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Research Article

Fisetin: From Dietary Source to Therapeutic Possibilities

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Abstract

Fisetin is a plant-derived flavonoid found in various fruits, vegetables, and plants, such as strawberries, apples, and onions, that has garnered attention for its broad pharmacological activities. Fisetin, which has anti-inflammatory, anti-cancer, neuroprotective, and antioxidant benefits, is essential for shielding cells from oxidative stress, which contributes to the emergence of cancer, neurological diseases, and other long-term illnesses. It has been shown to modulate inflammatory pathways like NF-κB and MAPK, potentially aiding in managing diseases such as arthritis and cardiovascular disorders. Additionally, fisetin has demonstrated neuroprotective effects, improving cognitive functions and mitigating oxidative damage in neurodegenerative diseases like Alzheimer's and Parkinson's. Animal studies have further validated the therapeutic potential of fisetin, with rodent models showing enhanced memory, reduced neuroinflammation, and increased brain-derived neurotrophic factor (BDNF) levels. In cancer research, fisetin has been shown to inhibit tumor growth by inducing apoptosis and suppressing metastasis. Moreover, fisetin improves glucose metabolism in diabetic animal models, reducing hyperglycemia and improving insulin sensitivity, while also positively affecting lipid profiles, potentially reducing cardiovascular risks. The objective of this review is to evaluate the existing research on fisetin, focusing on its sources, pharmacological activities, and mechanisms of action, with an emphasis on findings from animal studies. It aims to provide insights into fisetin's therapeutic potential for conditions like neurodegeneration, cancer, diabetes, and inflammation, offering a comprehensive reference for researchers and healthcare professionals. Keywords: fisetin, flavonoids, neuroprotection, anticancer, diabetes, antioxidant, animal studies, therapeutic potential.

Keywords: Fisetin; Flavonoids; Neuroprotection; Anticancer; Diabetes; Animal Studies

Introduction

Fisetin (3,7,3',4'-tetrahydroxyflavone) is a flavonoid widely recognized for its potent antioxidant, anti-inflammatory, and neuroprotective properties. This polyphenolic compound is naturally found in various fruits and vegetables, with particularly high concentrations in strawberries, apples, grapes, onions, and cucumbers (Table 1). Fisetin's chemical structure contributes to its ability to scavenge free radicals and modulate cellular pathways, which makes it of interest in the field of pharmacology. Historically, fisetin has been used in traditional medicine, especially in Asian cultures, where it was valued for its therapeutic properties in treating inflammatory conditions, skin ailments, and supporting overall health. In modern times, the focus has shifted towards its potential as a natural therapeutic agent in the management of age-related diseases, including neurodegenerative disorders like Alzheimer's and Parkinson's. This resurgence of interest in fisetin aligns with growing evidence supporting its ability to regulate oxidative stress, inflammation, and other biological pathways implicated in chronic conditions [1-3].

Phytochemicals, naturally occurring compounds in plants, have long been recognized for their therapeutic potential, especially in modern medicine, where they serve as valuable alternatives or complements to synthetic drugs. These bioactive substances possess a wide range of pharmacological properties, including anti-inflammatory, antioxidant, antimicrobial, and anticancer effects, making them important candidates for treating chronic diseases. Phytochemicals can act on multiple biological pathways, often modulating cellular processes like oxidative stress, inflammation, and apoptosis. As the focus shifts toward more natural and sustainable therapies, compounds like fisetin have garnered significant attention. Fisetin, a flavonoid found in common fruits and vegetables such as strawberries and apples, has shown promise as a potential therapeutic agent for age-related diseases, including neurodegenerative disorders like Alzheimer's and Parkinson's disease. Its antioxidant, anti-inflammatory, and neuroprotective properties make it an appealing candidate for combating the effects of aging, reducing oxidative damage, and improving brain health. Furthermore, fisetin's ability to influence critical biological processes such as cellular signaling and autophagy highlights its potential in the prevention and treatment of other chronic conditions, including cardiovascular diseases and metabolic disorders [4-6].

The primary aim of this review is to provide a comprehensive summary of the current findings on fisetin, focusing on its pharmacological properties, mechanisms of action, and clinical relevance. Fisetin, a naturally occurring flavonoid with a diverse range of biological activities, has attracted considerable attention in recent years due to its potential therapeutic applications in various health conditions, particularly age-related diseases. This review seeks to synthesize the most recent studies, encompassing *in vitro, in vivo*, and clinical research, to explore fisetin's mechanisms of action, including its antioxidant, anti-inflammatory, neuroprotective, and anticancer effects. Furthermore, this review will delve into the cellular and molecular pathways that fisetin influences, such as oxidative stress regulation, autophagy, apoptosis, and cellular signaling. The scope of the review also extends to the clinical relevance of fisetin, highlighting its potential therapeutic applications in managing chronic conditions such as Alzheimer's disease, Parkinson's disease, cardiovascular diseases, and metabolic disorders. Finally, we will discuss the safety profile, bioavailability, and future directions for fisetin research, with the aim of identifying its role in modern medicine as a natural and effective therapeutic agent.

Food Source	Fisetin Content (mg per 100g)
Strawberries	0.4 - 1.0 mg
Apples (Red Delicious)	0.3 - 0.4 mg
Grapes	0.4 - 0.5 mg
Kiwifruit	0.4 mg
Cucumbers	0.2 - 0.3 mg
Onions (Red)	0.2 - 0.3 mg
Persimmons	1.0 - 2.0 mg
Mulberries	2.0 - 3.0 mg
Tomatoes	0.1 - 0.2 mg
Pears	0.2 mg

Table 1: Sources of Fisetin.

- **Absorption:** Fisetin is absorbed primarily through the gastrointestinal tract via passive diffusion, meaning it moves from higher to lower concentration without energy input. Despite this absorption, fisetin's bioavailability is considered low due to its poor aqueous solubility. After ingestion, fisetin reaches peak plasma concentrations in about 1–2 hours, but the total amount that enters systemic circulation is limited due to its rapid metabolism.
- **Distribution:** Once absorbed, fisetin is distributed throughout the body via the bloodstream. It binds to plasma proteins, allowing it to circulate and reach various tissues, including the brain, suggesting its ability to cross the blood-brain barrier. However, despite this potential, fisetin's tissue concentrations are generally low due to its rapid metabolism and short half-life.
- **Metabolism:** Fisetin undergoes rapid metabolism in the liver, primarily through phase I enzymes such as cytochrome P450, converting fisetin into various metabolites like geraldol, glucuronides, and sulfates. These metabolites are often less bioactive than the parent compound, reducing the overall therapeutic effectiveness of fisetin.
- **Excretion:** Fisetin and its metabolites are primarily excreted through urine, with a relatively short half-life of about 2–4 hours. This quick elimination means that fisetin does not remain in the body for long, contributing to the need for frequent dosing to maintain therapeutic effects [7].

- **Bioavailability:** The bioavailability of fisetin is notably low, with estimates ranging around 44%. This low bioavailability is primarily due to fisetin's poor water solubility and rapid first-pass metabolism in the liver, which leads to the majority of the compound being metabolized before it can enter systemic circulation. In addition, fisetin undergoes extensive phase I and phase II metabolism, including conjugation to glucuronides and sulfates, which reduces its pharmacologically active form. The lipophilic nature of fisetin also means it tends to be poorly absorbed in the aqueous environment of the gastrointestinal tract, further limiting its bioavailability. Recent advances in formulation strategies have sought to improve fisetin's absorption and bioavailability. Techniques such as the development of nanoparticle formulations, micellar delivery systems, and solid lipid nanoparticles aim to enhance fisetin's solubility and stability, allowing for improved absorption and a more sustained release in the body. Co-administration with absorption enhancers like piperine (from black pepper) has also been studied to increase fisetin's bioavailability by inhibiting its metabolism. Despite these efforts, fisetin remains a challenging compound in terms of bioavailability, though innovations in drug delivery technologies show promise in overcoming these barriers [8].

Pharmacological properties of Fisetin

Due to its wide variety of pharmacological actions, Fisetin is a viable contender for the treatment of several diseases. Its activities include antioxidant, anticancer, neuroprotective, antidiabetic, gastrointestinal and cardioprotective effects. Below is a detailed discussion of its key pharmacological actions.

Antioxidant properties of fisetin

Fisetin, a flavonoid widely found in fruits like strawberries, apples, and grapes, demonstrates strong antioxidant properties that play a crucial role in neutralizing oxidative stress. Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is implicated in aging, neurodegenerative diseases, cardiovascular diseases, and cancer. The primary mechanism by which fisetin exerts its antioxidant effects is through its ability to scavenge free radicals. Fisetin is capable of donating electrons to free radicals, stabilizing them and preventing the oxidative damage they would typically cause to cellular components like proteins, lipids, and DNA This direct scavenging action contributes to fisetin's ability to reduce cellular oxidative damage in various tissues, including the brain and liver.

Additionally, fisetin modulates the Nrf2 signaling pathway, which plays a pivotal role in regulating the body's endogenous antioxidant defenses. By activating Nrf2, fisetin promotes the expression of antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). These enzymes help neutralize ROS, further strengthening the cellular defense against oxidative damage. Fisetin also increases the expression of heme oxygenase-1 (HO-1), another critical antioxidant enzyme, through the Nrf2 pathway, leading to enhanced protection against oxidative stress Beyond this, fisetin has been shown to protect mitochondrial function, which is particularly important because mitochondria are a primary source of ROS. By reducing ROS production in mitochondria, fisetin prevents mitochondrial dysfunction, which is often a key event in the development of degenerative diseases, such as Alzheimer's and Parkinson's. This mitochondrial protection ensures that cells maintain their energy production and overall health, mitigating the negative effects of oxidative stress on cellular function [9,10].

Furthermore, fisetin's antioxidant effects extend to the inhibition of lipid peroxidation, which is the process by which ROS damage lipids, leading to cell membrane disruption and contributing to inflammation and disease. By stabilizing cell membranes and reducing lipid peroxidation, fisetin contributes to maintaining cellular integrity and function. Overall, fisetin's ability to scavenge free radicals, enhance endogenous antioxidant defenses, protect mitochondria, and prevent lipid peroxidation underlies its potent antioxidant properties, making it a promising agent for managing oxidative stress-related conditions. In summary, fisetin's antioxidant properties are multifaceted, involving direct free radical scavenging, modulation of antioxidant enzymes, mitochondrial protection, and inhibition of lipid peroxidation, all of which contribute to its ability to mitigate oxidative stress and protect cellular health. These mechanisms make fisetin a valuable compound in the prevention and management of diseases associated with oxidative damage [11]. Table 2 summarizing animal studies that have investigated the antioxidant properties of fisetin.

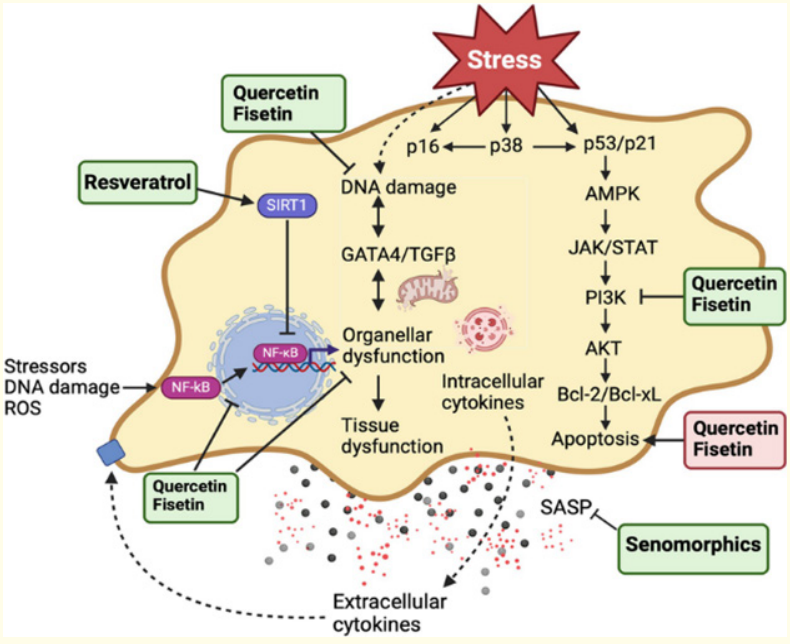

Figure 1: Antioxidant Mechanism of Fisetin [12].

Model	Animal	Dose	Outcome	References
Oxidative Stress Induced by Doxorubicin	Rats (Sprague-Dawley)	10–20 mg/kg/day (oral)	Fisetin showed significant reduction in malondialdehyde (MDA) levels and enhanced SOD and catalase activities, indicating strong antioxidant effects.	[13]
Diabetic Retinopathy Model	Rats (Wistar)	50 mg/kg/day (oral)	Fisetin reduced oxidative stress markers, including ROS and protein carbonylation, and improved retinal histology, suggesting antioxidant and protective effects in diabetic retinopathy.	[14]
Chronic Unilateral Kidney Injury	Mice (C57BL/6)	10 mg/kg/day (oral)	Significant reduction in oxidative stress markers, such as MDA and ROS, and increased HO-1 expression, indicating antioxidant and protective effects in kidney injury.	[15]
Alzheimer's Disease Model	Mice (APP/PS1 transgenic)	10 mg/kg/day (oral)	Fisetin significantly lowered Aβ plaque deposition and reduced oxidative damage, improving memory and cognitive function through its antioxidant properties.	[16]
Cerebral Ischemia/Reperfusion Injury	Rats (Wistar)	20 mg/kg (intraperitoneal)	Fisetin attenuated brain tissue damage by reducing oxidative stress (ROS) and enhancing antioxidant enzyme activities, suggesting neuroprotective and antioxidant effects.	[17]
Acetaminophen-Induced Hepatotoxicity	Rats (Sprague-Dawley)	50 mg/kg (oral)	Fisetin reduced liver injury by lowering oxidative stress markers (MDA, ROS) and improving antioxidant enzyme activities (SOD, catalase).	[18]
Obesity and Hyperlipidemia Model	Mice (C57BL/6J)	5 mg/kg/day (oral)	Fisetin showed antioxidant effects by reducing ROS, MDA, and improving SOD and GPx activity, indicating its protective role against obesity-related oxidative damage.	[19]

Table 2: Studies on Antioxidant Properties of Fisetin.

Anti-inflammatory properties of fisetin

Fisetin, a natural flavonoid found in various fruits and vegetables, demonstrates potent anti-inflammatory properties through several well-established mechanisms. One of its primary actions is the inhibition of the NF-κB pathway, a central regulator of inflammation that controls the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. By suppressing the activation of NF-κB, fisetin reduces the expression of these cytokines, thereby mitigating inflammatory responses. Additionally, fisetin downregulates COX-2 expression, an enzyme involved in the production of pro-inflammatory prostaglandins like PGE2, which are associated with pain and swelling. This inhibition occurs through the suppression of the MAPK pathway, which regulates COX-2 expression. Fisetin also exerts its anti-inflammatory effects by modulating the NLRP3 inflammasome, a key complex in the innate immune system that triggers the release of inflammatory cytokines like IL-1β. Fisetin prevents the assembly of the NLRP3 inflammasome and the activation of caspase-1, thus reducing inflammation at a cellular level. Moreover, fisetin is an effective antioxidant, capable of scavenging reactive oxygen species (ROS), which are known to exacerbate inflammatory processes. By reducing ROS, fisetin helps lower oxidative stress, which is a major contributor to chronic inflammation. Furthermore, fisetin inhibits the expression of iNOS (inducible nitric oxide synthase), a key enzyme involved in producing nitric oxide (NO), which promotes inflammation (Table 3). Fisetin also blocks TLR4 signaling, a crucial pathway in the immune response that can trigger excessive inflammation when activated. These combined effects reducing ROS, inhibiting inflammatory pathways like NF-κB and COX-2, and modulating the inflammasome make fisetin a highly effective natural compound for reducing inflammation and potentially managing inflammatory diseases such as arthritis, cardiovascular disorders, and neurodegenerative conditions [20-22].

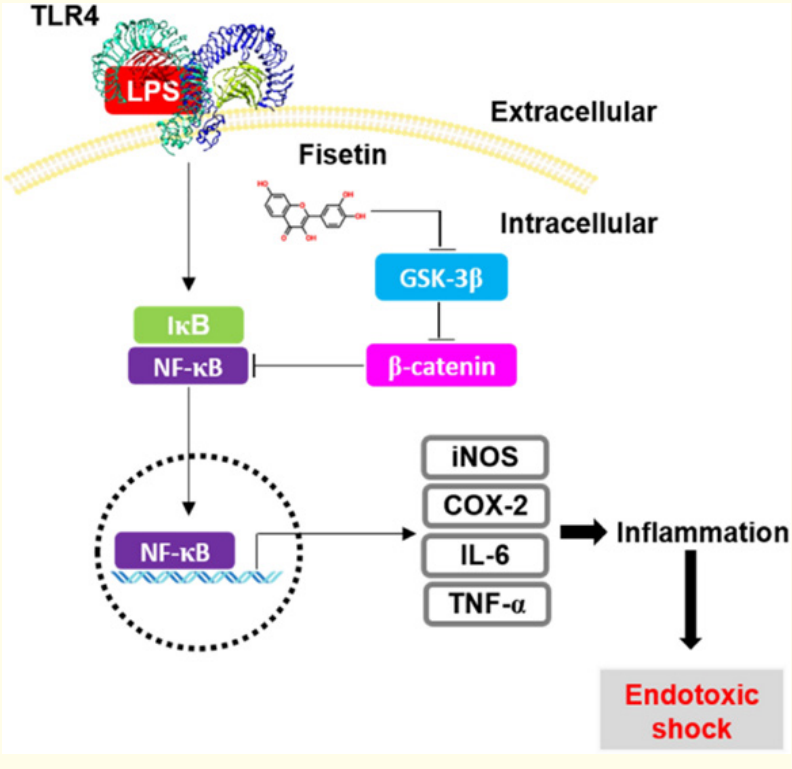

Figure 2: Anti-inflammatory Mechanism of Fisetin [22].

Model	Animal	Dose	Outcome	References
Arthritis Induced by Complete Freund's Adjuvant (CFA)	Rats (Wistar)	10–20 mg/kg/day (oral)	Fisetin significantly reduced paw edema, pro-inflammatory cytokines (TNF-α, IL-1β), and COX-2 expression, suggesting anti-inflammatory effects.	[23]
LPS-Induced Inflammation	Mice (C57BL/6)	20 mg/kg/day (oral)	Fisetin reduced TNF-α and IL-6 levels and inhibited the NF-**κB** pathway, showing significant anti-inflammatory effects.	[24]
Colitis Induced by DSS (Dextran Sodium Sulfate)	Mice (C57BL/6)	10 mg/kg/day (oral)	Fisetin ameliorated colitis by reducing inflammatory cytokines (IL-6, TNF-α) and modulating the NF-**κB** pathway, highlighting its anti-inflammatory potential in gut inflammation.	[25]

Table 3: Studies on Anti-inflammatory Properties of Fisetin.

Neuroprotective properties of fisetin

Fisetin, a flavonoid found in various fruits, has demonstrated significant neuroprotective properties in several studies. It exerts its protective effects primarily through its antioxidant activity, scavenging reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidants like superoxide dismutase (SOD) and catalase, which reduce oxidative stress a key contributor to neurodegeneration. Fisetin also modulates inflammation by inhibiting the activation of microglia and reducing the release of pro-inflammatory cytokines such as TNF-α and IL-6, primarily by affecting the NF-κB and NLRP3 inflammasome pathways. Additionally, fisetin activates the Nrf2/ARE pathway, enhancing the expression of cytoprotective proteins like heme oxygenase-1 (HO-1), which further protects neurons from oxidative damage. In Alzheimer's disease, fisetin has been shown to reduce amyloid-β (Aβ) plaque deposition and inhibit tau hyperphosphorylation, both key features of the disease, through modulation of the GSK-3β pathway. Moreover, fisetin helps mitigate excitotoxicity by modulating glutamate receptors, protecting neurons from damage caused by excessive glutamate. Fisetin also protects mitochondrial function, preventing mitochondrial dysfunction and ROS production, which is critical in maintaining neuronal health. These combined mechanisms make fisetin a promising candidate for the prevention and treatment of neurodegenerative diseases like Alzheimer's disease and Parkinson's disease, as it helps combat oxidative stress, inflammation, and neuronal apoptosis [5,26,27]. Table 4, provides a summary of various animal models that investigate the neuroprotective properties of fisetin. The studies demonstrate fisetin's potential in managing a range of neurodegenerative diseases and cognitive disorders through its antioxidant, anti-inflammatory, and neuroprotective effects, such as improving memory, preserving neurons, and reducing oxidative stress and neuroinflammation.

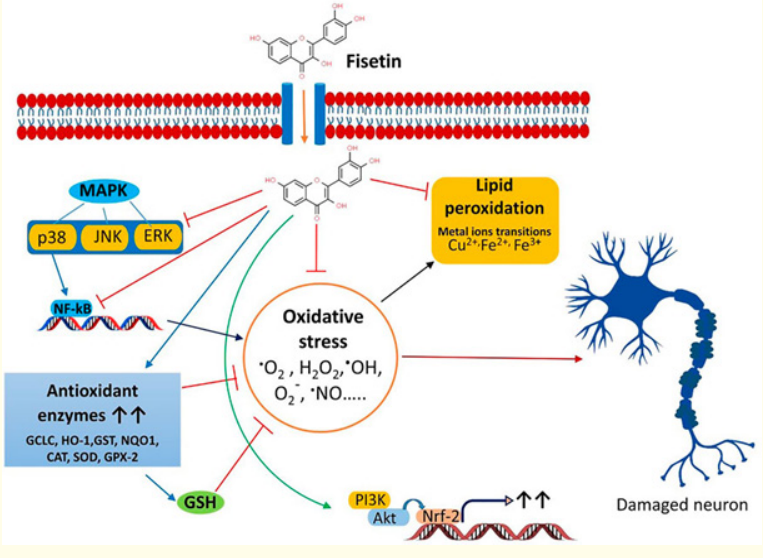

Figure 3: Neuroprotective mechanism of Fisetin [5].

Model	Animal	Dose	Outcome	References
Alzheimer's Disease (Amyloid-β Model)	Mice (C57BL/6J)	10 mg/kg/day (oral)	Fisetin reduced amyloid-β (Aβ) plaque deposition, improved cognitive function, and inhibited tau hyperphosphorylation in Alzheimer's disease models.	[26,28]
Parkinson's Disease (MPTP Model)	Mice (C57BL/6J)	5–20 mg/kg/day (oral)	Fisetin significantly improved motor function and preserved dopaminergic neurons in the substantia nigra by reducing oxidative stress and neuroinflammation.	[29]
Neurodegeneration (3-Nitropropionic Acid Model)	Rats (Sprague-Dawley)	50 mg/kg/day (oral)	Fisetin exhibited neuroprotective effects by reducing oxidative stress, enhancing mitochondrial function, and preserving striatal neurons in Huntington's disease models.	[30]
Cognitive Decline (Scopolamine-Induced Memory Impairment)	Rats (Sprague-Dawley)	25 mg/kg/day (oral)	Fisetin significantly improved memory and learning abilities, reduced oxidative damage in the hippocampus, and restored acetylcholine levels.	[31]
Chronic Stress-Induced Neuroinflammation	Mice (C57BL/6J)	10 mg/kg/day (oral)	Fisetin ameliorated neuroinflammation and reduced depression-like behaviors by modulating oxidative stress and inflammatory pathways.	[32]
Neurotoxicity (LPS-Induced Neuroinflammation)	Mice (C57BL/6J)	10–20 mg/kg/day (oral)	Fisetin reduced LPS-induced inflammation, inhibited microglial activation, and preserved cognitive function in neuroinflammation models.	[33]

Table 4: Studies on Neuroprotective Properties of Fisetin.

Anticancer properties of fisetin

Fisetin exerts its anticancer effects through a variety of intricate molecular mechanisms that target key cellular processes involved in tumorigenesis. One of the most notable mechanisms is its ability to activate tumor suppressor pathways, particularly through the p53 protein. P53 is often referred to as the "guardian of the genome" because it regulates critical cellular processes, such as DNA repair, cell cycle arrest, and apoptosis (programmed cell death), in response to cellular stress or DNA damage. In many cancers, p53 is either mutated or downregulated, leading to uncontrolled cell growth and evasion of apoptosis. Fisetin has been shown to restore or enhance the function of p53, promoting cell cycle arrest and apoptosis in cancer cells. This results in the suppression of tumor growth by halting the cell cycle at key checkpoints, preventing the proliferation of abnormal cancer cells. Moreover, fisetin-induced p53 activation also leads to the expression of pro-apoptotic proteins, further amplifying cancer cell death and preventing their survival [34]. Another critical pathway regulated by fisetin is the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, which is implicated in the regulation of inflammation, immune response, cell survival, and metastasis. In the context of cancer, the NF-κB pathway is often constitutively activated, promoting tumorigenesis by inducing the expression of anti-apoptotic proteins, inflammatory cytokines, and factors that drive metastasis. This results in increased cancer cell proliferation, invasion, and resistance to cell death. Fisetin has been shown to inhibit the activation of NF-κB, thereby downregulating the expression of pro-inflammatory cytokines (such as TNF-α, IL-6) and anti-apoptotic proteins (such as Bcl-2). By suppressing NF-κB activity, fisetin reduces tumor growth, invasion, and metastasis, offering a potent mechanism of action in controlling cancer progression [35,36].

The AKT/mTOR signaling pathway is another crucial target of fisetin. This pathway is frequently dysregulated in cancer cells, leading to enhanced cell survival, growth, metabolism, and resistance to apoptosis. AKT (also known as Protein Kinase B) activates a cascade of downstream signaling events that stimulate mTOR (mechanistic target of rapamycin), which in turn promotes protein synthesis, cell growth, and survival. In many cancers, overactivation of the AKT/mTOR pathway contributes to tumorigenesis and resistance to chemotherapy. Fisetin has been shown to inhibit both AKT and mTOR, leading to reduced cell proliferation, decreased protein synthesis, and enhanced apoptosis in cancer cells. By modulating this pathway, fisetin disrupts the mechanisms that cancer cells rely on for survival and growth, making it an effective agent in limiting tumor progression [37,38]. Fisetin also plays a role in epigenetic regulation, influencing gene expression without altering the underlying DNA sequence. It affects histone modification, particularly histone acetylation, and DNA methylation, both of which are key processes in the regulation of gene expression. Histone

acetylation loosens the DNA structure, making it more accessible for transcription, while DNA methylation often silences gene expression. In cancer, dysregulated epigenetic modifications contribute to the activation of oncogenes and the silencing of tumor suppressor genes. Fisetin can modulate these epigenetic marks, reactivating tumor suppressor genes and downregulating oncogenes. This leads to the restoration of normal cellular processes, including apoptosis, differentiation, and cell cycle control, all of which are frequently disrupted in cancer cells [39].

Autophagy, a cellular process that involves the degradation and recycling of damaged or dysfunctional organelles and proteins, also plays a key role in fisetin's anticancer effects. In cancer cells, autophagy can act as a double-edged sword: it may either promote tumorigenesis by helping cancer cells survive under stress or suppress tumor progression by eliminating damaged cellular components (Table 5). Fisetin regulates autophagy by modulating the expression of autophagy-related genes, influencing both pro-survival and pro-death autophagic pathways [40]. In some contexts, fisetin induces autophagic cell death, particularly in stressed cancer cells, thereby enhancing cancer cell elimination. In other cases, fisetin's ability to regulate autophagy may limit the survival of cancer cells under nutrient deprivation or chemotherapy-induced stress, further inhibiting tumor growth.

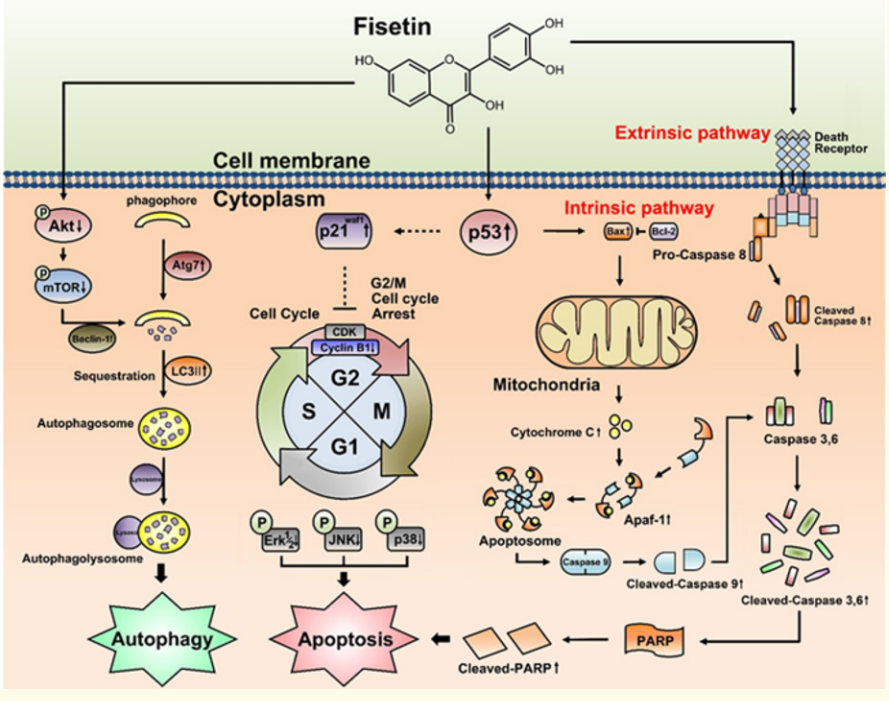

Figure 4: Anticancer Mechanism of Fisetin [41].

Model	Animal	Dose	Outcomes	Reference
Colorectal cancer	Mice	50 mg/kg body weight (oral)	Fisetin inhibited tumor growth, reduced tumor volume, and enhanced apoptosis in colorectal cancer cells.	[42-44]
Breast cancer (MDA-MB-231)	Mice	10-20 mg/kg body weight (oral)	Fisetin suppressed tumor growth, inhibited angiogenesis, and reduced metastasis.	[45,46]
Hepatocellular carcinoma	Rats	50 mg/kg body weight (oral)	Fisetin significantly reduced tumor size, induced apoptosis, and decreased serum levels of tumor markers (AFP).	[47]
Non-small cell lung cancer	Mice	20 mg/kg body weight (oral)	Fisetin suppressed lung tumor growth, reduced inflammation, and induced cell cycle arrest in lung cancer cells.	[48,49]
Ovarian cancer	Mice	40 mg/kg body weight (oral)	Fisetin decreased tumor growth and inhibited cell proliferation in ovarian cancer.	[50]
Breast cancer (4T1)	Mice	30 mg/kg body weight (oral)	Fisetin reduced tumor volume, inhibited metastasis, and decreased angiogenesis in breast cancer.	[51,52]
Prostate cancer (TRAMP model)	Mice	50 mg/kg body weight (oral)	Fisetin reduced prostate tumor volume and inhibited cell proliferation and migration.	[53]
Skin cancer (DMBA-initiated)	Mice	100 mg/kg body weight (oral)	Fisetin reduced tumor incidence, decreased tumor size, and inhibited skin cancer progression.	[54]
Gastric cancer	Mice	50 mg/kg body weight (oral)	Fisetin reduced tumor growth, promoted apoptosis, and decreased metastasis in gastric cancer cells.	[55,56]
Cervical cancer	Rats	60 mg/kg body weight (oral)	Fisetin inhibited tumor growth, enhanced apoptosis, and modulated key cancer-related signaling pathways.	[57]

Table 5: Studies on Anticancer Properties of Fisetin.

Antidiabetic properties of fisetin

Fisetin, a flavonoid found in various fruits and vegetables, has shown promising antidiabetic properties, primarily through its ability to improve insulin sensitivity, reduce blood glucose levels, and alleviate key factors involved in diabetes pathogenesis. It enhances the body's response to insulin, which helps reduce insulin resistance, a hallmark of type 2 diabetes. In animal studies, fisetin has demonstrated the ability to lower blood glucose levels, potentially by improving glucose metabolism. Additionally, fisetin possesses anti-inflammatory properties, which can counteract chronic inflammation often associated with insulin resistance. Its strong antioxidant activity helps mitigate oxidative stress, a significant contributor to diabetes and its complications, by scavenging free radicals and protecting pancreatic beta cells from damage. Fisetin also supports the preservation of beta cell function, improving insulin production and secretion. Furthermore, fisetin inhibits the enzyme α-glucosidase, which plays a role in breaking down complex carbohydrates into simple sugars in the digestive system. By inhibiting this enzyme, fisetin may help prevent rapid glucose absorption from the gut, thus reducing postprandial blood sugar spikes [58]. Fisetin exerts its antidiabetic effects through several key mechanisms of action that regulate glucose metabolism, insulin sensitivity, and inflammation. One important mechanism is the activation of the AMP-activated protein kinase (AMPK) pathway, a critical regulator of cellular energy balance. AMPK activation enhances glucose uptake in muscle cells and stimulates fat oxidation, both of which contribute to improved insulin sensitivity and reduced blood glucose levels. This pathway is vital for maintaining energy homeostasis, particularly in tissues like muscles and the liver, where glucose and fat metabolism are central to metabolic control [59,60].

Another crucial mechanism of fisetin's action is its inhibition of the NF-kB (nuclear factor kappa B) pathway, which plays a central role in regulating inflammation. Chronic inflammation is a key factor in the development of insulin resistance and beta-cell dysfunction in diabetes. By suppressing this inflammatory pathway, fisetin helps reduce the inflammatory burden that contributes to insulin resistance, improving glucose metabolism and preserving beta-cell function, which is essential for proper insulin secretion.Fisetin also helps combat the harmful effects of advanced glycation end products (AGEs), which are formed when sugars bind to proteins or lipids, leading to inflammation, tissue damage, and the progression of

diabetic complications. As an antioxidant, fisetin can prevent the formation of AGEs, thus protecting tissues from oxidative damage and inflammatory responses that often exacerbate diabetes and its associated complications [61-63].

The regulation of PPAR-γ (Peroxisome Proliferator-Activated Receptor Gamma) is another mechanism by which fisetin improves glucose metabolism. PPAR-γ is a receptor involved in regulating glucose and lipid metabolism. By activating PPAR-γ, fisetin enhances insulin sensitivity, reduces inflammation, and supports glucose homeostasis, helping to maintain balanced blood sugar levels [64]. Finally, fisetin also inhibits gluconeogenesis in the liver, which is the process by which the liver produces glucose from non-carbohydrate sources. In people with diabetes, excessive gluconeogenesis can contribute to elevated blood glucose levels. Fisetin's ability to suppress this process helps reduce the overproduction of glucose, thereby contributing to the regulation of blood sugar levels, especially in individuals with type 2 diabetes. Through these combined mechanisms, fisetin provides a multi-target approach to managing diabetes by improving insulin sensitivity, reducing inflammation, protecting against oxidative stress, and regulating glucose production and absorption [65,66]. Different studies suggest that fisetin has significant potential in managing diabetes and improving glucose metabolism in animal models (Table 6).

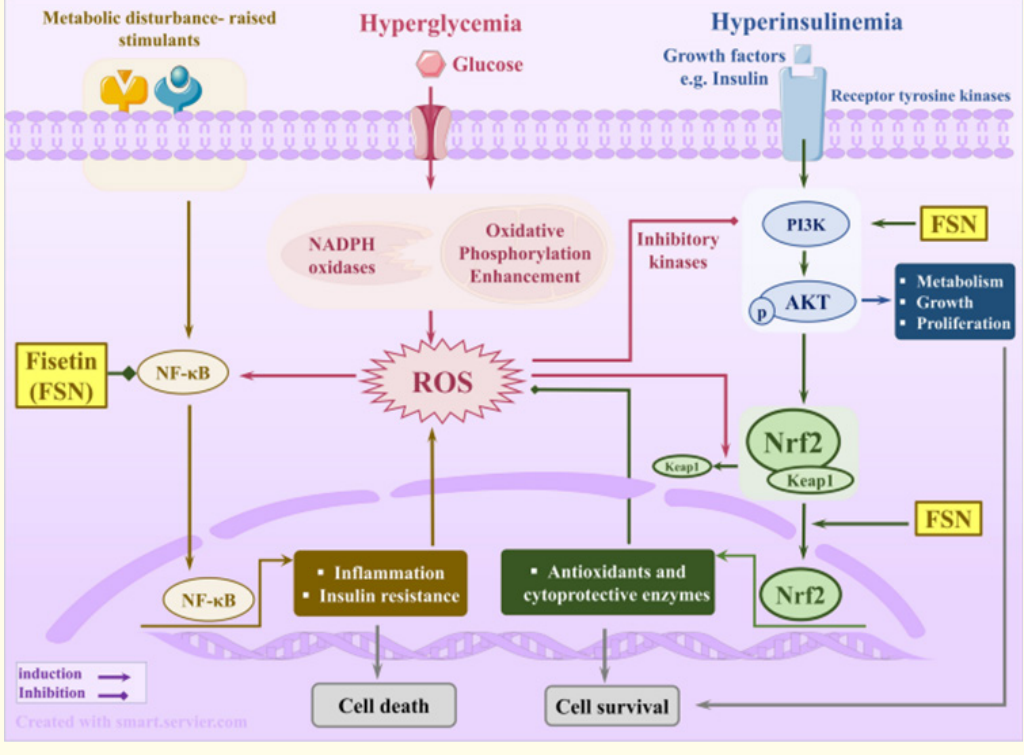

Figure 5: Antidiabetic Mechanism of Fisetin [67].

Animal Model	Dose	Outcome	Reference
Streptozotocin-induced diabetic rats	10, 20, 40 mg/kg (oral)	Fisetin significantly reduced blood glucose levels and improved insulin sensitivity. It also exhibited antioxidant effects.	[68,69]
High-fat diet-induced diabetic rats	10 mg/kg (oral)	Fisetin improved glucose tolerance, reduced insulin resistance, and lowered blood glucose levels.	[70]
Diabetic mice (db/db)	30 mg/kg (oral)	Fisetin decreased fasting blood glucose, improved lipid profiles, and showed anti-inflammatory effects.	[71]
KK-Ay mice (obesity-related type 2 diabetes)	30 mg/kg (oral)	Fisetin improved insulin sensitivity, reduced adiposity, and significantly lowered blood glucose levels.	[58]
C57BL/6J mice (diet-induced obesity)	10, 20 mg/kg (oral)	Fisetin improved insulin resistance, reduced body weight, and enhanced glucose tolerance.	[72]

Table 6: Studies on Antidiabetic Properties of Fisetin.

Cardioprotective properties of fisetin

Fisetin, a flavonoid found in various fruits and vegetables, exerts significant cardioprotective effects through several key mechanisms. One of its primary actions is its potent antioxidant activity, where it neutralizes reactive oxygen species (ROS), reducing oxidative stress that is known to damage endothelial cells and contribute to cardiovascular diseases like atherosclerosis and hypertension. By scavenging ROS, fisetin prevents cellular damage and maintains endothelial function. It also exerts anti-inflammatory effects by inhibiting the NF-κB pathway, which downregulates pro-inflammatory cytokines and enzymes. This helps reduce vascular inflammation, a major contributor to the progression of heart disease. Furthermore, fisetin enhances endothelial function by increasing the production of nitric oxide (NO), which promotes vasodilation and improves blood flow, thus lowering blood pressure and reducing the risk of hypertension [73-75].

In addition to these effects, fisetin improves lipid metabolism by lowering levels of total cholesterol and LDL (bad cholesterol) while increasing HDL (good cholesterol), which helps prevent plaque buildup in the arteries and reduces the risk of atherosclerosis. Fisetin also has anti-thrombotic properties, preventing excessive platelet aggregation and clot formation, which can lead to heart attacks and strokes. By inhibiting thrombotic factors, fisetin reduces the risk of cardiovascular events. Another important mechanism is its regulation of glucose metabolism. Fisetin enhances insulin sensitivity and reduces blood glucose levels, which is particularly beneficial for preventing diabetic cardiomyopathy, a complication of diabetes that contributes to heart failure [76]. Additionally, fisetin can promote angiogenesis, the formation of new blood vessels, which is crucial for improving blood supply to the heart, especially in cases of myocardial ischemia or after a heart attack. Fisetin also protects heart muscle cells from apoptosis (programmed cell death), a process that contributes to heart damage in conditions like heart failure and ischemia [77]. By modulating apoptotic pathways and reducing oxidative stress, fisetin helps preserve cardiomyocyte function and integrity. Through these various mechanism's antioxidant, anti-inflammatory, lipid-regulating, antithrombotic, and cell-protective fisetin demonstrates strong cardioprotective effects, making it a promising natural compound for the prevention and management of cardiovascular diseases (Table 7).

Antiaging properties of fisetin

Fisetin, a flavonoid found in various fruits and vegetables, has shown significant potential in promoting anti-aging effects through multiple mechanisms. One of its key actions is its potent antioxidant activity, where fisetin scavenges free radicals, reducing oxidative stress—a major contributor to cellular aging and age-related diseases. It also exerts anti-inflammatory effects by modulating inflammatory pathways, inhibiting pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as the NF-κB pathway. This helps mitigate chronic inflammation, which accelerates aging and age-associated disorders like arthritis and cardiovascular diseases. Additionally, fisetin helps preserve telomere length by influencing telomerase activity, thus potentially extending cell lifespan and delaying cellular senescence [84,85]. Moreover, fisetin activates

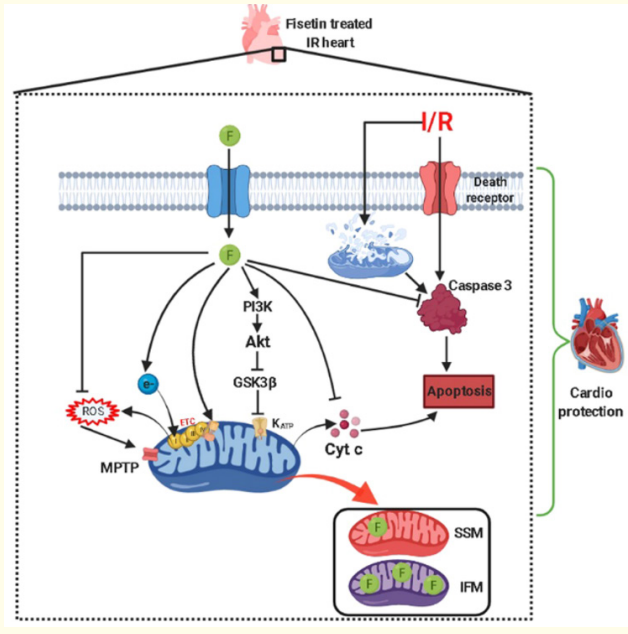

Figure 6: Cardioprotective Mechanism of Fisetin [78].

Animal Model	Animal Type	Dose	Study Outcome	Reference
Myocardial Infarction (MI) Model	Rats (Wistar)	10, 20, or 40 mg/kg/day (oral)	Fisetin significantly reduced infarct size, improved heart function, and lowered markers of oxidative stress and inflammation.	[79]
Ischemia-reperfusion Injury Model	Mice (C57BL/6)	25 mg/kg (intraperitoneal)	Fisetin improved heart function, reduced myocardial injury, and decreased levels of inflammatory cytokines.	[80]
Hypertension-Induced Heart Model	Rats (Spontaneously Hypertensive)	10 mg/kg/day (oral)	Fisetin reduced blood pressure, oxidative stress, and heart fibrosis in hypertensive rats.	[81]
Cardiac Remodeling Model (Post-MI)	Rats (Sprague-Dawley)	30 mg/kg/day (oral)	Fisetin reduced oxidative stress markers, improved heart structure, and prevented adverse cardiac remodeling.	[82]
Diabetic Cardiovascular Model	Rats (Streptozotocin-Induced Diabetic)	10 mg/kg (oral)	Fisetin improved heart function, reduced oxidative stress, and prevented cardiac fibrosis in diabetic rats.	[83]

Table 7: Studies on Cardioprotective Properties of Fisetin.

autophagy, a critical process that removes damaged cellular components, helping to maintain cell function and reduce the accumulation of cellular debris associated with aging. It also activates sirtuins, particularly SIRT1, which are involved in DNA repair, mitochondrial function, and regulating inflammation, further promoting longevity and cellular health. Fisetin's role in mitochondrial health is another crucial aspect of its anti-aging properties, as it supports mitochondrial biogenesis and enhances cellular energy production, slowing age-related metabolic decline [86].

Fisetin also aids in DNA repair by upregulating repair enzymes, thus protecting cells from DNA damage, which can lead to mutations and age-related diseases such as cancer. It has been shown to possess anti-senescence activity, inhibiting the formation of se-

nescent cells that accumulate over time and contribute to aging. By preventing senescent cell buildup, fisetin helps delay aging and reduces the risk of diseases such as cardiovascular conditions and osteoarthritis. Neuroprotectively, fisetin modulates neuroinflammation, reduces oxidative stress, and promotes neurogenesis, making it a promising agent in preventing neurodegenerative diseases like Alzheimer's. Finally, fisetin's protective effects extend to the skin, where it helps reduce UV-induced oxidative stress, inhibits collagen degradation, and promotes skin elasticity, thus helping to preserve a youthful appearance [87,88]. Table 8 summarizing animal studies on the anti-aging activity of fisetin.

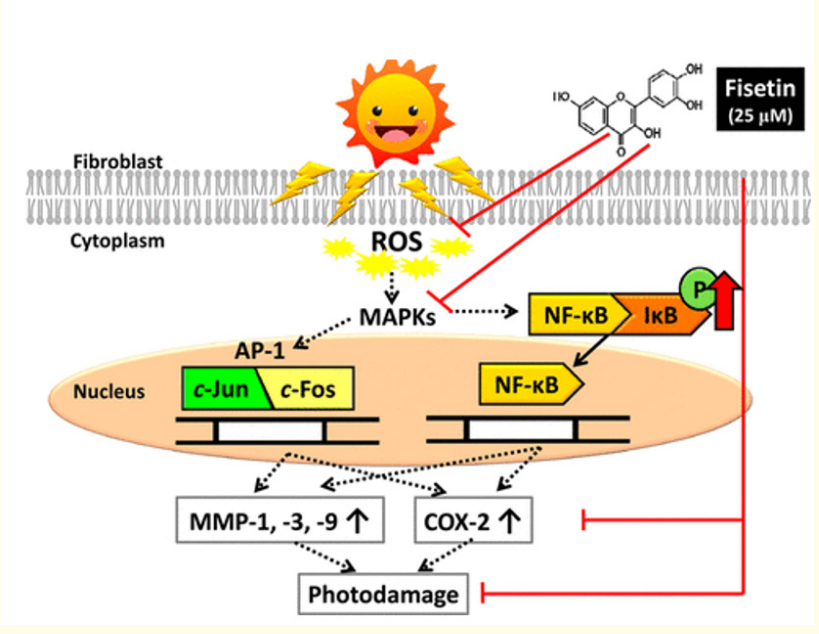

Figure 7: Anti-ageing effect of Fisetin by suppressing Photodamage [89].

Animal Model	Animal Type	Dose	Study Outcome	Reference
Age-related oxidative stress model	Mice (C57BL/6)	25 mg/kg/day (oral)	Fisetin reduced oxidative stress, improved skin elasticity, and extended lifespan in aged mice.	[90]
Cellular senescence model	Rats (Sprague-Dawley)	10 mg/kg/day (oral)	Fisetin reduced the number of senescent cells, improved physical activity, and restored tissue regeneration.	[86]
Neurodegenerative aging model	Mice (C57BL/6)	30 mg/kg/day (oral)	Fisetin improved cognitive function, reduced neuroinflammation, and protected against memory decline.	[5]
UV-induced skin aging model	Mice (C57BL/6)	10 mg/kg/day (oral)	Fisetin prevented UV-induced skin damage, reduced wrinkles, and improved collagen synthesis.	[91]
Mitochondrial dysfunction model	Rats (Wistar)	20 mg/kg/day (oral)	Fisetin enhanced mitochondrial function, increased energy production, and delayed age-related metabolic decline.	[92]
Cardiovascular aging model	Rats (Spontaneously Hypertensive)	10 mg/kg/day (oral)	Fisetin improved cardiovascular function, reduced blood pressure, and decreased heart fibrosis.	[93]
Aging-induced neurodegeneration	Mice (C57BL/6)	25 mg/kg/day (oral)	Fisetin extended lifespan, reduced neurodegeneration, and protected neurons from oxidative damage.	[94]
Autophagy dysfunction model	Mice (C57BL/6)	20 mg/kg/day (oral)	Fisetin enhanced autophagic activity, cleared damaged cellular components, and reduced aging-related tissue damage.	[95]

Table 8: Studies on anti-aging Properties of Fisetin.

Immunomodulatory properties of fisetin

Fisetin, a naturally occurring flavonoid, has shown significant immunomodulatory effects through various mechanisms, making it a promising agent for regulating immune responses. One of its key actions is its anti-inflammatory activity, where fisetin inhibits the NF-κB signaling pathway, a major regulator of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. By suppressing this pathway, fisetin helps reduce chronic inflammation, which is crucial in the treatment of autoimmune disorders and inflammatory conditions like rheumatoid arthritis and inflammatory bowel disease. Additionally, fisetin modulates cytokine production, shifting the balance toward anti-inflammatory cytokines like IL-10, while suppressing pro-inflammatory cytokines. This balance is essential for maintaining immune system homeostasis and preventing excessive immune activation [96].

Fisetin also influences the activation and function of various immune cells, including T cells, macrophages, and dendritic cells. It regulates T cell differentiation and promotes a balance between different T helper cell subsets (Th1, Th2, and Treg), which is crucial for immune tolerance. In macrophages, fisetin promotes a shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, helping to reduce immune system overactivation. Furthermore, fisetin's potent antioxidant properties reduce oxidative stress, which is known to exacerbate immune dysfunction. By scavenging reactive oxygen species (ROS), fisetin prevents immune cell damage and promotes healthy immune function [97]. Moreover, fisetin inhibits the activity of pro-inflammatory enzymes like cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), which are involved in the production of inflammatory mediators such as prostaglandins and leukotrienes. This action helps alleviate conditions where these enzymes are overactive, such as in rheumatoid arthritis and asthma. Fisetin also activates the Nrf2 pathway, a key regulator of cellular antioxidant defense, further enhancing its anti-inflammatory and immunomodulatory effects. Additionally, fisetin can inhibit the JAK/STAT signaling pathway, which plays a role in the activation of immune cells and inflammatory responses, helping to prevent excessive immune activation and chronic inflammation [98]. The immunomodulatory activity of fisetin in animal studies given in Table 9.

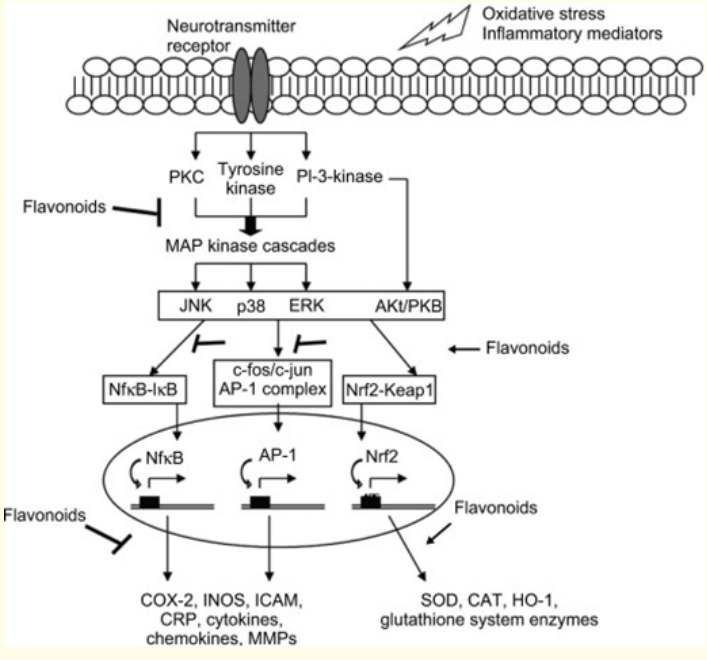

Figure 8: Immunomodulatory mechanism of Fisetin [99].

Animal Model	Animal Type	Dose	Study Outcome	Reference
Inflammatory bowel disease (IBD) model	Mice (C57BL/6)	10 mg/kg/day (oral)	Fisetin reduced colitis symptoms, decreased inflammatory cytokines (TNF-α, IL-6), and improved gut barrier function.	[100]
Autoimmune encephalomyelitis model	Mice (C57BL/6)	25 mg/kg/day (oral)	Fisetin enhanced Treg function, suppressed Th1/Th17 responses, and alleviated symptoms of autoimmune encephalomyelitis.	[6]
Rheumatoid arthritis model	Rats (Sprague-Dawley)	10 mg/kg/day (oral)	Fisetin reduced joint inflammation, decreased serum levels of pro-inflammatory cytokines (IL-1β, TNF-α), and reduced paw swelling.	[101]
Dendritic cell activation model	Mice (BALB/c)	15 mg/kg/day (oral)	Fisetin reduced dendritic cell activation and antigen presentation, leading to decreased immune response in an allergic model.	[102]

Table 9: Studies on Immunomodulatory Properties of Fisetin

Conclusion

Fisetin, a flavonoid found in fruits and vegetables, has shown significant therapeutic potential in animal studies across several areas. Its antioxidant properties help reduce oxidative stress, protecting cells from damage and supporting overall health. Fisetin improves insulin sensitivity and regulates blood sugar levels, showing promise for managing diabetes**.** It provides cardioprotective effects by reducing blood pressure, improving lipid profiles, and protecting the heart from damage. Fisetin also acts as an immunomodulator**,** reducing inflammation and regulating immune responses in autoimmune conditions. Its anticancer properties inhibit tumor growth and induce cell death. As an anti-aging agent, it combats oxidative stress, preserves telomere length, and enhances cellular repair. Additionally, neuroprotective effects have been observed, with fisetin protecting the brain from neurodegeneration and improving cognitive function. These findings highlight fisetin's broad potential for treating chronic diseases, aging-related conditions, and immune-related disorders.

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