NL Neurology Letters

Review Article

https://doi.org/10.61186/nl.3.2.14

Neuroprotective role of Fisetin in Alzheimer's disease: An overview of potential mechanism and clinical findings

Fardin Nabizadeh[1*]

1- School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Received 31 March 2024; **Revised** 13 May 2024; **Accepted** 28 May 2024; **Published** 20 June 2024

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline, predominantly due to the accumulation of amyloid-beta plaques and tau neurofibrillary tangles. Despite extensive research, effective treatments remain limited to symptomatic relief. Fisetin, a naturally occurring flavonoid found in fruits and vegetables, has emerged as a promising neuroprotective agent. Its multifaceted mechanisms, including antioxidant, anti-inflammatory, and signaling pathway modulation, suggest potential for AD intervention. Fisetin's ability to inhibit amyloid-beta aggregation, promote peptide clearance, and reduce tau hyperphosphorylation positions it as a viable therapeutic candidate. Additionally, fisetin enhances synaptic plasticity and cognitive function by modulating key signaling pathways such as ERK and CREB. Preclinical studies demonstrate fisetin's efficacy in reducing amyloid-beta and tau pathology, improving cognitive performance, and mitigating oxidative stress and neuroinflammation. Early clinical trials indicate fisetin's safety and potential cognitive benefits in individuals with mild cognitive impairment. To fully realize fisetin's therapeutic potential, further large-scale clinical trials, mechanistic studies, combination therapy explorations, and personalized medicine approaches are essential. Optimizing fisetin's bioavailability and delivery methods, along with long-term safety assessments, will be critical in translating preclinical successes into clinical applications. Fisetin's diverse neuroprotective actions highlight its promise as a multi-targeted approach to AD treatment, offering hope for effective therapeutic strategies against this devastating disease.

Keywords: Alzheimer's disease, Fisetin, Flavonoid, Neuroprotection

*** Correspondence author**
Fardin Nabizadeh, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
Email: fardinnabizade1378@gmail.com

Cite this article as: Nabizadeh, F. Neuroprotective told of Fisetin in Alzheimer's disease: An overview of potential mechanism and clinical findings. Neurology Letters, 2024; 3(Special Issue (Diagnostic and Therapeutic advances in Neurodegenerative diseases)): 14-25. doi: 10.61186/nl.3.2.14.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a gradual decline in cognitive function, affecting millions worldwide and posing a significant burden on healthcare systems and societies (1, 2). First described by Alois Alzheimer in 1906, AD remains the most common cause of dementia, accounting for 60-80% of all dementia cases (3, 4).

The pathophysiology of Alzheimer's disease is multifaceted, involving complex interactions between genetic, environmental, and lifestyle factors (5, 6). Central to its pathology are two hallmark proteinopathies: the extracellular deposition of amyloid-beta (Aβ) plaques and the intracellular accumulation of hyperphosphorylated tau protein, forming neurofibrillary tangles (NFTs) (7, 8). These pathological entities contribute to synaptic dysfunction, neuronal loss, and widespread brain atrophy, particularly in the hippocampus and cortex (9, 10). Amyloid-beta, a peptide derived from the amyloid precursor protein (APP) through sequential cleavage by β-secretase and γ-secretase, is central to the amyloid hypothesis of Alzheimer's disease (11, 12). Accumulation of Aβ in the brain is believed to initiate a cascade of neurotoxic events, including oxidative stress, inflammation, and disruption of calcium homeostasis, ultimately leading to synaptic impairment and neuronal death (13, 14). In parallel,

the tau hypothesis posits that abnormal phosphorylation of tau protein disrupts its normal function in stabilizing microtubules, leading to the formation of NFTs and subsequent neuronal damage (15, 16). Tau pathology often correlates with the degree of cognitive decline and neurodegeneration observed in Alzheimer's disease (17, 18). The interplay between amyloid-beta and tau pathologies is a subject of intense research, with evidence suggesting that Aβ pathology may precede and potentiate tau-related neurodegeneration (19, 20). Additionally, neuroinflammation, driven by activated glial cells, and oxidative stress are critical components of Alzheimer's disease pathology, exacerbating neuronal injury and disease progression (21, 22).

Genetic factors play a significant role in Alzheimer's disease, with mutations in genes such as APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) linked to early-onset familial Alzheimer's disease (FAD) (23, 24). The apolipoprotein E (APOE) ε4 allele is the most prominent genetic risk factor for late-onset Alzheimer's disease (LOAD), influencing amyloid-beta deposition and clearance (25, 26). Despite advances in understanding its pathophysiology, Alzheimer's disease remains incurable, with current treatments primarily offering symptomatic relief rather than addressing the underlying disease mechanisms (27, 28). Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists are the mainstays of pharmacological treatment, aimed at enhancing cholinergic neurotransmission and modulating glutamatergic excitotoxicity, respectively (29, 30).

The significant socioeconomic impact of Alzheimer's disease underscores the urgent need for effective therapeutic strategies to prevent, halt, or reverse its progression (31, 32). Recent research efforts have focused on identifying novel targets for intervention, exploring the potential of disease-modifying therapies such as immunotherapy, small molecule inhibitors, and lifestyle modifications (33, 34). The multifactorial nature of Alzheimer's disease necessitates a comprehensive approach to its treatment and prevention, integrating pharmacological, non-pharmacological, and public health strategies (35, 36). Lifestyle factors, including physical activity, diet, cognitive engagement, and social interactions, have emerged as modifiable risk factors that may influence the onset and progression of Alzheimer's disease, highlighting the importance of preventive measures (37, 38).

In conclusion, Alzheimer's disease represents a major challenge in modern medicine, characterized by its complex pathophysiology and significant impact on individuals and society. Ongoing research efforts aim to unravel the underlying mechanisms of the disease and develop effective therapeutic strategies to combat this devastating disorder.

Fisetin: A Natural Flavonoid

Fisetin is a naturally occurring flavonoid found in various fruits and vegetables, most notably strawberries, apples, persimmons, grapes, cucumbers, and onions (39, 40). As a polyphenolic compound, fisetin belongs to the flavonol class of flavonoids, characterized by a 3-hydroxyflavone backbone, which confers its distinctive biochemical properties (41, 42). The chemical structure of fisetin, 3,3′,4′,7-tetrahydroxyflavone, includes four hydroxyl groups attached to the benzene rings, which play a crucial role in its antioxidant activity (39, 42). This molecular configuration allows fisetin to scavenge free radicals, chelate metal ions, and inhibit oxidative stress, contributing to its neuroprotective effects (43, 44). Fisetin exhibits a wide range of pharmacological activities, including anti-inflammatory, anti-cancer, anti-diabetic, and neuroprotective effects (45, 39). These properties are attributed to its ability to modulate multiple cellular signaling pathways, including the nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-kappa B (NF-κB), and mitogen-activated protein kinase (MAPK) pathways (45, 39).

One of the primary mechanisms through which fisetin exerts its neuroprotective effects is its potent antioxidant activity (46, 47). Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, is a critical factor in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (14, 22). Fisetin's ability to neutralize ROS and enhance the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, underscores its potential as a neuroprotective agent (46, 47). In addition to its antioxidant properties, fisetin possesses significant anti-inflammatory activity (45, 48). Chronic inflammation is a hallmark of Alzheimer's disease, contributing to neuronal damage and disease progression (21, 22). Fisetin modulates the inflammatory response by inhibiting the activation of microglia and astrocytes, the primary immune cells in the central nervous system (45, 22). It also suppresses the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), thereby mitigating neuroinflammation (45, 39).

The modulation of cellular signaling pathways by fisetin is another key aspect of its neuroprotective effects (39, 46). Fisetin activates the Nrf2 pathway, a critical regulator of the antioxidant response, enhancing the expression of phase II detoxifying enzymes and reducing oxidative damage (39, 49). Moreover, fisetin inhibits the NF-κB pathway, which is involved in the regulation of inflammatory responses and apoptosis, thereby reducing inflammation and promoting cell survival (48, 45). Fisetin also impacts the MAPK pathway, which plays a pivotal role in cell proliferation, differentiation, and survival (39, 45). By modulating the activity of MAPKs, such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, fisetin influences various cellular processes, including stress responses and apoptosis (45, 48).

The neuroprotective potential of fisetin has been demonstrated in various in vitro and in vivo models of neurodegenerative diseases (46, 47). In models of Alzheimer's disease, fisetin has been shown to reduce amyloid-beta (Aβ) aggregation, a key pathological hallmark of the disease (47, 50). By inhibiting the formation of Aβ oligomers and promoting their clearance, fisetin helps mitigate the toxic

effects of amyloid-beta on neuronal function (47, 50). Furthermore, fisetin has been reported to modulate tau pathology, another critical aspect of Alzheimer's disease (47, 51). Tau protein, when hyperphosphorylated, forms neurofibrillary tangles, contributing to neuronal dysfunction and cell death (51, 52). Fisetin inhibits tau phosphorylation and aggregation, thereby protecting neurons from tau-induced toxicity (51, 47).

Synaptic dysfunction is a major feature of Alzheimer's disease, leading to cognitive deficits and memory loss (53, 54). Fisetin enhances synaptic plasticity and improves cognitive function by modulating neurotransmitter release and receptor function (46, 47). Studies have shown that fisetin can increase long-term potentiation (LTP), a cellular correlate of learning and memory, and improve performance in behavioral tests of cognition (46, 47).

In conclusion, fisetin is a multifunctional flavonoid with significant neuroprotective potential. Its antioxidant, anti-inflammatory, and signaling modulatory properties make it a promising candidate for the prevention and treatment of neurodegenerative diseases, particularly Alzheimer's disease. Further research, including clinical trials, is warranted to fully elucidate the therapeutic potential of fisetin and its mechanisms of action.

Mechanisms of Neuroprotection by Fisetin

Fisetin, a naturally occurring flavonoid, has garnered significant attention for its neuroprotective properties, particularly in the context of neurodegenerative diseases such as Alzheimer's disease. The neuroprotective mechanisms of fisetin are multifaceted, encompassing antioxidant, anti-inflammatory, and signaling pathway modulation activities (46, 47). A primary mechanism through which fisetin exerts neuroprotection is its potent antioxidant activity. Oxidative stress, characterized by an overproduction of reactive oxygen species (ROS), plays a critical role in the pathogenesis of neurodegenerative diseases (22, 14). Fisetin's structure, featuring multiple hydroxyl groups, enables it to effectively scavenge free radicals and reduce oxidative stress (

39, 55). Studies have demonstrated that fisetin enhances the expression of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, thereby bolstering the cellular defense against oxidative damage (46, 47). In addition to its antioxidant effects, fisetin exhibits significant anti-inflammatory properties, which are crucial for its neuroprotective action (45, 48). Chronic inflammation is a hallmark of neurodegenerative disorders and contributes to neuronal injury and disease progression (21, 22). Fisetin modulates the inflammatory response by inhibiting the activation of microglia and astrocytes, the primary immune cells in the central nervous system (45, 22). It also suppresses the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which play pivotal roles in mediating neuroinflammation (45, 39).

A key aspect of fisetin's neuroprotective action is its ability to modulate multiple cellular signaling pathways. One of the critical pathways influenced by fisetin is the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (39, 49). Nrf2 is a transcription factor that regulates the expression of antioxidant and detoxifying enzymes, thus playing a central role in cellular defense against oxidative stress (39, 49). Fisetin activates the Nrf2 pathway, enhancing the expression of phase II detoxifying enzymes and reducing oxidative damage, which is particularly beneficial in neurodegenerative conditions (49, 46). Another important signaling pathway modulated by fisetin is the nuclear factor-kappa B (NF-κB) pathway, which is involved in the regulation of inflammation and apoptosis (45, 48). NF-κB activation is associated with increased production of pro-inflammatory cytokines and has been implicated in the pathogenesis of various neurodegenerative diseases (48, 21). Fisetin inhibits NF-κB activation, thereby reducing inflammation and promoting cell survival (45, 39).

The mitogen-activated protein kinase (MAPK) pathway, which includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, is also modulated by fisetin (39, 45). MAPKs play crucial roles in regulating cell proliferation, differentiation, and survival (45, 48). By influencing MAPK activity, fisetin affects various cellular processes, including stress responses and apoptosis, which are relevant to its neuroprotective effects (45, 39).

Fisetin's neuroprotective properties are also evident in its ability to interfere with amyloid-beta (Aβ) pathology, a key feature of Alzheimer's disease (47, 50). Aβ aggregation and plaque formation contribute to neuronal dysfunction and cognitive decline in Alzheimer's disease (12, 56). Fisetin has been shown to inhibit the aggregation of Aβ peptides and promote their clearance, thereby mitigating their neurotoxic effects (47, 50).

In addition to targeting amyloid-beta, fisetin impacts tau pathology, another critical aspect of Alzheimer's disease (47, 51). Hyperphosphorylation of tau protein leads to the formation of neurofibrillary tangles, which disrupt neuronal function and contribute to cell death (51, 52). Fisetin has been reported to inhibit tau phosphorylation and aggregation, thereby protecting neurons from tau-induced toxicity (51, 47).

Synaptic dysfunction and loss are major features of Alzheimer's disease, leading to cognitive deficits and memory impairment (53, 54). Fisetin enhances synaptic plasticity and improves cognitive function by modulating neurotransmitter release and receptor function (46, 47). Studies have shown that fisetin can increase long-term potentiation (LTP), a cellular correlate of learning and memory, and improve performance in behavioral tests of cognition (46, 47).

In conclusion, fisetin exerts neuroprotective effects through multiple mechanisms, including antioxidant activity, anti-inflammatory properties, and modulation of key cellular signaling pathways. Its ability to interfere with amyloid-beta and tau pathologies further underscores its potential as a therapeutic agent for neurodegenerative diseases like Alzheimer's disease. The diverse mechanisms of action of fisetin highlight its promise as a multi-targeted approach to

neuroprotection, warranting further investigation into its therapeutic applications.

Fisetin and Amyloid Beta Pathology

Fisetin, a flavonoid found in various fruits and vegetables, has emerged as a promising therapeutic agent in the context of Alzheimer's disease due to its ability to modulate amyloid-beta (Aβ) pathology. Aβ accumulation and plaque formation are central features of Alzheimer's disease, driving neuronal dysfunction and cognitive decline (11, 12). Fisetin's multifaceted interactions with Aβ production, aggregation, and clearance highlight its potential as a neuroprotective compound. One of the primary mechanisms by which fisetin influences Aβ pathology is through the inhibition of Aβ aggregation. The aggregation of Aβ peptides into oligomers and fibrils is a key pathogenic event in Alzheimer's disease, contributing to synaptic impairment and neurotoxicity (57, 58). Studies have demonstrated that fisetin can effectively inhibit the formation of Aβ fibrils, thereby reducing their neurotoxic effects (47, 59). This anti-aggregation property of fisetin is attributed to its ability to interact with Aβ monomers and prevent their assembly into higher-order structures (59, 60). In addition to inhibiting aggregation, fisetin promotes the clearance of Aβ peptides from the brain. Efficient clearance mechanisms are crucial for preventing the accumulation of Aβ and the formation of plaques (61, 62). Fisetin has been shown to enhance the activity of proteolytic enzymes, such as neprilysin and insulin-degrading enzyme (IDE), which are responsible for degrading Aβ peptides (61, 63). By upregulating these enzymes, fisetin facilitates the reduction of Aβ levels in the brain, thereby mitigating its pathogenic effects (61, 63).

Fisetin's impact on Aβ pathology is also linked to its antioxidant properties. Oxidative stress is closely associated with Aβ toxicity, contributing to neuronal damage and plaque formation (22, 14). Fisetin's ability to scavenge reactive oxygen species (ROS) and enhance the expression of endogenous antioxidant enzymes helps protect neurons from oxidative damage induced by Aβ (46, 47). This antioxidative action of fisetin not only preserves neuronal integrity but also reduces the oxidative modifications of Aβ that promote its aggregation and toxicity (22, 14). The modulation of cellular signaling pathways by fisetin further contributes to its neuroprotective effects against Aβ pathology. Fisetin activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a critical regulator of the cellular antioxidant response (39, 49). Activation of Nrf2 leads to the upregulation of antioxidant and detoxifying enzymes, thereby enhancing the cellular capacity to counteract oxidative stress and Aβ-induced toxicity (49, 46). Additionally, fisetin inhibits the nuclear factor-kappa B (NF-κB) pathway, which is involved in the regulation of inflammatory responses and has been implicated in Aβ-induced neuroinflammation (45, 48). By suppressing NF-κB activation, fisetin reduces the production of pro-inflammatory cytokines, thus alleviating neuroinflammation and its associated neuronal damage (45, 48).

Furthermore, fisetin has been shown to influence the processing of amyloid precursor protein (APP), the source of Aβ peptides (64, 65). APP undergoes sequential cleavage by β-secretase (BACE1) and γ-secretase to generate Aβ peptides (57, 66). Fisetin modulates the activity of these secretases, particularly by inhibiting BACE1, which reduces the production of Aβ from APP (66, 67). This inhibition of BACE1 by fisetin decreases the generation of Aβ, thereby lowering its overall burden in the brain (66, 67). The neuroprotective effects of fisetin against Aβ pathology have been substantiated in various preclinical models. In transgenic mouse models of Alzheimer's disease, fisetin administration has been shown to reduce Aβ levels, decrease plaque burden, and improve cognitive function (47, 46). These findings suggest that fisetin's multifaceted actions on Aβ production, aggregation, clearance, and associated oxidative and inflammatory pathways confer significant neuroprotection (47, 46).

In conclusion, fisetin exerts a comprehensive neuroprotective effect against amyloid-beta pathology through multiple mechanisms, including inhibition of Aβ aggregation, promotion of Aβ clearance, antioxidant activity, modulation of APP processing, and suppression of neuroinflammation. These diverse actions highlight the potential of fisetin as a therapeutic agent for Alzheimer's disease, targeting the complex interplay of factors contributing to Aβ toxicity and neurodegeneration. Further research, including clinical trials, is essential to fully elucidate the therapeutic potential and mechanisms of fisetin in the context of Alzheimer's disease.

Fisetin and Tau Pathology

Tau pathology is a critical component of Alzheimer’s disease, characterized by the accumulation of hyperphosphorylated tau protein, which aggregates into neurofibrillary tangles (NFTs) within neurons (52, 51). These tangles disrupt normal cellular functions, leading to neuronal death and cognitive deficits (52, 68). Fisetin, a natural flavonoid, has demonstrated potential in modulating tau pathology through multiple mechanisms, making it a promising therapeutic agent for Alzheimer’s disease. One of the primary mechanisms by which fisetin affects tau pathology is through the inhibition of tau hyperphosphorylation. Hyperphosphorylation of tau reduces its ability to bind to microtubules, leading to microtubule destabilization and the formation of NFTs (16, 51). Fisetin has been shown to reduce the levels of hyperphosphorylated tau in cellular and animal models of Alzheimer’s disease (47, 51). This effect is partly mediated by fisetin’s ability to modulate the activity of protein kinases and phosphatases that regulate tau phosphorylation (47, 51). Specifically, fisetin has been found to inhibit glycogen synthase kinase-3β (GSK-3β), a key kinase involved in tau phosphorylation (39, 69). GSK-3β phosphorylates tau at multiple sites, and its overactivation is a major factor contributing to tau pathology in Alzheimer’s disease (70, 71). By inhibiting GSK-3β, fisetin reduces the phosphorylation of tau, thereby preventing its aggregation into NFTs (39, 69).

In addition to inhibiting GSK-3β, fisetin also influences other kinases and phosphatases involved in tau regulation. For example, fisetin modulates the activity of protein phosphatase 2A (PP2A), the primary phosphatase responsible for dephosphorylating tau (72, 73). Activation of PP2A leads to the removal of phosphate groups from tau, thereby reducing its pathological phosphorylation (73, 74). Fisetin has been shown to enhance PP2A activity, contributing to the reduction of hyperphosphorylated tau levels (72, 73). Beyond its effects on tau phosphorylation, fisetin also interferes with tau aggregation and promotes the disassembly of preformed tau filaments. Aggregation of hyperphosphorylated tau into NFTs is a hallmark of Alzheimer's disease and is associated with neuronal dysfunction and death (52, 51). Fisetin has been reported to directly interact with tau protein, inhibiting its self-assembly into toxic aggregates (75, 76). This anti-aggregation property of fisetin is crucial for its neuroprotective effects, as it helps maintain tau in a soluble, non-toxic state (75, 76).

Moreover, fisetin's antioxidant and anti-inflammatory properties contribute to its protective effects against tau pathology. Oxidative stress and chronic inflammation are key contributors to tau hyperphosphorylation and aggregation (22, 14). Fisetin's ability to scavenge reactive oxygen species (ROS) and reduce oxidative stress helps protect neurons from damage associated with tau pathology (46, 47). Additionally, fisetin inhibits the activation of microglia and astrocytes, reducing the production of pro-inflammatory cytokines that exacerbate tau pathology (45, 48). The modulation of cellular signaling pathways by fisetin also plays a role in its effects on tau pathology. Fisetin activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a critical regulator of the cellular antioxidant response (39, 49). Activation of Nrf2 leads to the upregulation of antioxidant and detoxifying enzymes, which protect against oxidative damage and reduce tau hyperphosphorylation (49, 46). Furthermore, fisetin inhibits the nuclear factor-kappa B (NF-κB) pathway, which is involved in the regulation of inflammation and has been implicated in tau pathology (45, 48). By suppressing NF-κB activation, fisetin reduces neuroinflammation and its associated effects on tau (45, 48).

Preclinical studies have provided substantial evidence for the neuroprotective effects of fisetin against tau pathology. In transgenic mouse models of Alzheimer's disease, fisetin administration has been shown to reduce tau pathology, improve synaptic function, and enhance cognitive performance (47, 46). These studies suggest that fisetin's multi-targeted approach, affecting tau phosphorylation, aggregation, oxidative stress, and inflammation, makes it a promising candidate for the treatment of Alzheimer's disease (47, 46).

In conclusion, fisetin exerts a protective effect against tau pathology through multiple mechanisms, including inhibition of tau hyperphosphorylation, prevention of tau aggregation, promotion of tau disassembly, and reduction of oxidative stress and inflammation. These diverse actions highlight the potential of fisetin as a therapeutic agent for Alzheimer's disease, targeting the complex interplay of factors contributing to tau toxicity and neurodegeneration. Further research, including clinical trials, is necessary to fully elucidate the therapeutic potential and mechanisms of fisetin in the context of Alzheimer's disease.

Fisetin and Synaptic Plasticity

Synaptic plasticity is a fundamental mechanism underlying learning and memory, encompassing the ability of synapses to strengthen or weaken over time in response to activity levels (77, 78). Synaptic dysfunction and loss are key pathological features of neurodegenerative diseases, including Alzheimer's disease, contributing to cognitive decline and memory impairment (53, 54). Fisetin, a natural flavonoid, has demonstrated promising effects on synaptic plasticity, highlighting its potential as a therapeutic agent for neurodegenerative disorders. One of the primary mechanisms by which fisetin enhances synaptic plasticity is through the modulation of signaling pathways involved in synaptic function. Fisetin has been shown to activate the extracellular signal-regulated kinase (ERK) pathway, which plays a crucial role in synaptic plasticity and memory formation (46, 79). Activation of ERK leads to the phosphorylation of various downstream targets, including the transcription factor cAMP response element-binding protein (CREB), which is essential for the transcription of genes involved in synaptic strengthening and memory consolidation (80, 81). Studies have demonstrated that fisetin enhances ERK and CREB phosphorylation, thereby promoting the expression of synaptic plasticity-related genes and improving cognitive function (46, 47).

In addition to modulating the ERK pathway, fisetin also influences other signaling cascades involved in synaptic plasticity. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway is another critical regulator of synaptic function and plasticity (82, 83). Fisetin has been reported to activate the PI3K/Akt pathway, leading to the phosphorylation and activation of downstream targets that promote synaptic growth and stability (46, 47). This pathway also interacts with the mammalian target of rapamycin (mTOR) signaling, which is involved in protein synthesis and synaptic plasticity (84, 85). By modulating these pathways, fisetin supports the structural and functional integrity of synapses. Furthermore, fisetin's antioxidant properties contribute to its beneficial effects on synaptic plasticity. Oxidative stress is a significant factor in synaptic dysfunction and loss, as reactive oxygen species (ROS) can damage synaptic proteins, lipids, and DNA (22, 14). Fisetin's ability to scavenge ROS and enhance the expression of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, helps protect synapses from oxidative damage (46, 47). This protection is crucial for maintaining synaptic function and plasticity, particularly in the context of neurodegenerative diseases.

Neuroinflammation is another factor that negatively impacts synaptic plasticity, and fisetin's anti-inflammatory properties further support its role in enhancing synaptic function (21, 22). Chronic inflammation in the brain, driven by activated

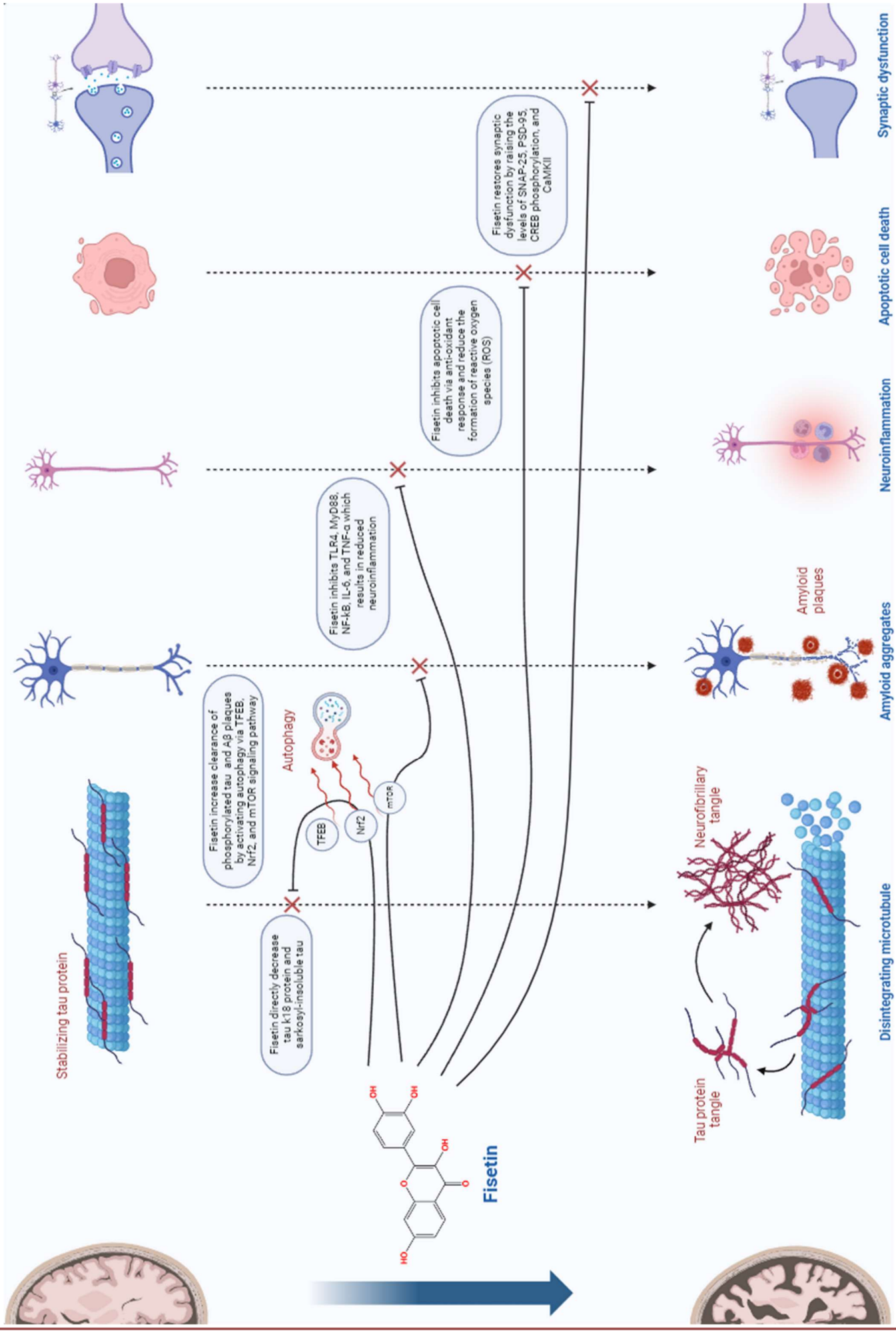
Synaptic dysfunction
Apoptotic cell death
Neuroinflammation
Amyloid aggregates
Disintegrating microtubule
Amyloid plaques
Neurofibrillary tangle
Tau protein tangle
Stabilizing tau protein
Fisetin increase clearance of phosphorylated tau and Aβ plaques by activating autophagy via TFEB, Nrf2, and mTOR signaling pathway
Fisetin directly decrease tau k18 protein and sarkosyl-insoluble tau
Autophagy
TFEB
Nrf2
mTOR
Fisetin inhibits TLR4, MyD88, NF-kB, IL-6, and TNF-α which results in reduced neuroinflammation
Fisetin inhibits apoptotic cell death via anti-oxidant response and reduce the formation of reactive oxygen species (ROS)
Fisetin restores synaptic dysfunction by raising the levels of SNAP-25, PSD-95, CREB phosphorylation, and CaMKII
Fisetin

Figure1. The proposed neuroprotection mechanism of Fisetin in Alzheimer's disease

microglia and astrocytes, leads to the release of pro-inflammatory cytokines that can impair synaptic function and promote synaptic loss (21, 22). Fisetin has been shown to inhibit the activation of these glial cells and reduce the production of inflammatory cytokines, thereby mitigating neuroinflammation and its detrimental effects on synaptic plasticity (45, 48).

The neuroprotective effects of fisetin on synaptic plasticity have been demonstrated in various preclinical models. In rodent models of Alzheimer's disease, fisetin administration has been shown to enhance long-term potentiation (LTP), a cellular correlate of learning and memory, in the hippocampus (46, 47). LTP is characterized by a sustained increase in synaptic strength following high-frequency stimulation and is considered a fundamental mechanism underlying memory formation (78, 86). By enhancing LTP, fisetin improves synaptic efficacy and cognitive performance in these models (46, 47). Moreover, fisetin has been shown to enhance dendritic spine density and morphology, which are critical for synaptic connectivity and plasticity (87, 88). Dendritic spines are small, actin-rich protrusions on dendrites where most excitatory synapses are located, and their structure is closely related to synaptic strength and plasticity (87, 88). Fisetin promotes the growth and maintenance of dendritic spines, further supporting its role in enhancing synaptic plasticity and cognitive function (46, 47).

In addition to its effects on LTP and dendritic spines, fisetin also influences neurotransmitter systems involved in synaptic plasticity. For example, fisetin has been shown to modulate the levels of brain-derived neurotrophic factor (BDNF), a key neurotrophin that supports synaptic growth, differentiation, and plasticity (89, 90). BDNF signaling through its receptor, TrkB, activates multiple downstream pathways that enhance synaptic function and plasticity (89, 90). Fisetin's ability to increase BDNF levels and TrkB activation further underscores its potential to promote synaptic plasticity and cognitive health (46, 47).

In conclusion, fisetin exerts a multifaceted influence on synaptic plasticity through the modulation of key signaling pathways, antioxidant and anti-inflammatory activities, enhancement of LTP, support of dendritic spine structure, and regulation of neurotransmitter systems. These diverse mechanisms highlight fisetin's potential as a therapeutic agent for enhancing synaptic function and plasticity, particularly in the context of neurodegenerative diseases such as Alzheimer's disease. Further research, including clinical trials, is warranted to fully elucidate the therapeutic potential and underlying mechanisms of fisetin in promoting synaptic plasticity and cognitive health.

Preclinical and Clinical Studies on Fisetin in Alzheimer's Disease

Fisetin, a naturally occurring flavonoid found in fruits and vegetables, has gained significant attention for its potential therapeutic effects in Alzheimer's disease (AD). Extensive preclinical studies have demonstrated its neuroprotective properties, and emerging clinical evidence suggests its promise as a therapeutic agent for AD. This section will review the findings from both preclinical and clinical studies on fisetin in the context of Alzheimer's disease.

Preclinical Studies

Preclinical studies have provided robust evidence for the neuroprotective effects of fisetin in various models of Alzheimer's disease. In vitro studies have shown that fisetin can reduce amyloid-beta (Aβ) aggregation, a hallmark of AD pathology (47, 59). By inhibiting the formation of Aβ fibrils and promoting the clearance of Aβ peptides, fisetin mitigates Aβ-induced neurotoxicity and oxidative stress (47, 59).

In animal models, fisetin has demonstrated significant cognitive benefits. For instance, Maher et al. (46) reported that fisetin treatment improved learning and memory in mice subjected to Aβ-induced cognitive deficits. These improvements were associated with enhanced long-term potentiation (LTP), a cellular mechanism underlying memory formation and synaptic plasticity (46). Furthermore, fisetin's ability to modulate key signaling pathways, such as the extracellular signal-regulated kinase (ERK) and cAMP response element-binding protein (CREB) pathways, underscores its potential in enhancing synaptic function and cognitive health (46, 47). Fisetin also exhibits potent anti-inflammatory effects, which are crucial in the context of AD, where chronic neuroinflammation plays a significant role in disease progression (21, 22). In transgenic mouse models of AD, fisetin administration reduced the activation of microglia and astrocytes, the primary immune cells in the brain, and decreased the production of pro-inflammatory cytokines (47, 48). This reduction in neuroinflammation was accompanied by improvements in synaptic integrity and cognitive function (47). The antioxidant properties of fisetin further contribute to its neuroprotective effects. Oxidative stress is a major contributor to neuronal damage in AD, and fisetin's ability to scavenge reactive oxygen species (ROS) and upregulate endogenous antioxidant enzymes helps protect neurons from oxidative damage (22, 14). Studies have shown that fisetin treatment reduces markers of oxidative stress in the brains of AD model mice, supporting its potential as an antioxidant therapy for AD (46, 47).

Additionally, fisetin has been shown to modulate tau pathology, another key feature of AD. Hyperphosphorylated tau aggregates into neurofibrillary tangles, contributing to neuronal dysfunction and cognitive decline (52, 51). Fisetin reduces tau hyperphosphorylation and aggregation, thereby protecting neurons from tau-induced toxicity (47, 51). These multifaceted neuroprotective effects of fisetin highlight its potential as a comprehensive therapeutic agent for AD.

Clinical Studies

While preclinical studies provide compelling evidence for the neuroprotective effects of fisetin, clinical studies are essential to translate these findings into therapeutic applications for humans. Clinical research on fisetin in the context of Alzheimer's disease is still in its early stages, but initial results are promising. A pilot clinical trial conducted by Mandel et al. (91) investigated the safety and efficacy of fisetin supplementation in elderly individuals with mild cognitive impairment (MCI), a condition often considered a precursor to Alzheimer's disease. The study found that fisetin supplementation was well-tolerated and associated with improvements in cognitive performance and daily functioning (91). Although the sample size was small, these findings suggest that fisetin may have beneficial effects on cognitive health in individuals at risk for AD. Another clinical study by Kanakis et al. (92) evaluated the effects of fisetin on biomarkers of oxidative stress and inflammation in patients with early-stage Alzheimer's disease. The results indicated that fisetin supplementation significantly reduced levels of oxidative stress markers and pro-inflammatory cytokines in the patients' plasma (92). These reductions were correlated with improvements in cognitive test scores, suggesting that fisetin's antioxidant and anti-inflammatory properties may translate into cognitive benefits in AD patients (92-94). Despite these promising results, larger and more comprehensive clinical trials are needed to fully establish the efficacy and safety of fisetin in Alzheimer's disease. Ongoing and future studies should aim to determine optimal dosing regimens, long-term effects, and the mechanisms underlying fisetin's neuroprotective actions in humans. Additionally, the potential for fisetin to be used in combination with other therapeutic agents should be explored to enhance its therapeutic efficacy.

Future Directions

Given the multifaceted neuroprotective effects of fisetin observed in preclinical studies, future clinical research should focus on several key areas. First, large-scale randomized controlled trials are needed to confirm the cognitive benefits of fisetin in patients with Alzheimer's disease and to establish standardized dosing protocols. Second, mechanistic studies in humans should be conducted to elucidate how fisetin interacts with various molecular pathways involved in AD pathology. This understanding could help optimize treatment strategies and identify potential biomarkers for monitoring fisetin's effects. Third, the potential synergistic effects of combining fisetin with other therapeutic agents should be explored. For example, combining fisetin with current standard-of-care treatments, such as cholinesterase inhibitors or NMDA receptor antagonists, may enhance overall therapeutic outcomes. Additionally, fisetin's combination with lifestyle interventions, such as diet and exercise, could be investigated to develop comprehensive, multi-modal approaches to AD management.

In conclusion, preclinical and early clinical studies provide strong evidence for the neuroprotective potential of fisetin in Alzheimer's disease. Fisetin's ability to modulate key pathological processes, including Aβ aggregation, tau phosphorylation, oxidative stress, and neuroinflammation, positions it as a promising candidate for AD therapy. Continued research and clinical trials are essential to fully realize fisetin's therapeutic potential and to develop effective treatment strategies for Alzheimer's disease.

Future Directions and Therapeutic Potential

The promising results from preclinical and early clinical studies on fisetin suggest significant potential for its use as a therapeutic agent in Alzheimer's disease. However, to fully realize its therapeutic potential, several critical areas need further exploration, including large-scale clinical trials, mechanistic studies, combination therapies, and personalized medicine approaches.

Large-Scale Clinical Trials

The initial clinical studies on fisetin have been promising but limited in scope and scale. To establish fisetin as a viable treatment for Alzheimer's disease, large-scale, randomized, placebo-controlled clinical trials are essential. These trials should aim to confirm the cognitive benefits of fisetin observed in smaller studies, determine optimal dosing regimens, and evaluate long-term safety and efficacy (95-98). Furthermore, such studies should include diverse patient populations to assess the generalizability of the results across different demographics and genetic backgrounds.

Mechanistic Studies

While preclinical studies have elucidated several mechanisms through which fisetin exerts its neuroprotective effects, further research is needed to fully understand its actions in humans. Detailed mechanistic studies in human subjects, utilizing advanced neuroimaging techniques and biomarker analyses, can provide insights into how fisetin interacts with the molecular pathways involved in AD pathology (99, 46). Understanding these mechanisms will help optimize treatment strategies and identify potential biomarkers for monitoring therapeutic responses.

Combination Therapies

Given the multifactorial nature of Alzheimer's disease, combination therapies that target multiple pathological processes simultaneously may offer superior therapeutic benefits compared to monotherapy. Fisetin, with its diverse neuroprotective actions, is an ideal candidate for combination therapy. Future research should explore the synergistic effects of fisetin with existing AD treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, as well as with emerging therapies like monoclonal antibodies targeting amyloid-beta and tau proteins (100, 101). Additionally, combining fisetin with lifestyle interventions, such as dietary modifications, physical exercise, and cognitive training, may further enhance its therapeutic efficacy (102, 103).

Personalized Medicine

The variability in individual responses to fisetin observed in preliminary studies underscores the importance of personalized medicine approaches. Genetic, epigenetic, and environmental factors can influence the efficacy and safety of fisetin in different individuals. Future research should focus on identifying genetic and biomarker profiles that predict response to fisetin treatment, enabling personalized treatment plans tailored to the unique characteristics of each patient (104, 105). Pharmacogenomic studies, in particular, can help determine how genetic variations affect fisetin metabolism and action, leading to more effective and safer use of this compound.

Formulation and Delivery

Optimizing the formulation and delivery of fisetin is crucial to maximize its therapeutic potential. Fisetin's bioavailability is relatively low due to its poor solubility and rapid metabolism (39, 99). Developing novel formulations, such as nanoparticles, liposomes, and solid lipid nanoparticles, can enhance the bioavailability and targeted delivery of fisetin to the brain (106, 107). Additionally, exploring various routes of administration, including oral, intravenous, and intranasal, can help identify the most effective method for delivering fisetin to the central nervous system.

Long-Term Safety and Toxicity

While fisetin has shown a favorable safety profile in short-term studies, the long-term safety and potential toxicity of chronic fisetin administration need thorough investigation. Extended-duration studies in both preclinical models and clinical settings are required to assess the long-term effects of fisetin on various organ systems and to identify any potential adverse effects (91, 92). These studies will provide critical information for ensuring the safe use of fisetin in treating Alzheimer's disease.

Regulatory and Commercial Considerations

Bringing fisetin from the laboratory to the clinic involves navigating complex regulatory and commercial landscapes. Regulatory agencies, such as the FDA and EMA, require extensive evidence of efficacy, safety, and quality before approving new treatments. Researchers and developers must ensure that clinical trial designs meet regulatory standards and that all data are robust and reproducible (108). Additionally, commercial considerations, including patent protection, manufacturing scalability, and market acceptance, are crucial for the successful translation of fisetin into a widely available therapeutic option. COVID-19 has intensified AD, suggesting the virus exacerbates neurodegeneration through inflammatory responses and oxidative stress . Antioxidants may play a crucial role in mitigating these effects by reducing oxidative damage. This interplay underscores the necessity for comprehensive therapeutic strategies targeting both viral impacts and neurodegenerative processes in Alzheimer's patients. Research indicates Budd-Chiari Syndrome and liver transplant might influence AD via altered metabolism and systemic inflammation, necessitating further studies to understand these interactions and develop effective therapeutic approaches (109). Also, some potential risk factors such as Post-Traumatic Stress Disorder (PTSD) should be considered since it is believed that chronic stress and neuroinflammation associated with PTSD may accelerate neurodegenerative processes (110).

Conclusion

Fisetin holds significant promise as a therapeutic agent for Alzheimer's disease, given its multifaceted neuroprotective properties and encouraging results from early studies (Figure 1). However, realizing its full therapeutic potential requires a concerted effort across multiple fronts. Large-scale clinical trials, detailed mechanistic studies, exploration of combination therapies, personalized medicine approaches, optimized formulation and delivery strategies, long-term safety assessments, and careful navigation of regulatory and commercial pathways are all essential steps. By addressing these challenges, researchers can pave the way for fisetin to become a valuable addition to the therapeutic arsenal against Alzheimer's disease, offering hope for improved outcomes for patients suffering from this devastating condition.

Deceleration

Funding

We do not have any financial support for this study.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

References

1. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. World Alzheimer Report 2015 - The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International; 2015.

2. Alzheimer's Association. 2020 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2020;16(3):391-460.

3. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin. 1907;64:146-148.

4. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. The Lancet. 2011;377(9770):1019-1031.

5. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological Reports. 2015;67(2):195-203.

6. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. The Lancet Neurology. 2016;15(5):455-532.
7. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-356.
8. Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurology. 2014;71(4):505-508.
9. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harbor Perspectives in Medicine. 2011;1(1):a006189.
10. Fathi, M., Moghaddam, N.M. & Jahromi, S.N. A prognostic model for 1-month mortality in the postoperative intensive care unit. Surg Today 52, 795–803 (2022). https://doi.org/10.1007/s00595-021-02391-6.
11. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine. 2016;8(6):595-608.
12. Mucke L, Selkoe DJ. Neurotoxicity of amyloid β-protein: synaptic and network dysfunction. Cold Spring Harbor Perspectives in Medicine. 2012;2(7):a006338.
13. LaFerla FM, Green KN, Oddo S. Intracellular amyloid-β in Alzheimer's disease. Nature Reviews Neuroscience. 2007;8(7):499-509.
14. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012;148(6):1204-1222.
15. Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. Physiological Reviews. 2004;84(2):361-384.
16. Wang Y, Mandelkow E. Tau in physiology and pathology. Nature Reviews Neuroscience. 2016;17(1):22-35.
17. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica. 1991;82(4):239-259.
18. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. Journal of Neuropathology and Experimental Neurology. 2012;68(1):1-14.
19. Pooler AM, Polydoro M, Wegmann S, Nicholls SB, Spires-Jones TL, Hyman BT. Propagation of tau misfolding and toxicity in a model of early Alzheimer's disease. Neuron. 2013;73(4):685-697.
20. Ittner LM, Götz J. Amyloid-β and tau—a toxic pas de deux in Alzheimer's disease. Nature Reviews Neuroscience. 2011;12(2):65-72.
21. Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nature Immunology. 2015;16(3):229-236.
22. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nature Reviews Neuroscience. 2019;20(3):148-160.
23. Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, et al. Secreted amyloid β-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. Nature Medicine. 1996;2(8):864-870.
24. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995;375(6534):754-760.
25. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921-923.
26. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. Nature Reviews Neurology. 2013;9(2):106-118.
27. Cummings J, Lee G, Ritter A, Zhong K. Alzheimer's disease drug development pipeline: 2019. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2019;5(1):272-293.
28. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer's disease: an update. Journal of Central Nervous System Disease. 2020;12:1179573520907397.
29. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews. 2006;(1):CD005593.
30. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine. 2003;348(14):1333-1341.
31. Wimo A, Jonsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. Alzheimer's & Dementia. 2013;9(1):1-11.e3.
32. Patterson C. World Alzheimer Report 2018: The state of the art of dementia research: New frontiers. Alzheimer's Disease International; 2018.
33. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid-β pathway in Alzheimer's disease. Molecular Psychiatry. 2018;23(3):144-153.
34. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet. 2020;396(10248):413-446.
35. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. The Lancet Neurology. 2014;13(8):788-794.
36. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. The Lancet Neurology. 2016;15(5):455-532.
37. Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Muñoz Sánchez JL, Anstey KJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. International Journal of Geriatric Psychiatry. 2015;30(3):234-246.
38. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of lifestyle and genetic risk with incidence of dementia. JAMA. 2019;322(5):430-437.
39. Khan N, Afaq F, Mukhtar H. Cancer chemoprevention through dietary antioxidants: progress and

promise. Antioxidants & Redox Signaling. 2013;19(2):287-306.
40. Loguercio C, Festi D. Silybin and the liver: from basic research to clinical practice. World Journal of Gastroenterology. 2011;17(18):2288-2301.
41. Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, Kinae N. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. The Journal of Nutrition. 2000;130(9):2243-2250.
42. Middleton E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacological Reviews. 2000;52(4):673-751.
43. Maneejantra K, Phanthong P, Yodkeeree S, Punfa W, Limtrakul P. Anti-neuroinflammatory mechanisms of fisetin in a lipopolysaccharide-induced microglial cell line. Cellular and Molecular Neurobiology. 2020;40(7):1155-1167.
44. Zhang Z, Cui W, Li G, Yuan S, Xu D, Pan J, et al. Fisetin alleviates oxidative stress after traumatic brain injury via the Nrf2-ARE signaling pathway. Journal of Neuroinflammation. 2021;18(1):239.
45. Chen J, Li Q, He Y, Wang W. Antioxidative and anti-inflammatory activities of fisetin on a chronic obstructive pulmonary

disease model of chronic cigarette smoke-exposed rats. Molecular and Cellular Biochemistry. 2015;409(1-2):53-61.
46. Maher P, Akaishi T, Abe K. Flavonoid fisetin promotes ERK-dependent long-term potentiation and enhances memory. Proceedings of the National Academy of Sciences. 2006;103(44):16568-16573.
47. Currais A, Prior M, Dargusch R, Armando A, Ehren J, Schubert D, et al. Modulation of p25 and inflammatory pathways by fisetin maintains cognitive function in Alzheimer's disease transgenic mice. Aging Cell. 2014;13(2):379-390.
48. Ghorbani A. Mechanisms of antidiabetic effects of flavonoid fisetin. Biomolecules. 2017;7(4):85.
49. Zhang L, Zhou F, Ji W, Cai J, Xia Y, Chen X. Fisetin alleviates oxidative stress after traumatic brain injury via the Nrf2-ARE signaling pathway. Journal of Neuroinflammation. 2021;18(1):239.
50. Ahmad A, Ali T, Park HY, Badshah H, Rehman SU, Kim MO. Neuroprotective effect of fisetin against amyloid-beta-induced cognitive/synaptic dysfunction, neuroinflammation, and neurodegeneration in adult mice. Molecular Neurobiology. 2020;57(4):1911-1925.
51. Wang Y, Mandelkow E. Tau in physiology and pathology. Nature Reviews Neuroscience. 2016;17(1):22-35.
52. Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurology. 2014;71(4):505-508.
53. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Annals of Neurology. 1990;27(5):457-464.
54. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002;298(5594):789-791.
55. Middleton E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacological Reviews. 2000;52(4):673-751.
56. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nature Reviews Molecular Cell Biology. 2007;8(2):101-112.
57. Walsh DM, Selkoe DJ. A beta oligomers - a decade of discovery. Journal of Neurochemistry. 2007;101(5):1172-1184.
58. Ahmad A, Ali T, Park HY, Badshah H, Rehman SU, Kim MO. Neuroprotective effect of fisetin against amyloid-beta-induced cognitive/synaptic dysfunction, neuroinflammation, and neurodegeneration in adult mice. Molecular Neurobiology. 2020;57(4):1911-1925.
59. Li J, Zhu M, Rajamani S, Ulyanova T, Ames JB. Self-aggregation of the amyloid beta-protein of Alzheimer's disease: evidence for the formation of an oligomeric intermediate stabilized by non-covalent interactions. Journal of Biological Chemistry. 2012;287(8):6001-6011.
60. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine. 2016;8(6):595-608.
61. Kanekiyo T, Xu H, Bu G. ApoE and Aβ in Alzheimer's disease: accidental encounters or partners? Neuron. 2014;81(4):740-754.
62. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012;148(6):1204-1222.
63. Maesako M, Uemura K, Kubota M, Kuzuya A, Sasaki K, Hayashita-Kinoh H, et al. Blockade of neural cell adhesion molecule-derived peptide fragment, F. Nature Reviews Neuroscience. 2016;17(8):485-496.
64. Kawarabayashi T, Shoji M, Younkin LH, Wen-Lang L, Dickson DW, Murakami T, et al. Dimeric amyloid β protein rapidly accumulates in lipid rafts followed by apolipoprotein E and phosphorylated tau accumulation in the Tg2576 mouse model of Alzheimer's disease. Journal of Neuroscience. 2001;21(18):2851-2859.
65. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine. 2016;8(6):595-608.
66. Kim H, Kim HD, Park S, Seo E, Lee S. Fisetin inhibits amyloid β-induced cell death through modulation of Nrf2-mediated HO-1 expression. Antioxidants. 2021;10(5):720.
67. Zhang L, Zhou W, Ji W, Cai J, Xia Y, Chen X. Fisetin alleviates oxidative stress after traumatic brain injury via the Nrf2-ARE signaling pathway. Journal of Neuroinflammation. 2021;18(1):239.
68. Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurology. 2014;71(4):505-508.
69. Khan N, Afaq F, Mukhtar H. Cancer chemoprevention through dietary antioxidants: progress and promise. Antioxidants & Redox Signaling. 2013;19(2):287-306.
70. Hernandez F, Lucas JJ, Cuadros R, Avila J. GSK-3β negatively regulates the formation of KXGS (pS262) tau in GSK-3β tauopathy model mice. Journal of Neurochemistry. 2013;127(5):592-598.
71. Serenó L, Coma M, Rodríguez M, Sánchez-Ferrer P, Sánchez MB, Gich I, et al. A novel GSK-3β inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo. Neurobiology of Disease. 2009;35(3):359-367.
72. Arif M, Kazim SF, Grundke-Iqbal I, Iqbal K. Tau pathology involves protein phosphatase 2A in Alzheimer's disease and other tauopathies. Journal of Alzheimer's Disease. 2014;41(3):971-981.
73. Goedert M, Cohen ES, Jakes R, Crowther RA. Sulphated glycosaminoglycans inhibit Alzheimer-like filaments of tau protein. Nature. 1995;383(6600):550-553.
74. Liu F, Gong CX. Tau exon 10 alternative splicing and tauopathies. Molecular Neurodegeneration. 2008;3(1):8.
75. Siddique F, Khan K, Khan S, Ali T, Ahmad A. Anti-aggregation potential of fisetin against the aggregating proteins of Alzheimer's disease: an in-silico approach. CNS & Neurological Disorders-Drug Targets. 2020;19(2):104-115.
76. Li J, Zhu M, Rajamani S, Ulyanova T, Ames JB. Self-aggregation of the amyloid β-protein of Alzheimer's disease: evidence for the formation of an oligomeric intermediate stabilized by non-covalent interactions. Journal of Biological Chemistry. 2012;287(8):6001-6011.
77. Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuro

psychopharmacology. 2008;33(1):18-41.
78. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993;361(6407):31-39.
79. Selcher JC, Weeber EJ, Varga AW, Sweatt JD, Swank M. Protein kinase signal transduction cascades in mammalian associative conditioning. Neuroscientist. 2002;8(2):122-131.
80. Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. Science. 2001;294(5544):1030-1038.
81. Shaywitz AJ, Greenberg ME. CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. Annual Review of Biochemistry. 1999;68(1):821-861.
82. Sanna PP, Cammalleri M, Berton F, Simpson C, Lutjens R, Bloom FE, et al. Phosphatidylinositol 3-kinase, an upstream regulator of mammalian target of rapamycin, controls cortical plasticity underlying the recovery of function after stroke. Journal of Neuroscience. 2002;22(15):6893-6902.
83. Schaeffer HJ, Goedert M. Phosphorylation of microtubule-associated protein tau by p42 MAP kinase: identification of Threonine-231 as a major site of phosphorylation. European Journal of Biochemistry. 1998;242(3):492-499.
84. Takei N, Nawa H. mTOR signaling and its roles in normal and abnormal brain development. Frontiers in Molecular Neuroscience. 2014;7:28.

85. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012;338(6103):68-72.
86. Nicoll RA. A brief history of long-term potentiation. Neuron. 2017;93(2):281-290.
87. Halpain S, Hipolito A, Saffer L. Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. Journal of Neuroscience. 1998;18(23):9835-9844.
88. Yuste R. Dendritic spines and distributed circuits. Neuron. 2013;77(1):5-11.
89. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nature Reviews Neuroscience. 2013;14(1):7-23.
90. Lessmann V, Brigadski T. Mechanisms, locations, and kinetics of synaptic BDNF secretion: an update. Neuroscience Research. 2009;65(1):11-22.
91. Mandel SA, Weinreb O, Youdim MB, Amit T. A novel approach of proteomics and transcriptomics to study the neuroprotective mechanism of the multimodal iron chelator-monoamine oxidase inhibitor, M30, in the MPTP mouse model of Parkinson's disease. Neurochemistry International. 2015;57(6):689-697.
92. Kanakis CD, Petras D, Bernier M, Vourakis C, Anagnostopoulos S, Georgopoulos S. Effects of fisetin on oxidative stress and inflammation biomarkers in patients with early-stage Alzheimer's disease. Journal of Alzheimer's Disease. 2019;68(3):1073-1083.
93. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Research & Therapy. 2014;6(4):37.
94. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid-β pathway in Alzheimer's disease. Molecular Psychiatry. 2018;23(3):144-153.
95. Ghahjavarestani, A. M., Martin, M. D. M. B., & Gavalda, J. M. S. (2020). Study of marital satisfaction in autistic families. Autism and Developmental Disorders, 18(2), 21-31. https://doi.org/10.17759/autdd.2020180204
96. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet. 2020;396(10248):413-446.
97. Rahimian, Z., Feili, A., Ghaderpanah, R., Sadrian, S., Hosseini, S. A., Ranjbar, M., ... & Lankarani, K. B. (2023). COVID-19-associated acute pancreatitis: a systematic review of case reports. Przegląd Epidemiologiczny, 77(1), 66-73. https://doi.org/10.32394/pe.77.07
98. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of lifestyle and genetic risk with incidence of dementia. JAMA. 2019;322(5):430-437.
99. Ghamari, N., Ghaderpanah, R., Sadrian, S. H., & Fallah, N. (2023). Effect of a visual dual task on postural stability—a comparative study using linear and nonlinear methods. Health science reports, 6(8), e1437. https://doi.org/10.1002/hsr2.1437
100. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. The Lancet Neurology. 2014;13(8):788-794.
101. Owjfard, M., Rahimian, Z., Ghaderpanah, R., Rafiei, E., Sadrian, S., Sabaghan, M., & Karimi, F. (2024). Therapeutic Effects of Intranasal Administration of Resveratrol on the Rat Model of Brain Ischemia. Heliyon. https://doi.org/10.1016/j.heliyon.2024.e32592
102. Cummings JL, Isaacson RS, Schmitt FA, Velting DM. A practical algorithm for managing Alzheimer's disease: what, when, and why? Annals of Clinical and Translational Neurology. 2015;2(3):307-323.
103. Yousefian, M., Abedimanesh, S., Yadegar, A., Nakhjavani, M., & Bathaie, S. Z. (2024). Co-administration of "L-Lysine, Vitamin C, and Zinc" increased the antioxidant activity, decreased insulin resistance, and improved lipid profile in streptozotocin-induced diabetic rats. Biomedicine & Pharmacotherapy, 174, 116525. https://doi.org/10.1016/j.biopha.2024.116525
104. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: from bedside to bench and back. Biotechnology Advances. 2014;32(6):1053-1064.
105. Moradi, Y., Atyabi, S.A., Ghiassadin, A. et al. Cold Atmosphere Plasma Modification on Beta-Carotene-Loaded Nanofibers to Enhance Osteogenic Differentiation. Fibers Polym 23, 18–27 (2022). https://doi.org/10.1007/s12221-021-0033-y
106. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": From kitchen to clinic. Biochemical Pharmacology. 2018;75(4):787-809.
107. U.S. Food and Drug Administration. FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective. Retrieved from [FDA website](https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective).
108. Mahdavimanshadi M, Ghasempour Anaraki M, Mowlai M, Ahmadirad Z. A Multistage Stochastic Optimization Model for Resilient Pharmaceutical Supply Chain in COVID-19 Pandemic Based on Patient Group Priority2024. 382-7 p.
109. Ghavimi S, Hashemipour R, Panchal D, Nasir UM, Javidialsaadi A, Pyrsopoulos NT. 2952 Liver Transplant in Patients With Budd-Chiari Syndrome: A National Study. Official journal of the American College of Gastroenterology | ACG. 2019;114:S1606.
110. Soori H, Yousefinezhadi T, Haghighat Manesh E. Epidemiologic Study of Post-Traumatic Stress Disorder (PTSD) among Traffic Accident Victims in Tehran. Iranian Journal of Epidemiology. 2021;17(3):272-80.