, and caspase-3 activation [27]. Furthermore, fisetin activates survival pathways like PI3K/Akt and AMPK, which promote mitochondrial biogenesis and energy homeostasis. Through these processes, fisetin maintains neuronal mitochondrial integrity, inhibits apoptosis, and contributes to its overall neuroprotective effect in neurodegenerative disorders [28].

5.4 Modulation of Synaptic Function and Plasticity

Synaptic dysfunction and lack of flexibility are early manifestations of neurodegenerative illnesses that are intimately linked to cognitive impairment. Fisetin improves synaptic function and plasticity by increasing BDNF and activating the TrkB signaling pathway. This stimulates the PI3K/Akt and MAPK/ERK pathways, which are

required for synaptic protein synthesis, dendritic spine development, and long-term potentiation (LTP). Fisetin also boosts the expression of synaptic proteins such synapsin-I and PSD-95, which enhances synaptic integrity and neurotransmission [29]. Fisetin reduces oxidative stress and neuroinflammation, preventing synaptic damage caused by β-amyloid toxicity. Overall, fisetin promotes neural connection, learning, and memory by maintaining synaptic structure and increasing activity-dependent synaptic plasticity [30].

5.5 Regulation of Apoptotic and Cell Survival Pathways

Fisetin protects neurons by suppressing apoptosis and boosting cell survival signaling, both of which are critical in neurodegenerative disorders. It inhibits the mitochondria-mediated intrinsic apoptotic pathway by enhancing anti-apoptotic Bcl-2 and lowering pro-apoptotic Bax, which prevents cytochrome-c release and caspase-9/caspase-3 activation. Fisetin promotes pro-survival pathways such as PI3K/Akt and ERK, hence improving neuronal survival, metabolism, and stress resistance. Fisetin reduces oxidative stress and neuroinflammation, which further inhibits apoptosis-inducing signals. Overall, fisetin alters the cellular balance from planned cell death to neuronal survival and functional maintenance in neurodegenerative diseases [31].

5.6 Enhancement of Autophagy

In neurodegenerative disorders, impaired autophagy leads to the buildup of misfolded proteins and damaged organelles. Fisetin promotes autophagy via activating AMPK and suppressing the mTOR signaling pathway, which are important regulators of autophagic flux. This stimulates autophagosome production and helps clear harmful protein clumps such β-amyloid, hyperphosphorylated tau, and damaged mitochondria. Fisetin decreases cellular stress, neuroinflammation, and apoptosis via enhancing autophagic degradation. Overall, fisetin-mediated autophagy repair promotes neuronal homeostasis and survival, which contributes to its neuroprotective properties in neurodegenerative illnesses [32].

6. Crosstalk Between BDNF Signaling and Tau Pathology: Fisetin

BDNF signaling is crucial for maintaining tau homeostasis through the Akt–glycogen synthase kinase-3β (GSK-3β) pathway. In AD, diminished BDNF levels hinder Akt activation, resulting in the disinhibition of GSK-3β and subsequent hyperphosphorylation of tau. By enhancing BDNF expression and Akt signaling, fisetin indirectly reduces GSK-3β activity, thus mitigating pathological tau phosphorylation. Furthermore, fisetin has demonstrated the ability to inhibit tau aggregation and promote the clearance of abnormal tau species, which lessens tau-related synaptic toxicity. Notably, pathological tau can inhibit CREB activation and BDNF transcription, creating a self-perpetuating cycle of neurodegeneration. Fisetin interrupts this harmful cycle by concurrently addressing tau pathology and reinstating BDNF signaling [33] .

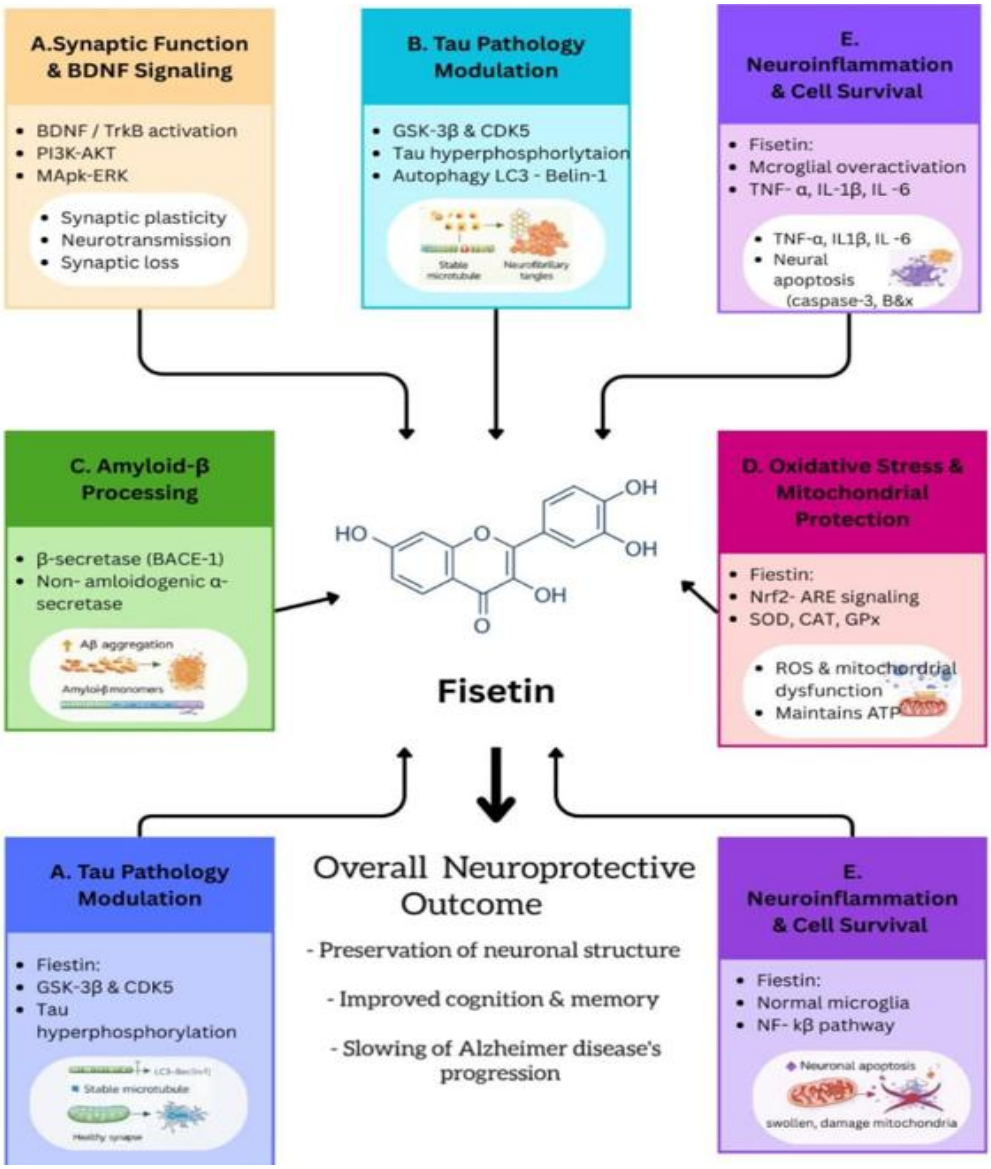

Figure.1: Multitarget Neuroprotective Action of Fisetin in AD

7. Preclinical and Clinical Studies

7.1 Preclinical Studies

Preclinical research show that fisetin has neuroprotective benefits, however clinical trials are needed to apply these findings to human treatment. Although clinical research on fisetin in AD is still in its early phases, preliminary results show promise. Mandel et al conducted a pilot clinical experiment to assess the safety and efficacy of fisetin supplementation in older adults with moderate cognitive impairment (MCI), a condition linked to AD. The study indicated that fisetin supplementation was well-tolerated and led to improved cognitive performance and everyday functioning [34]. Despite the limited sample size, these data indicate that fisetin may improve cognitive health in patients at risk for AD. Kanakis et al. investigated the impact of fisetin on indicators of oxidative stress and inflammation in patients with early-stage AD. Fisetin supplementation effectively reduced oxidative stress indicators and pro-inflammatory cytokines in plasma. Fisetin's antioxidant and anti-inflammatory effects have been linked to improved cognition test results in AD [35]. Further clinical trials are need to determine the efficacy and safety of fisetin in AD, despite promising results. Future research should focus on appropriate dose regimens, long-term effects, and the mechanisms behind fisetin's neuroprotective benefits in human. Additionally Combining fisetin with other medicinal treatments could improve its efficacy [36].

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8. Limitations and Future Perspectives

8.1 Limitation of fisetin in AD

Despite its promise neuroprotective and multitarget qualities, fisetin's therapeutic use in AD is hampered by a number of issues. Fisetin has low water solubility, oral bioavailability, fast metabolism, and limited blood-brain barrier penetration, resulting in insufficient brain concentrations. The lack of large-scale human clinical trials, as well as uniform dosage and treatment duration, further impedes its clinical translation [39]. Furthermore, fisetin exhibits low chemical stability and pleiotropic target activity, which may result in varied therapeutic outcomes. Potential interactions with cytochrome P450 enzymes, as well as insufficient evidence supporting its efficacy in the moderate to advanced stages of AD, are significant challenges**.**

8.2 Future Perspective

Future research on fisetin in AD should aim to overcome its pharmacokinetic limitations while increasing its disease-modifying potential. Advanced drug delivery systems, such as Nano formulations, liposomes, and solid lipid nanoparticles, may improve fisetin's bioavailability, chemical stability, and blood-brain barrier penetration. Structural optimization and prodrug development could further improve its pharmacokinetic profile and target specificity [36]. Importantly, future studies should emphasize fisetin’s ability to restore BDNF-mediated signaling pathways to support synaptic plasticity and cognitive function, while simultaneously attenuating Tau hyperphosphorylation and aggregation through modulation of kinases and enhancement of autophagy. Well-designed, large-scale clinical trials incorporating BDNF and phosphorylated Tau as biomarkers are essential to establish optimal dosing, safety, and therapeutic efficacy. Collectively, these approaches may position fisetin as a promising multitarget, disease-modifying candidate for AD [40].

9. Conclusion

Collectively, preclinical data points to fisetin being a strong neuroprotective flavonoid with important therapeutic implications in AD. Fisetin's therapeutic effects are achieved by multi-target regulation of important pathogenic pathways, with a focus on BDNF signaling and tau pathology, which are critical to synaptic integrity, neuronal survival, and cognitive function. Fisetin may alleviate the neurotrophins shortage seen in AD by increasing BDNF-mediated neurotrophic support and activating downstream signaling cascades involved in synaptic plasticity. Fisetin inhibits tau hyperphosphorylation and aggregation by modulating kinase activity and increasing autophagy-lysosomal clearance processes, lowering neurofibrillary tangle-associated neurotoxicity**.** Fisetin has antioxidant, anti-inflammatory, and anti-amyloidogenic effects that help reduce oxidative stress, decrease neuroinflammatory signaling, and limit amyloid-β-induced neuronal damage. It also directly affects BDNF and tau. This pleiotropic mechanism of action is especially useful in the setting of AD, which is caused by multiple and interconnected molecular events rather than a single pathogenic trigger.

Despite these promising results, the majority of evidence for fisetin's neuroprotective impact comes from in vitro and animal studies, emphasizing the need for more translational research. Future research should prioritize clinical validation, new delivery modalities to overcome bioavailability restrictions, and deeper mechanistic studies to better understand the specific interaction between BDNF restoration and tau pathology regulation. Overall, fisetin is a promising natural, multi-mechanistic candidate for the development of disease-modifying or complementary treatment methods in AD.

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