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Fisetin: An Extensive Analysis of Its Therapeutic Potential and Pharmacological Properties

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Abstract: First discovered in Venetian sumach in 1833, fisetin is a flavonol that can be found in fruits like strawberries, apples, and onions. Fisetin, which has anti-inflammatory, antioxidant, anticancer, and neuroprotective properties, affects important pathways like MAPK and NF-κB. It lowers oxidative stress, inhibits angiogenesis, and decreases osteoclast development in diabetic heart cells. Additionally, fisetin reduces inflammation in microglia and macrophages, which may help cure neuroinflammatory and neurodegenerative disorders. Improved drug delivery techniques, such as SNEDDS, increase the medication's solubility and bioavailability, bolstering its therapeutic potential and highlighting the need for more study.

Keywords: Fisetin • Anti-inflammatory • Neuroprotective • Antioxidant • Drug delivery • Therapeutic potential

Introduction

Fruits and vegetables such as cucumbers, strawberries, apples, persimmons, grapes, and onions contain the yellow polyphenol flavonoid fisetin, with strawberries being the most abundant food source. Its structure was verified by Kostanecki in the 1890s after it was initially isolated from Venetian sumach in 1833. Anti-inflammatory, antioxidant, anti-cancer, antinociceptive, antifungal, and antibacterial properties are all displayed by fisetin. Its low gastrointestinal absorption and poor water solubility, however, restrict its biological effects. The origin, increased bioavailability, and therapeutic potential of fisetin for anti-diabetic, anti-angiogenic, antioxidant, anti-inflammatory, and neuroprotective applications in vitro and in vivo are the main topics of this review.

Fisetin's Physicochemical Profile and Molecular Structure

Numerous common fruits and plants, such as apples, strawberries, grapes, and onions, contain fisetin. Because of its 3OH group, which is augmented by 3'OH and 4'OH groups, as well as a 2-3 carbon double bond (SAR), it is prized for its health-promoting bioactive qualities, which are primarily antioxidative. With a log P of 1.97 and a molecular weight of 286.24 g. mol^{-1}, fisetin exhibits moderate lipophilicity.

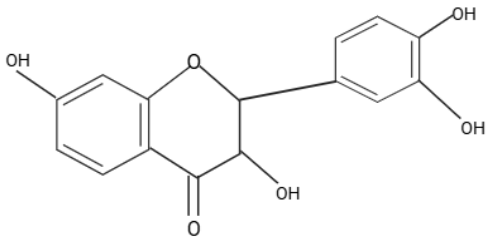

Fig. 1: Fisetin's structure

It enhances solubility and cytotoxicity against HeLa and MCF-7 cells when combined with β- and γ-cyclodextrins, and it forms a stable complex with β-cyclodextrin but not α-cyclodextrin. Fisetin has a variety of functions, according to pharmacological research, including anticancer, anti-inflammatory, neuroprotective, neurotrophic, antiangiogenic, and antiproliferative properties Fisetin is a viable option for medications and supplements because of these qualities.

Fisetin is a pale-yellow flavonoid compound with the chemical formula $C_{15}H_{10}O_6$ and a molecular weight of 286.26 $g.mol^{-1}$. 5-Desoxyquercetin, 3,3′,4′,7-Tetrahydroxyflavone, 7,3′,4′-Trihydroxyflavonol, Cotinin, Festin, Fitin, and 4′-flavon-3-ol are some of its aliases. Fisetin's pKa of 7.42 indicates its acidic dissociation property, its melting point is 330°C, and its log P value of 3.2 indicates moderate lipophilicity. Its pharmacokinetic behaviour and bioavailability in biological systems are influenced by these physicochemical properties. Numerous plant-based foods, such as apples, strawberries, fruits, vegetables, herbs, and medicinal plants, contain the bioactive flavonoid fisetin. Some of the most common sources of fisetin are listed in Table 1.

Sources of Fisetin

Table 1: Fisetin's sources, geographical origins, and industrial uses (Sip et al. 2023., Yi et al. 2014)

Source	Geographical Origin	Industrial Applications
Fruits		
Strawberry (Species of *Fragaria*)	Europe, North America	Suppresses NF-κB and PGE_2/COX-2 signalling, which has anticancer effects.
Apple (*Malus* species)	Europe, Asia	Apoptosis and suppresses colon cancer through the Wnt/EGFR/NF-κB/COX-2 pathways.
Diospyros species, or persimmon	East Asia, Japan	Inhibits NF-κB activation triggered by TNF and suppresses the expression of COX-2.
Vegetables		
Allium cepa, or onion	Global distribution	Suppresses COX-2 and lowers inflammatory mediators without influencing COX-1.

Other dietary sources of fisetin are included in Figure 2, along with their concentrations.

Outcomes of in vitro investigations

The advantages of tailored biomaterial modifications are validated by in vitro research. Reaction prediction is aided by cascade-focused methods in disease applications and animal models.

Antidiabetic effect

Fisetin improves antioxidant defences in diabetic cardiomyocytes, lowering oxidative stress, inflammation, and apoptosis, according to in vitro research. Additionally, it increases antioxidant genes and decreases ROS in PE-induced cardiomyocyte hypertrophy, suggesting that DCM treatment may be possible. (Dong et al., 2018)

Antiangiogenic

Fisetin (0–50 μM) inhibited tube formation on Matrigel by 85% after 16 hours, reducing angiogenesis in HUVECs in vitro. In a dose- and time-dependent manner, fisetin (25–50 μM) decreased VEGF-induced HUVEC migration (37–66%) and proliferation (52–92%). By downregulating surviving, triggering caspases, and raising the BAX/Bcl-2 ratio, it caused apoptosis.

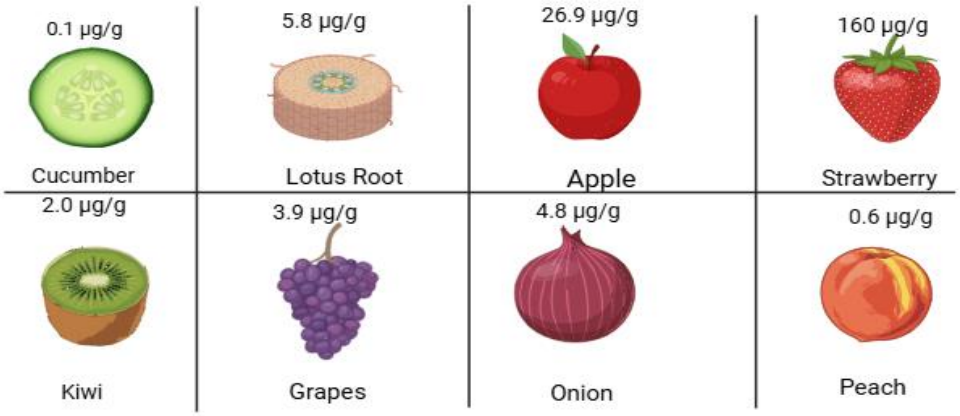

Fig. 2: Dietary sources of fisetin. (Following the acid hydrolysis of their parent glycosides, the amounts of fisetin in freeze-dried fruits and vegetables were measured).(Kimira et al.,1998)

Antioxidative

As demonstrated by Western blot and immunofluorescence, fisetin decreased PCNA expression and, beginning at 1 µM, inhibited Ang II-induced migration and proliferation of rat aortic VSMCs. By lowering ROS through PON2 overexpression, fisetin prevented Ang II-induced VSMC migration and proliferation. These effects were reversed by PPARγ inhibition, demonstrating its involvement in the mechanism.

Osteoarthritic

Fisetin stabilizes MKP-1 (via proteasome suppression) to block MAPK and NF-κB signalling, which in turn downregulates cathepsin K, MMP9, TRAP, and CTR. This decreases RANKL-induced osteoclastogenesis and TRAP activity in a dose-dependent manner.

Anti inflammatory

Fisetin provides protection against brain diseases, heart ischemia, UVB damage, and metabolic dysfunction by inhibiting NF-κB nuclear translocation in LPS-activated RAW 264.7 macrophages, decreasing NO, PGE_2, IL-6, TNF-α, iNOS, and COX-2 in a dose-dependent manner. Additionally, it inhibits TLR4-mediated NF-κB signalling through the GSK-3β/β-catenin and NF-κB pathways to stop LPS-induced acute lung damage, macrophage activation, and dendritic cell maturation.

Neuroinflammatory

Fisetin inhibits PGE2, NO, TNF-α, IL-1β, COX-2, and iNOS, demonstrating potent anti-inflammatory actions in microglia. It lowers the generation of inflammatory mediators by blocking NF-κB p65 activation, IκB degradation, and p38 MAPK signalling.(Da Silva et al., 1997; Jongeneel 1995)

Fig. 3: Pharmacological effects of fisetin

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By preventing microglial activation and shielding neurons from oxidative stress, fisetin lessens microglia-induced neurotoxicity in B35 cells, suggesting that it may be a safe neuroprotective and anti-inflammatory drug.

Neuroprotective

In Parkinson's models, fisetin improves stability, solubility, absorption, and neuroprotection by scavenging free radicals, lowering lipid peroxidation, and increasing GSH, SOD, and CAT. When it is formulated as <200 nm nano-emulsions/SNEDDS, it crosses the blood-brain barrier, lowers α-synuclein, modulates BDNF, and lowers IL-6 and TNF-α.

Antidiabetic potential

To prevent inflammation, ROS, AGEs, hyperglycaemia, renal injury, and fibrosis, fisetin suppresses CD36 and TGFβ/SMAD2/3 signalling. It also prevents the development of foam cells caused by oxLDL by either downregulating CD36 or modulating NLRP3, which protects macrophages and endothelium.

Anti-inflammatory actions

Nephroprotective

By lowering blood uric acid through urate transporters, reducing inflammation (TNF-α, IL-6, MCP-1), maintaining kidney structure, and reducing fibrosis through TGF-β and STAT3 pathway suppression, fisetin (50–100 $mg.kg^{-1}$) exhibits therapeutic potential in hyperuricemic nephropathy.

Ophthalmometry

Fisetin preserves retinal function by lowering pro-inflammatory cytokines and NF-κB activity, improving RGC survival, and lowering microglial activation in DBA/2J mice (GPNMB/Tyrp1 mutants) by lowering IOP, inflammation, and oxidative damage.

Anti-osteoporotic

By reducing the RANKL/OPG ratio and inflammatory cytokines, increasing GSH, CAT, and SOD defences to reduce oxidative stress and MDA, and improving calcium absorption through ER/VDR interactions—thereby reducing osteoclast activity—Fisetin reduces OVX-induced osteoporosis.

Sepsis-associated encephalopathy

By inhibiting the NLRP3 inflammasome in endothelial cells and reducing IL-1R1, pNF-κB, TNF-α, and iNOS in microglia, fisetin lessens inflammation in sepsis-associated encephalopathy. Additionally, it shows promise against sepsis-related brain injury by lowering oxidative stress, promoting mitophagy, preserving the blood-brain barrier, and enhancing cognition.

Anti psoriatic

In psoriasis models, fisetin outperforms rapamycin and mitigates atopic dermatitis by binding mTOR/S6K1 to inhibit Akt/mTOR signalling, which suppresses T-cell activation and keratinocyte proliferation, lowering IL-17A, IFN-γ, IL-4, and IL-31 while increasing IL-10 through enhanced autophagy (Atg5, LC3A/B).

Neuroprotective

Fisetin lowers GFAP levels, a crucial indicator of inflammation, which in turn reduces neuroinflammation in Alzheimer's disease. This demonstrates its capacity to reduce neuroinflammatory reactions associated with malfunctioning of the cholinergic system in the cortex and hippocampus.

Fisetin reverses the inflammation caused by amyloid β in the brain via lowering caspase-3. Increased dosages appear to protect against neuroinflammation and damage in Alzheimer's disease by lowering GFAP, inflammation, and apoptosis.

Gastrointestinal disorder

In DSS-induced colitis, fisetin reduces MPO, COX-2, iNOS, and pro-inflammatory cytokines by suppressing Akt/p38 MAPK phosphorylation and limiting NF-κB activation (p65–DNA binding, IκBα phosphorylation), while also restoring MDA and GSH levels.

Anti-oxidative activity

Neuroinflammatory potential

Fisetin improves learning and memory in $Aβ_{1–42}$–induced systems by activating PI3K/Akt in AD models, which reduces oxidative stress, Aβ accumulation, tau hyperphosphorylation,

neuroinflammation, and caspase-3-mediated neuron death.

Antidiabetic

Fisetin triggers Nrf2-mediated antioxidant defences to protect against diabetic cardiomyopathy by preserving β-cells and insulin production, lowering inflammation, cholesterol, hyperglycaemia, and mitochondrial apoptosis.

Amyotrophic Lateral Sclerosis

In ALS associated with SOD1 mutations, fisetin, a naturally occurring antioxidant flavonoid, may lessen oxidative stress. Targeting protein aggregation and oxidative stress brought on by mutant SOD1, it protects neurons by reducing ROS, reestablishing redox equilibrium, and enhancing motor function in ALS models.(Cookson et al., 2002; Miana-Mena et al., 2011)

Fisetin activates the ERK pathway, which increases antioxidants and fortifies cells against oxidative damage. It is a promising treatment for ALS since it also decreases hSOD1 protein aggregates that are connected to ALS-linked mutant and wild-type ALS.

Neuroprotective potential

Diabetic Neuropathy

Fisetin inhibits COX-2, microglial activation, and HSP70, which ameliorates diabetic nephropathy and neuropathy. Fisetin also activates Nrf2 to increase antioxidants (CAT, SOD, HO-1, NQO1, GPx), decreases ROS and NF-κB–driven cytokines, stabilizes mitochondrial proteins to prevent neuronal death, and improves synaptic plasticity, neurite outgrowth, and ATP production.

Anti-angiogenic potential

As Anti-cancerous agent

By halting angiogenesis, inducing cell cycle arrest, and inducing apoptosis, fisetin prevents tumour growth. It reduces the creation of blood vessels and the survival of cancer cells by lowering important molecules including VEGF and MMPs.(Singh et al.2005)

Table 3: A summary of the formulation, bioavailability, and bioactivity of fisetin-loaded delivery methods.

SN	Delivery System	Bioavailability	Experiment models and treatment	Main outcomes	References
1	Nano cochleates (FIS-NC)	It Is 141 times more than free fisetin.	Tested in MCF-7 cells by sulforhodamine B assay	Lower GI50 compared to blank nano cochleates and free fisetin solution.	(Bothiraja et al., 2014)
2	Nano emulsion (FIS-NE)	Twenty-four times more than free fisetin	FIS-NE (36.6 mg.kg^{-1}) against free fisetin (223 mg.kg^{-1}) in Lewis lung carcinoma-bearing mice	Significantly slowed the growth of tumours in a dose-dependent way.	(Ragelle et al., 2012)
3	Self-nanoemulsifying drug delivery system (FIS-SNEDDS)	FIS-SNEDDS has a relative bioavailability of 151.58%.	Rats with rotenone-induced Parkinson's disease (PD) model	Increased BDNF, α-synuclein, GSH, SOD, CAT, and motility; decreased TBARS, nitrite, TNF-α, IL-6, and catalepsy.	(Kumar et al; 2019, 2020)
4	Liposomal (FIS-L)	47 times more than free fisetin	Mice with Lewis lung cancer were given FIS-L (21 mg.kg^{-1}).	Tumour growth was slowed by 1.6 days by free fisetin and by 3.3 days by 21 mg. kg^{-1} FIS-L.	(Seguin et al., 2013)
5	Polymeric NP (FIS-PN)	-	Simulated intestine (pH 7.4) and stomach (pH 1.2, 2 hours) environments.	Compared to acarbose, increased the α-glucosidase inhibitory action by 20 times.	(Sechi et al., 2016)
6	Ethosomes (FIS-BE)	-	Mice exposed to UV light received FIS-BE treatment.	Compared to untreated mice, the tumor incidence decreased to 49% from 96%.	(Moolakkadath et al., 2019)

Reports on fisetin formulations

With an emphasis on chemical stability and distributed state changes, numerous research has attempted to increase fisetin's bioavailability using a variety of delivery modalities.Despite fisetin's medicinal potential, innovative drug delivery methods are necessary for its successful use. Carrier

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formulations, animal models, treatments, and important results are compiled in Table 3.

Table 4: Recent Patents:

SN	Country Name	Patent ID	Title of Patent
1	US	US 11,376,295 B2	Technique for producing fisetin-rich an extract from Rhus verniciflua is used to treat cancer that has spread.
2	US	US20240002357A1	Novel 4'-substituted fisetin analogues for cancer treatment.
3	US	US 2010/0010078 A1	Method of administering Fisetin through oral, transdermal, or topical dose forms.
4	US	US 2021/0145806 A1	Treatment and diagnosis options for brain cancer.

And recent international patents are shown and compiled in Table 4.

Future possibilities

A common dietary polyphenol, fisetin, has potential applications in nutrition and medicine. Research is required to improve its transport, boost its bioactivity through chemical modification, and examine its interactions with chemotherapy. Improved farming and plant biotechnology can enable the sustainable production of foods high in fisetin. Food, medicine, and cosmetics can all use fisetin because of its many uses.

Conclusion

Fisetin is a naturally occurring flavonol found in a wide variety of fruits and vegetables. Its hydroxyl groups provide it potent anti-inflammatory, neuroprotective, and antioxidant properties. Preclinical research indicates that it may modify the NF-κB and MAPK pathways to treat cancer, diabetes, and neurological conditions. More clinical trials are required to demonstrate safety and efficacy, but improved delivery systems such as SNEDDS have improved its solubility and bioavailability. Fisetin can treat chronic illnesses and promote preventative health, according to this review.

Abbreviations

1. SAR- Relationship between Structure and Activity
2. FIT- Fisetin (while "Fisetin" is typically written out, "FIT" is used once).
3. NF-κB -Nuclear Factor-Kappa B
4. COX-2- Cyclooxygenase-2
5. TNF-α- Tumour Necrosis Factor-Alpha
6. iNOS- Inducible Nitric Oxide Synthase
7.NO- Nitric Oxide
8. IL-6 Interleukin-6
9. TLR4- Toll-Like Receptor 4 (TLR4)
10.GSK-3β- Glycogen Synthase Kinase-3β
11. IL-1β- Beta Interleukin-1
12. MAPK- Mitogen-Activated Protein Kinase
13.TBARS-Thiobarbituric Acid Reactive Substances
14.BDNF-Brain-Derived Neurotrophic Factor
15.SNEDDS- Drug Delivery System with Self-Nano emulsification
16.HUVECs- Human Umbilical Vein Endothelial Cells, or HUVECs

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