Neuroprotective Role of Fisetin in the Treatment and Prevention of Alzheimer's Disease

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Abstract

Progressive neurodegeneration characterizes Alzheimer's disease (AD) which causes cognitive decline, synaptic dysfunction, oxidative stress, mitochondrial dysfunction, neuroinflammation, and neuronal death. The limited relief afforded by available therapies highlights the need for multifunctional medications that target multiple disease processes. Fisetin, a naturally occurring flavonol found in strawberries, apples, and onions, has extraordinary potential as a neuroprotective agent due to its anti-inflammatory, anti-apoptotic, and antioxidant properties. Fisetin can cross the blood–brain barrier where it exerts neurotrophic effects through its ability to increase brain-derived neurotrophic factor (BDNF) and stimulate multiple signaling pathways including ERK/MAPK and CREB which collectively increases synaptic plasticity and long-term potentiation. Fisetin also protects mitochondrial function by reducing oxidative stress, maintaining membrane potential and inhibiting apoptosis through cytochrome c. Fisetin inhibits tau hyperphosphorylation, amyloid-beta (Aβ) accumulation, and neuroinflammation while suppressing glial activation and pro-inflammatory cytokine release. In addition, fisetin has senolytic activity by activating the clearance of senescent cells and restoring a healthier neuronal context. Collectively, these multitarget activities support further clinical research of fisetin's therapeutic promise for both Alzheimer's disease prevention and treatment [5][6][8][9].

Keywords: Fisetin; Alzheimer's disease; Neuroprotection; Oxidative stress; Neuroinflammation; Amyloid-beta; Tau hyper-phosphorylation; Synaptic plasticity; Senolytic activity; Mitochondrial dysfunction

1.Introduction

Almost 60 to 80 percent of dementia cases worldwide are attributed to Alzheimer's disease (AD), which is the most common form of dementia. The neurodegenerative disease advances over time and is characterized by typical behavior, memory loss, cognitive impairment, and ultimately the inability to perform daily activities. The incidence of Alzheimer's disease is increasing rapidly as the global population ages, posing severe issues for healthcare systems, caregivers, and society at large.

Alois Alzheimer first described the disease in 1906. It is defined by the accumulation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein and extracellular amyloid-beta (Aβ) plaques within the brain [31].

The pathophysiology of AD is increasingly becoming understood due to recent advances in imaging techniques, biomarker research, and knowledge of genetic and molecular mechanisms. These advances also pave the way for potential disease-modifying therapies [32].

Several plant derived phytochemicals have exhibited promising potential in the prevention and treatment of Alzheimer's disease (AD) due to their antioxidant, anti-inflammatory, and neuroprotective activities. Some of the

phytochemicals used are Curcumin, Resveratrol, Quercetin, Fisetin, Berberine, Withanolides, etc. This review article focuses on the role of Fisetin in the treatment and prevention of Alzheimer's disease.

One naturally occurring flavonoid, fisetin (3,3′,4′,7-tetrahydroxyflavone), can be found in a wide variety of fruits and vegetables such as cucumbers, strawberries, apples, persimmons, grapes, and onions. Fisetin is a polyphenol of the flavonol subclass that has gained much interest due to the numerous biological actions it possesses that include senotherapeutic, neuroprotective, anti-inflammatory, anti-cancer, and antioxidant properties [9][8]. Fisetin is a lead compound for the therapeutic treatment of most chronic diseases because, unlike other flavonoids, it has a distinct ability to modulate various cellular signaling pathways. Fisetin has also been described as possessing the ability to penetrate the blood-brain barrier, thereby making it a potential drug in the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases [15].

2. Fisetin

Fisetin (3,3',4',7-tetrahydroxyflavone) is a bioactive flavonol that has gained substantial interest due to its senolytic, anti-inflammatory, antioxidant, and neuroprotective capabilities. Fisetin is a secondary metabolite that exists naturally in countless fruits, vegetables, nuts, and medicinal plants. Flavonoids are polyphenolic compounds that occur in enormous quantities in the kingdom of plants. Fisetin is an abundant yellow flavonol with important bioactive qualities and is a kind of flavonoid[8].Although Fisetin is less abundant in the human food supply than the more commonly known flavonoids quercetin or kaempferol, its pharmacological properties are especially potent as a senolytic drug.(Yousefzadeh et al., 2018).Fisetin(286.24 g/mol; C15H10O6) is a naturally-occurring flavonol and a type of flavonoid, specifically, a 3-hydroxyflavone (meaning there are hydroxyl at 3, 7, 3', and 4' locations). Fisetin exerts antioxidant activity via the free radical scavenging and metal ion chelation of the hydroxyl group [9].

Strawberries are the richest dietary source of fisetin [1]. Fisetin can also be found in other fruits as well including grapes, mangoes, persimmons and apple in both the peel and pulp along with quercetin [12]. Fisetin is primarily found in grape skins, where it is part of the polyphenolic profile of grapes along with other flavonoids such as resveratrol and catechins. Fisetin is also found in trace amounts in other fruits and plants. Trace amounts of fisetin have also been found in onions with the red varieties having a higher concentration. Tomato and cucumber have also been shown to be minor sources of fisetin. Due to low amounts found, those plants do not have a significant impact on daily intakes of fisetin [3]. In addition to common fruits and vegetables, there are some lesser known plant sources that have higher levels of fisetin. Fisetin contributes to a large proportion of the total polyphenolic content in the leaves and heartwood of *Rhus cotinus*, the smoke tree, and therefore represents one of the most concentrated natural sources [4]. In addition, lotus seeds, often used in traditional Chinese medicine, contain bioavailable amounts of fisetin and represent a practicable food source [18].

3. Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is a multifactorial, progressive neurodegenerative disorder that disproportionately involves brain areas responsible for memory, learning, and executive function—most notably the cerebral cortex and hippocampus. It is preceded by an interlocking cascade of molecular and cellular abnormalities terminating in failure at the synapse, neuronal loss, and diffuse cognitive impairment[19].

3.1. Amyloid-β Plaques Formation

Extracellular Aβ peptide deposition is considered one of the earliest and most striking pathological changes of AD. Aβ peptides are generated from the amyloid precursor protein (APP), a transmembrane protein that undergoes proteolytic cleavage by β-secretase (BACE1) and γ-secretase[4]. Of the isoforms generated, Aβ42 is the most hydrophobic and is predisposed to self-aggregate and form oligomers and eventually insoluble plaques. These Aβ deposits interfere with neuronal communication, weaken synaptic integrity and trigger harmful inflammatory responses in glial cells[14]. The amyloid cascade hypothesis holds that Aβ deposition is the central trigger of downstream pathophysiologic events in AD.

3.2. Neurofibrillary Tangles and Tau Hyperphosphorylation

In addition to Aβ disease, intracellular hyperphosphorylation-facilitated aggregation of tau protein into neurofibrillary tangles (NFTs) is another leading neuropathological feature. Tau is an axonal microtubule-associated protein whose normal function is the stabilization of microtubules in axons. In AD, tau becomes abnormally phosphorylated, releasing it from microtubules, causing it to misfold and form self-aggregates [20]. This, in turn, results in microtubule destabilization, axonal transport disruption, synaptic dysfunction, and eventually neuronal apoptosis[21].

3.3. Synaptic Dysregulation and Neuronal Loss

Synaptic loss is an early and important aspect of AD pathogenesis, preceding measurable neuronal loss and strongly associating with clinical cognitive impairment[22].Soluble Aβ oligomers are particularly implicated in synaptic toxicity because they disrupt long-term potentiation (LTP)—a necessary mechanism for learning and memory—by disrupting NMDA and AMPA receptor signaling and inducing postsynaptic receptor internalization [23].The cumulative effect of these disruptions leads to impaired synaptic plasticity, reduced neurotransmission, and progressive loss of functional connectivity in neural circuits.

3.4. Neuroinflammation

Neuroinflammation has a double-edged role in AD pathogenesis. Glial activation—especially of microglia and astrocytes—is initially involved in the clearance of Aβ aggregates and preservation of homeostasis. Chronic and dysregulated glial activation, however, leads to the prolonged release of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), chemokines, and reactive oxygen species, which further propagate neuronal damage and tau phosphorylation[24].This persistent inflammatory condition promotes neurodegeneration and may impair processes for Aβ clearance, resulting in its accumulation.

3.5. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress, defined as a disparity between the generation of reactive oxygen species (ROS) and the brain's antioxidant defenses, is significantly elevated in AD. Aβ itself causes oxidative damage to lipids, proteins, and DNA, and defective mitochondria add to the excessive generation of ROS and defective ATP synthesis [25].The hippocampus and cortex—areas of high metabolic rate—are especially susceptible to oxidative damage. Furthermore, oxidative stress can enhance tau hyperphosphorylation and Aβ aggregation, creating a vicious cycle that drives disease acceleration.

3.6. Disrupted Neurotransmitter Systems

Neurotransmitter deficiencies have been recognized in AD and lie at the center of the patients' cognitive dysfunctions. Destruction of cholinergic neurons from the basal forebrain results in a severe drop in acetylcholine content, which has been implicated to cause impairments in attention, learning, and memory [26].This provides the pharmacologic basis for treatment with cholinesterase inhibitors, which has the effect of increasing synaptic concentrations of acetylcholine and offering symptomatic relief. Other neurotransmitter systems, including glutamatergic and serotonergic systems, are similarly impacted, enhancing cognitive and behavioral disturbances.

3.7. Blood-Brain Barrier (BBB) Disruption

Recent research has brought to light the role of the blood-brain barrier in AD pathophysiology. Integrity of BBB is disrupted early during the disease process, resulting in elevated permeability and defective clearance of neurotoxic proteins like Aβ and tau[27].This disruption facilitates entry of peripheral immune constituents and inflammatory mediators into the brain parenchyma, increasing neuroinflammation and neuronal damage. In addition, BBB dysfunction has the potential to change cerebral perfusion and disrupt nutrient transport, introducing a secondary component of metabolic stress to an already compromised brain.

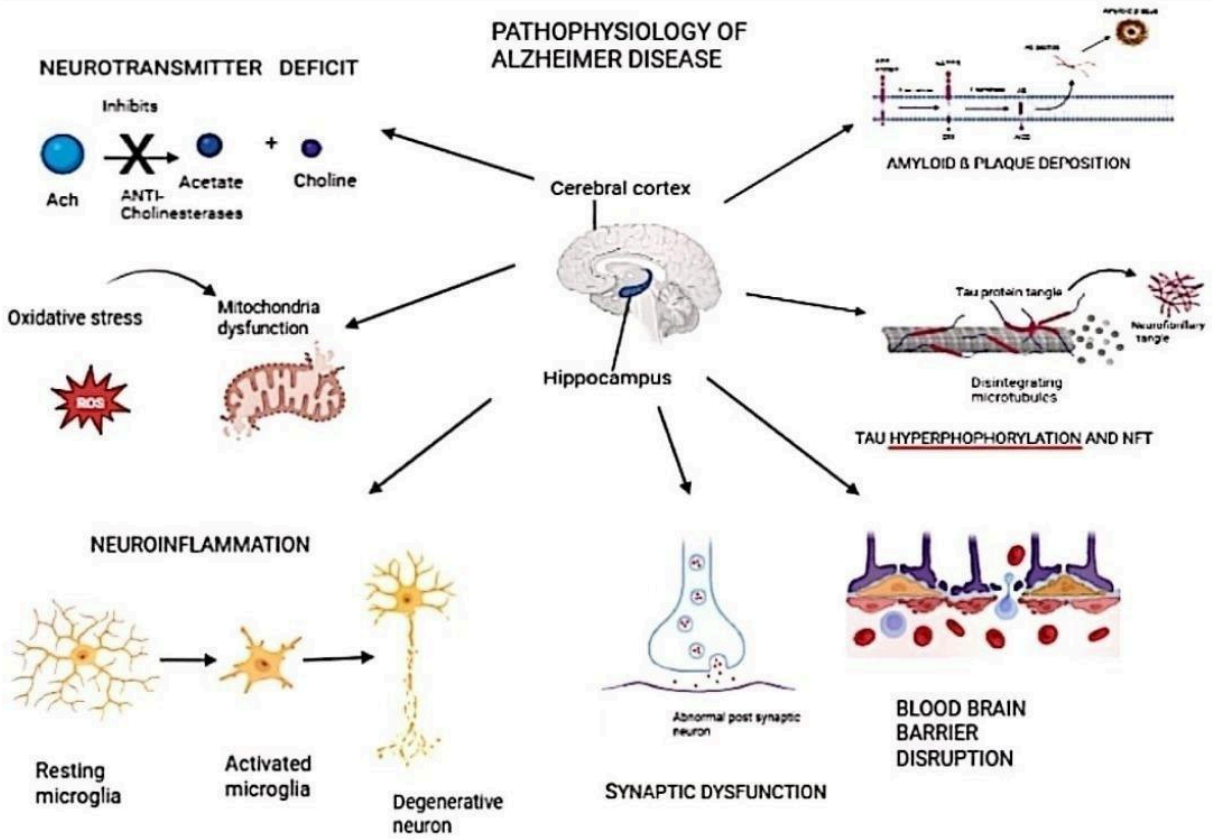

Fig.01. Key pathological mechanisms of Alzheimer's disease, including amyloid-β accumulation, tau tangles, synaptic loss, neuroinflammation, and neuronal degeneration.

Mechanism of Action

4.1. Antioxidant Activity of Fisetin

Oxidative stress is a major pathological feature involved in the etiology and progression of Alzheimer's disease (AD). Oxidative stress is a product of an imbalance between ROS production and antioxidant defense mechanisms of the brain. It detoxifies directly harmful reactive oxygen species (ROS) including superoxide and hydroxyl radicals that guard neurons from oxidative damage. Fisetin further modulates the Nrf2/ARE signaling pathway, increasing key antioxidant enzymes like HO-1, SOD, CAT, and GPx that replenish redox balance and protect mitochondrial function. Fisetin further regulates glutathione (GSH) levels by modulating the enzymes that metabolize it and thereby protects neurons from oxidative injury and mitochondrial injury. It also reduces oxidative load by inhibiting pro-oxidant enzymes like NOX, iNOS, and COX-2. Lastly, fisetin preserves mitochondrial integrity, preventing energy deficits and neuronal loss by stabilizing membrane potential and limiting apoptotic signaling[2][5][7][10][11].

4.2. Anti-inflammatory Activity of Fisetin

Fisetin possesses powerful anti-inflammatory activity of advantage in treating the neuroinflammation of Alzheimer's disease (AD). Fisetin suppresses microglia and astrocyte activation—a couple of major glial cells participating in brain inflammation—by decreasing the expression of markers Iba1 and GFAP. Suppression diminishes the secretion of pro-inflammatory mediators and is correlated with enhanced cognitive function in AD models.Fisetin also suppresses the production of inflammatory cytokines like TNF-α, IL-1β, and IL-6 by suppressing the NF-κB signaling pathway, an essential regulator of inflammation.In addition, it regulates MAPK signaling (i.e., ERK, JNK, and p38), thus inhibiting inflammatory signaling and stress responses in brain cells.Furthermore, fisetin suppresses the expression of COX-2 and iNOS, enzymes responsible for neurotoxicity through the production of prostaglandins and nitric oxide.Lastly, it was observed that fisetin inhibited NLRP3 inflammasome activation, a significant member of the innate immune system involved in chronic inflammation

in AD. Overall, these actions are illustrative of the therapeutic role of fisetin in preventing neuroinflammation and preserving neuronal health [2][5][7][28][29]

4.3Anti-Amyloidogenic

Fisetin, a naturally occurring flavonoid, demonstrates significant potential in mitigating Alzheimer's disease (AD) through its anti-amyloidogenic properties. Research indicates that fisetin can inhibit amyloid-beta (Aβ) aggregation, a critical factor in AD progression. In vitro studies have shown that fisetin prevents the formation of β-strands in tau proteins, thereby inhibiting tau aggregation and promoting disaggregation of tau filaments [39]. Additionally, fisetin has been observed to reduce Aβ accumulation and tau hyperphosphorylation in animal models. For instance, a study involving Aβ1–42-injected mice demonstrated that fisetin treatment led to decreased Aβ accumulation, reduced BACE-1 expression, and diminished tau hyperphosphorylation. These effects were associated with enhanced synaptic function and improved memory performance. Furthermore, fisetin's neuroprotective effects extend to modulating oxidative stress and inflammation, both of which contribute to AD pathology. By enhancing antioxidant enzyme activities and reducing markers of oxidative damage, fisetin helps mitigate the neurodegenerative processes associated with AD. These findings collectively underscore fisetin's multifaceted approach in combating AD through inhibition of amyloid aggregation, reduction of tau pathology, and modulation of oxidative stress and inflammation[39]

4.4 Tau Phosphorylation

Research indicates that fisetin reduces levels of phosphorylated tau, a key feature in AD pathology, through the activation of autophagy pathways. Specifically, fisetin activates transcription factors TFEB and Nrf2, which enhance the expression of genes involved in autophagy and lysosomal function. This activation leads to the degradation of phosphorylated tau via the autophagy-lysosome pathway. Moreover, fisetin inhibits mTORC1 signaling, further promoting autophagic processes and facilitating tau clearance. Inhibition of autophagy with specific inhibitors attenuates fisetin-induced tau degradation, confirming the critical role of autophagy in this mechanism[42]. Additionally, fisetin directly interacts with tau proteins, preventing their aggregation by inhibiting the formation of β-strands at aggregation-prone motifs. This interaction stabilizes tau in a non-toxic conformation, reducing its propensity to form neurofibrillary tangles. Collectively, fisetin's ability to modulate tau phosphorylation and aggregation positions it as a promising candidate for AD therapy[42].

4.5. Neurotropic and Synaptogenic effects

Fisetin, a naturally forming flavonol, shows potential as a neurotropic and synaptogenic drug; this is particularly relevant in the context of neurodegenerative diseases including Alzheimer's disease (AD). Alzheimer's disease, in addition to the presence of amyloid-β plaques and neurofibrillary tangles, will present with significant loss of synaptic integrity and neuronal function, especially in the hippocampus and cortex where memory and cognition take place [14]. Fisetin has shown to have neuroprotective effects by manipulating various signalling pathways for neuronal survival, growth and development, and synaptic plasticity. Notably, fisetin followed by ERK/MAPK signalling pathway can increase BDNF, a key regulator of neurogenesis and synaptic function[5][6][9]. This pathway is particularly important to Long term potentiation (LTP), a neuronal process shown as a basis for memory and memory learning, which is often disrupted in AD.

Furthermore, fisetin acts as a senotherapeutic agent, which has relevant implications for senescent cells in the aging brain because of their potential role in synapse loss associated with Alzheimer's disease and chronic inflammation. Notably, experimental findings reported an increase in cognitive performance and a decrease in bioburden of senescent cells observed in old rats [18]. This may provide an indirect opportunity to promote synaptogenesis by decreasing pro-inflammatory environments related to neurodegeneration. Fisetin's many impacts on neuroprotection and synaptic health is further emphasized by its ability to modulate glial cells and, reduce neuroinflammation, which also assists with promoting the maintenance of the synaptic environment [5][6].

4.6. Mitochondrial protection

Mitochondrial dysfunction is a key and early aspect of pathophysiology in Alzheimer's disease (AD), responsible for oxidative stress, poor calcium homeostasis, neuronal energy failure, and ultimately synapse loss and neurodegeneration [33]. In AD models, fisetin has shown great promise for reversing mitochondrial

dysfunction and preserving the mitochondria in many ways. Many of the mechanisms include: modulation of mitochondrial biogenesis, maintenance of mitochondrial membrane potential (Δψm), decrease of oxidative stress, and modulation of mitochondrial apoptotic signaling pathways.

Mitochondria are responsible for most of the reactive oxygen species (ROS) produced in neurons and an overabundance of ROS can induce lipid peroxidation, protein oxidation, and mitochondrial DNA damage in AD [34]. Fisetin has been shown to activate the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, subsequently increasing expression of antioxidant enzymes including heme oxygenase-1 (HO-1), catalase (CAT), and superoxide dismutase (SOD)[8][9]. By increasing Nrf2-mediated antioxidant defenses, fisetin helps scavenge excess ROS and maintain redox homeostasis, protecting neuronal cells' mitochondrial integrity. Neurons subjected to treatment with fisetin showed a statistically significant increase in ATP synthesis and mitochondrial respiration which are needed to develop synaptic transmission and plasticity.

Mitochondrial membrane potential (Δψm), is a critical step for buffer calcium and ATP generation. Loss of Δψm by the formation of Aβ peptides in AD is a decisive factor in mitochondrial depolarization and cell death. By maintaining Δψm and inhibiting the opening of the mitochondrial permeability transition pore (mPTP), fisetin prevented Aβ-induced mitochondrial depolarization in neuronal cells, was found[13]. In addition, makintaining Δψm in the optic nerve model channeled inhibition of downstream caspase-3 activation and the release of cytochrome c from the mitochondria; thus inhibiting mitochondrial-mediated apoptosis [10].

4. Preclinical study of fisetin in treatment of Alzheimer

5.1 In Vitro Studies

Fisetin exerts potent neuroprotective activity in Alzheimer's disease models via several mechanisms. Fisetin is neuroprotective against Aβ-induced cytotoxicity in neuronal cells, including SH-SY5Y and primary cortical neurons, through the inhibition of oxidative stress, mitochondrial damage, and caspase-3 activation, thus exerting antioxidant and anti-apoptotic activities.In rat hippocampal slice and neuroblastoma cell models, fisetin reversed critical antioxidant enzymes like superoxide dismutase (SOD) and catalase, maintained intracellular glutathione (GSH) levels, and suppressed lipid peroxidation. All these actions are predominantly mediated by the induction of the Nrf2/HO-1 pathway, which has a critical role in the modulation of cellular redox homeostasis. Further, fisetin inhibited tau hyperphosphorylation—a hallmark of Alzheimer's pathology—by inhibiting the activity of glycogen synthase kinase-3β (GSK-3β) in okadaic acid-treated PC12 cells. This would suggest that fisetin would also inhibit microtubule stabilization and tau-related neurodegeneration [2][5][6][7][10][28][29]

5.2 In Vivo Studies

Fisetin was found to possess promising therapeutic effectiveness in different models of neurodegeneration, such as Alzheimer's disease, in different animal models. Fisetin (25 mg/kg/day) administered chronically in APP/PS1 transgenic mice resulted in reduced amyloid plaque load and microglial activation, along with enhanced cognitive performance, suggesting its ability to influence disease progression.In a rat memory impairment model of scopolamine, fisetin (10–40 mg/kg) restored damaged memory effectively through the promotion of acetylcholine levels, inhibition of AChE activity, and the activation of brain-derived neurotrophic factor (BDNF) expression, displaying its cholinergic and neurotrophic properties. In addition, in a D-galactose-induced aging model, fisetin induced enhancement of mitochondrial activity, enhanced antioxidant enzyme activity, and alleviation of oxidative stress in the hippocampus and frontal cortex regions of the brain, indicating its general neuroprotective and anti-aging properties against sporadic Alzheimer's disease [5][6][7][30].

5. Clinical evidence and human studies

As promising as the early findings may be, further large-scale clinical investigations are required to ascertain the optimal dosage, validate the action of fisetin, and analyze the interactions with other therapies. One of the challenges in Alzheimer’s disease research is the risk that any biomarker-based treatment may advertise changes at the underlying biological processes which are not accompanied by meaningful clinical changes. To solve this problem, subsequent studies need to employ biomarkers that predict with high precision the progression and

impact of the treatment on the disease. Although biomarkers tend to help in tracking and guiding treatment, they equally complicate and escalate the costs of clinical trials [35]. Because of frailty and COVID-19, recent studies have looked into fisetin as a possible therapy due to its influence on age-associated cellular senescence. However, cellular senescence is also an essential counterpart for younger cells when it comes to tissue repair and tumor suppression and thus is regulated in a very delicate manner. The variability in results from animal studies highlights the necessity for targeted clinical trials in older patients or patients suffering from chronic diseases. Moreover, research that has been done critically on fisetin shows that it does mitigate some of the chemotherapy's adverse effects, especially concerning supportive cancer care medicine[38].

6. Future perceptions and Challenges

The promising therapeutic potential of fisetin in Alzheimer's disease (AD) has emerged from numerous preclinical studies revealing neuroprotective actions of fisetin. In light of these initial findings, the orientation of future clinical studies toward the following areas should be attempted. Firstly, well-designed randomized controlled trials will ascertain safety and efficacy dosing and confirm cognitive effects in AD patients. Secondly, mechanistic studies in human subjects to elucidate how fisetin interacts with molecular mechanisms underlying AD, e.g., tau hyperphosphorylation, oxidative stress, neuroinflammation, and deposition of amyloid-beta, are warranted. Such studies may even result in the identification of reliable biomarkers for assessing treatment efficacy[36].There are numerous hurdles that one must cross even with all the promise it has. One of them is low bioavailability that restricts fisetin usage to clinical applications and underscores the need for newer delivery systems. Then you have the fact that there are no large-scale human trials, which casts doubt on its long-term safety and efficacy. Fisetin use in healthy humans, most of all in youth, is rather worrying because we have a lot of healthy functions of cellular senescence in normal physiology. Regulatory hurdles lie ahead too, as reliance on biomarker-based endpoints- trendy in fisetin research-could make or break the drug's approval[36]. Therefore, there are many hindrances that have to be overcome after such potential. The limited bioavailability of fisetin renders it ineffective in the clinic and highlights the need for improving its administration systems. In addition, the lack of very comprehensive studies on humans casts doubt on the long-term safety and efficacy. Fisetin use in healthy humans, particularly in youth, is of concern, given the advantageous roles of cellular senescence in normal physiological functions. There are regulatory hurdles to cross because possible approval of medicinal drugs may be assisted or thwarted depending on whether biomarker-based endpoints popular in fisetin studies are supported [35].

7. Toxicity profile, Off-target effects and Safety challenges

Fisetin has potential as a potential drug candidate, especially regarding its potential to target cellular senescence and neurodegeneration found in instances of Alzheimer's disease. However, claims on such matters need a lot more supporting evidence to rule out its safety profile and any possible off-target effects before it is allowed for clinical use on a large scale[36].Fortunately, there were no indications of toxicity in animal studies. Mice treated with a high oral dose of 2,000 mg/kg for the acute toxicity test showed no evidence of adverse effects for 48 hours. Further, incorporation of fisetin at 0.05% into the diet for nine consecutive months did not lead to any adverse effects on body weight or organ function[38].Fisetin also proved to be of low genotoxicity risk, with a negative Ames test and absence of hERG channel activity inhibition or inhibition of major cytochrome P450 enzymes at tested levels, implying minimal risk for metabolic or cardiac toxicity. In vitro tests, however, indicate that at elevated doses (in excess of 20–100 μM), fisetin can negatively impact healthy, dividing cells, leading to concerns regarding unwanted effects in human trials based upon interindividual variability in metabolism and absorption[36].Furthermore, fisetin has been found to be a weak inhibitor of topoisomerase II with possible DNA- binding activity. Although its mutagenic and clastogenic activities are mostly weak and variable, these results highlight the need for careful dosing in clinical trials. Although well-tolerated in animal models even at high and long-term exposure, human evidence is still limited. Human trial side effects reported have been relatively mild, such as gastrointestinal complaints, fatigue, and headaches, with infrequent elevations of creatinine kinase[36].

Mild adverse effects reported in human studies include headache, fatigue, and gastrointestinal disturbances, infrequent elevations in creatine kinase levels. Caution should be exercised in giving fisetin, as it may inhibit CYP enzymes and interfere with the metabolism of other drugs, especially among the elderly, who tend to have

complicated drug regimens. Even when a margin is wide in the data for safety, yet long-term studies are important in humans to define limits of safe doses, check pharmaceutical interactions, and ascertain the suitability of the treatment for chronic use[38].

8.CONCLUSION:

With Alzheimer's disease (AD), fisetin, a flavonol that is found in many fruits and vegetables, is showing significant potential as a multifunctional neuroprotectant. Fisetin reduces amyloid-beta aggregation, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation - all pathological AD features - with its potent antioxidant and anti-inflammatory properties. Moreover, fisetin improves neuronal viability and synaptic efficacy through neurotrophic signaling (ERK/MAPK and CREB), increasing the concentration of brain-derived neurotrophic factor (BDNF) levels. Its senolytic properties and action of stabilizing mitochondrial function enhance its treatment efficacy in age-related neurodegenerative states. Preclinical studies in Alzheimer's disease models have revealed the potential of fisetin for disease modification, and not just symptom relief, repeatedly demonstrating an ability to improve cognitive function, reduce neuronal loss, and restore synaptic plasticity. In the future research, the efficacy, bioavailability, optimal dose, and long-term safety of fisetin must be assessed in human populations in well-designed clinical studies. If fisetin can be implemented into the clinic, we could have a new, natural, and potent solution to the dilemma of Alzheimer's disease [5][6][11].

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