# Exploring the Pharmacological Potential of Fisetin: A Comprehensive Review

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## ABSTRACT

Fisetin, a hydrophobic polyphenolic molecule, is a naturally occurring flavonoid commonly found in fruits and vegetables. The popularity of fisetin comes mainly from its many different medical uses. Known for its antioxidant and anti-inflammatory effects, fisetin is likely to be useful in the treatment of just about any inflammatory disease. Its ability to induce apoptosis (programmed cell death) and encourage tumor regression is another key reason fisetin's anti-cancer effects are so striking Furthermore, fisetin has excellent antibacterial capabilities, its spectrum encompassing all kinds of bugs: bacteria, viruses of many types and fungi. Notably, fisetin also exhibits neuroprotective and cardioprotective attributes, making it a compound of significant interest for multiple health-related applications. It also shows promise in controlling diabetes and shielding the skin from UV ray damage. Preclinical research has suggested the effectiveness of fisetin, but further investigation, including clinical trials, is necessary to confirm its safety and effectiveness in humans. Furthermore, this review would benefit future studies on fisetin's therapeutic potential.

Keywords: Fisetin, Flavonoid, Antioxidant, Anti-inflammatory, Anticancer, Neuroprotective, Cardioprotective, Antimicrobial, Antidiabetic, Skin protection.

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#### INTRODUCTION

Modern medicine uses natural medications, combining traditional knowledge and scientific study. For millennia, traditional therapy has relied on natural medicines derived from flora, fauna, or microorganisms, delivering a variety of therapeutic effects. In recent years, pharmaceutical and clinical segments have shown their interest in the potential of natural medicine to treat several health disorders.<sup>1</sup> In contrast to synthetic drugs, complex chemical compositions of natural medication, and work synergistically in the body to minimize the side effects. They are also traditionally significant and deeply rooted in conventional healing systems worldwide, providing holistic healthcare. A modern analytical technique identifies bioactive substances thereby simplifying natural medicine. These bioactive substances are useful in drug research and development, which leads to expand modern treatment options.<sup>2</sup> Lack of standards, quality control, and regulation continues to be a significant barrier that could restrict the use of traditional medicine as the preferred treatment.<sup>3</sup> As an excellent supplier of multiple medicines, plants generate a wide variety of bioactive molecules. We use organic plant

material in the manufacture of herbal medications.<sup>4</sup>

However, research and collaborations among traditional healers, scientists, and medical experts might reveal the entire medicinal value of natural drugs, enhancing modern medicine with time-tested remedies and gathering society's changing healthcare needs.<sup>5</sup> Present review covers the biological features of polyphenol fisetin (FTN) in human health, as well as its potential applications for preventing and treating illnesses. FTN is a flavonoid class of phytochemicals. Various vegetables, fruits, and medicinal plant species commonly contain this naturally occurring compound. FTN is well known for its strong anti-inflammatory and antioxidant features, as well as its possible therapeutic benefits against an array of ailments, including diabetes, cancer, neurodegenerative diseases, and cardiovascular conditions.<sup>6</sup>

FTN is found in strawberries, apples, grapes, onions, cucumbers, persimmons, and kiwifruit. Some fruits like mangoes, peaches, raspberries, rue, *Ginkgo biloba*, and Japanese wax tree have less content of FTN. This phyto compound has a flavonoid backbone with hydroxyl groups on the B ring at positions 3, 7, and 3', 4'. Its chemical formula is

C15H10O6 and molecular weight is 286.24 g/mol.<sup>7</sup>

Chemically, FTN is C<sub>15</sub>H<sub>10</sub>O<sub>6</sub>. Its structure consists of two aromatic rings (A and B) linked by a three-carbon bridge (C) (Figure 1). Biological activity is increased by hydroxyl groups (-OH) on the rings. Like flavonoids, FTN is soluble in polar solvents like ethanol and water. Normally, it is stable, but it may destroy its nature in acidic, basic, hot condition or even after its exposure to light.<sup>8</sup>

#### Pharmacokinetics and Pharmacodynamics of FTN

FTN bioavailability and pharmacological activity have been improved by certain chemicals features. The bioavailability of FTN and its pharmacological effects are influenced by the body's processes of absorption, distribution, metabolism, and excretion. FTN is mainly absorbed in the small intestine after dietary intake, most likely by passive diffusion as well as active transport mechanisms. After absorption, FTN is extensively breakdown, primarily in the liver where it interacts with sulphate and glucuronic acid. FTN's metabolites are then carried by the bloodstream to the kidneys, liver, intestines, and brain, among other areas of the body.<sup>9</sup>

Body mostly excretes FTN and its metabolites through the urine and faeces, with bile also playing a role in some clearance (Figure 2).

Low bioavailability of FTN is due to its rapid metabolism, limited absorption efficiency, and poor water solubility. Studies reveal that the systemic circulation preserves a relatively small portion of FTN that is consumed, which might be the reason for its restricted bioavailability.<sup>10</sup> To increase FTN's bioavailability, researchers have looked into an array of techniques, including prodrugs production, encapsulating FTN in nanoparticles, and combining FTN with absorption enhancers. FTN will have higher therapeutic potential and be more successful in treating and preventing a larger spectrum of diseases with improved stability, solubility, and absorption. More investigation is required to enhance FTN's bioavailability and administration techniques for clinical application.<sup>11</sup> Through an array distinct mechanisms of action, FTN impacts many molecular pathways across the body to provide its therapeutic benefits. FTN is an excellent antioxidant that provides protection against oxidative stress and the harm caused by free radicals, which in turn prevents damage of cells leading to inflammation. FTN has high neuroprotective potential due to its antioxidative properties; this means it may find application as a drug option for neurodegenerative ailments such as Parkinson's and Alzheimer's.<sup>12</sup>

The action of FTN also encompasses the regulation of signalling pathways including NF- $\kappa$ B and MAPK which are involved in down regulating pro-inflammatory cytokines and enzymes. These pathways denote inflammation itself; thus, in diseases like arthritis or inflammatory bowel disease where anti-inflammatory effect would be advantageous, FTN is able to exhibit its anti-inflammatory properties. Additionally, FTN demonstrates anti-cancer features by interfering with various cellular processes that promote cancer development and growth. This includes promoting apoptosis while inhibiting

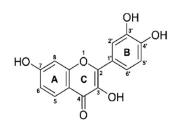


Figure 1: Chemical structure of FTN

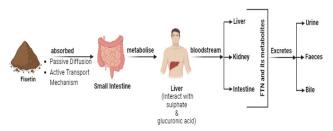


Figure 2: Pharmacokinetics and Pharmacodynamics of FTN

the proliferation of cancer cells – two ways to reduce tumor formation-via targeting PI3K/Akt Wnt/ $\beta$ -catenin as well as MAPK signaling pathways.<sup>13</sup> FTN's ability to interact with molecular targets that control angiogenesis, metastasis and immune regulation enhances its anti-cancer effect. FTN shows great therapeutic potential as a preventive and curative agent for several cancers by acting on multiple pathways.<sup>14</sup> The pharmacodynamics of FTN is associated with its antiinflammatory, neuroprotective, antioxidant and anticancer activities which in turn are responsible for its multi-therapeutic approach to many diseases.<sup>15</sup>

Further investigation into FTN's molecular targets and mechanisms of action may enhance its therapeutic potential and improve its clinical efficacy.

## Pharmacological Aspects of FTN

FTN, which is present in vegetables and fruits, has diverse applications in medicine. Among its best antioxidant properties of FTN are radical scavenging and lowering oxidative stress for Alzheimer's disease. Inflammation is reduced by FTN because it suppresses pro-inflammatory pathways. It combats cancer through changing cell proliferation, apoptosis and metastatic signaling pathways. As a result of these many pharmacological actions, this can be a hopeful preventive as well as curative drug towards a range of conditions (Figure 3).

## Antioxidant properties

Chemicals known as free radicals, which are molecules lacking a paired electron, are responsible for oxidative stress. Reactive oxygen species (ROS) are another factor that causes oxidative stress. Both pollution and ionizing radiation, as well as aerobic cellular respiration, internally generate ROS.<sup>16</sup> FTN, a naturally present flavonoid has powerful antioxidant qualities which also scavenges free radicals and lowers oxidative stress.<sup>17</sup>

Cellular damage and malfunction are triggered by oxidative stress, which leads to an imbalance between the

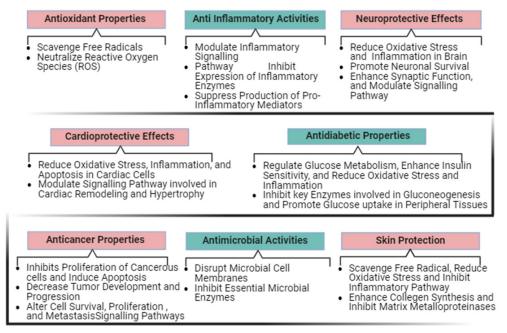


Figure 3: Pharmacological aspects of FTN

body's antioxidant defenses and the formation of reactive oxygen species (ROS). FTN's ability to neutralize free radicals, including peroxynitrite, hydroxyl, and superoxide anion radicals, is what gives it its antioxidant qualities.<sup>18</sup> FTN preserves cellular homeostasis and protects tissues and cells from oxidative damage by neutralizing these ROS.<sup>18</sup> Moreover, FTN stimulates the body's own natural antioxidant enzymes. Enzymes believed to be essential in eliminating reactive oxygen species (ROS) and protecting cells from oxidative stress includes superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). FTN stimulates the synthesis and activation of these kinds of enzymes, which strengthens cellular antioxidant defense mechanisms and lowers oxidative damage.<sup>19</sup> FTN's antioxidant ability is enhanced by its ability to bind metals. It attached to transition metal ions so they cannot catalyze (via Fenton and Haber-Weiss reactions) production of dangerous free radicals by copper and iron ions. In living organisms, FTN binds to metal ions to reduce the production of free radicals and oxidative stress.<sup>20</sup> Studies in preclinical models have demonstrated that FTN exerts antioxidant properties and preserves from oxidative aftermath in experimental models of heart disease, injury, cancer and neurodegeneration. The mechanisms through which FTN exerts its various pharmacological activities, including anti-inflammatory, neuroprotective, cardioprotective, and anticancer properties, are also attributed to its antioxidant properties.<sup>21</sup>

FTN's antioxidant properties have been the most important aspect of this compound in reducing oxidative stress, scavenging free radicals, and protecting cells and tissues from oxidative damage. More experimentation is required to elucidate the exact mechanisms through which FTN imparts antioxidant effects and assesses its therapeutic potential in pathologies associated with oxidative stress.<sup>22</sup>

#### Anti-inflammatory activity

Flavonoid compound FTN numerously found in fruits and vegetables can alters inflammatory signalling pathways and inhibits pro-inflammatory mediators, serve it as a powerful anti-inflammatory agent. Moreover, FTN could decrease the release of some important proinflammatory factors, such as inducible nitric oxidase synthase (iNOS) and cyclooxygenase-2 (COX-2) [20] COX-3, a brain-specific form of COX-1, COX-2 and brain iNOS, are enzymes that produce two prototypic inflammatory mediators, prostaglandins and nitric oxide. FTN prevents the action of these enzymes and thus results in a decreased production of inflammation triggering chemicals. Therefore, hindering the inflammatory response.<sup>23</sup>

In addition, FTN regulates several inflammatory signalling pathways that are essential for managing inflammation. FTN targets the nuclear factor-kappa B (NF-κB) signalling pathway, among other key pathways. A transcription factor that is required for the synthesis of genes which promote inflammation is, NF-B. FTN, inhibits the phosphorylation and degradation of  $I\kappa B\alpha$ , an inhibitory protein, inhibiting NF-kB from stimulating genes and inducing inflammation.<sup>24</sup> Moreover, mitogen-activated protein kinase (MAPK) pathway and other signalling pathways linked to inflammation are altered by FTN. The regulation of cellular responses to various stimulation, including inflammation, depends mainly on protein kinases, or MAPKs. By blocking MAPKs such as p38 MAPK, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) from activating, FTN reduces the inflammatory response.<sup>25</sup> One of the primary variables for FTN's significant anti-inflammatory effects is its ability to inhibit pro-inflammatory mediators and modulate inflammatory signalling pathways.<sup>26</sup> These findings emphasize FTN's therapeutic potential in the management of inflammatory disease and suggest for more research into its practical applications.

# Neuroprotective effects

The flavonoid phytomolecule FTN is present in an array of fruits and vegetables. It may have the potential to cure neurodegenerative illnesses by reducing the destruction and degeneration of neurons.<sup>19</sup> Among FTN's neuroprotective properties is antioxidant activity. Degeneration and injury to neurons have been brought on by oxidative stress, and these results in neurodegenerative diseases including Parkinson's and Alzheimer's. By scavenging free radicals and neutralizing ROS, FTN lowers oxidative stress in the brain. By preventing oxidative damage and preserving function, FTN shields neurons against degeneration.<sup>27</sup>

The anti-inflammatory properties of FTN decrease neuroinflammation, that's a hallmark of numerous neurodegenerative diseases. Neurodegenerative diseases progress faster and neurons are harmed by chronic brain inflammation. FTN lowers neuroinflammation and protects neurons by suppressing cytokines and other brain inflammatory mediators.<sup>28</sup>

Furthermore, FTN modifies signalling pathways associated with neuroprotection and neuronal survival. Enhancing neuronal survival and halting apoptosis is achieved by stimulating cell survival pathways, including the PI3K/Akt pathway. FTN also inhibits neurodegenerative processes in Alzheimer's disease, notably amyloid beta aggregation and tau protein hyper phosphorylation.<sup>29</sup> The neuroprotective qualities of FTN may aid in the management and prevention of neurodegenerative diseases. FTN has been shown in preclinical studies to improve cognitive function in animal models of Parkinson's and Alzheimer's disease and to lessen neurodegeneration. Additionally, FTN may enhance neurogenesis and synaptic plasticity, both of which are critical for brain function.<sup>30</sup>

FTN is a promising therapeutic and prophylactic for neurodegenerative diseases due to its antioxidant, antiinflammatory, and signalling pathway properties. Clinical trials and more research are required to determine the safety, effectiveness, and therapeutic potential of FTN in neurodegenerative disorders.

# Anticancer properties

Cancer is one of the most prevalent health problems people face today. Despite its poor survival rate and increasing incidence of new cases, it is undoubtedly one of the most alarming causes of death. A bad diet, an unhealthy lifestyle, genetics, and various forms of inflammation are the main causes of many illnesses.<sup>31</sup>

FTN is a common flavonoid found in fruits and vegetables that reduces the growth of tumours, causes apoptosis, and inhibits the growth and multiplication of cancer cells.<sup>13</sup> One of FTN's main anticancer effects is the inhibition of cancer cell proliferation and development. FTN interferes with signalling

pathways such PI3K/Akt, MAPK, and Wnt/β-catenin that are essential for cell survival and proliferation. FTN inhibits the proliferation and division of cancer cells by emphasizing these pathways. FTN also promotes apoptosis in cancer cells in a number of ways. Through the internal mitochondrial and extrinsic death receptor pathways, it induces caspases and apoptosis. Moreover, FTN controls both pro- and anti-apoptotic proteins, promoting the demise of cancer cells.<sup>14</sup> FTN inhibits the growth and progression of tumours by targeting cancer hallmarks such as invasion, metastasis, and angiogenesis. FTN reduces angiogenesis by blocking signalling pathways that lead to blood vessel growth, such as the VEGF pathway. MMPs, which are enzymes involved in tumour invasion and metastasis, as well as the migration and invasion of cancer cells, are suppressed by FTN.<sup>32</sup>

In preclinical research, FTN reduces the growth and spread of tumours in models of lung, colon, prostate, and breast cancer. FTN additionally enhances chemotherapy and radiation therapy by making cancer cells more susceptible to treatment-induced cell death.<sup>33</sup> FTN reduces tumour growth and progression, induces apoptosis, and inhibits the growth and proliferation of cancer cells, making it a promising choice for cancer prevention and treatment. Clinical trials and more research are needed for assessing the safety, effectiveness, and therapeutic potential of FTN in cancer patients.

# Antimicrobial activity

FTN is a flavonoid molecule found in a variety of fruits and vegetables. It is a potential antimicrobial agent as it exhibits antimicrobial activity against fungus, viruses, and bacteria. Investigations have demonstrated that FTN is a highly efficient antimicrobial agent against gram-positive and gramnegative bacteria. Bacterial infections grow less when their cell membranes are disrupted, vital biological functions are interfered with, and biofilm formation is decreased. *Salmonella typhimurium, Pseudomonas aeruginosa, Escherichia coli*, and *Staphylococcus aureus* are all suppressed by FTN.<sup>34</sup>

FTN also combats the hepatitis B, influenza, HIV, and HSV viruses. In addition to controlling the host immune system's reaction to viral infections, it inhibits the growth, adherence, reproduction, and penetration of viruses into host cells. In vitro and in-vivo data indicate FTN lowers viral load and replication.<sup>35</sup> FTN has demonstrated the function of Aspergillus fumigatus, Candida albicans, and Cryptococcus neoformans growth inhibition. It inhibits biofilm formation, mycelium, cell membrane and fungal growth. It has shown fungicidal activity against cutaneous and subcutaneous fungal infections in mice.<sup>36</sup> Due its high broad-spectrum antibacterial activity, FTN makes it an excellent candidate for the development of new antimicrobials compounds, the reformulation of the current drugs, and in the prevention and treatment of microbial infections. Because of this natural origin and its comparatively low toxicity, FTN can be a good alternative to conventional antimicrobials which can become resistant with deleterious results.37

Further investigation is required to investigate the mechanism underlying the antimicrobial activity of FTN, and to develop FTN effectively, safely, and as a potential alternative strategy for clinical practice. Anyway, FTN can be a naturally occurring antibiotic useful for recovering from microbial infections and for enhancing health.

# Cardioprotective effects

FTN is a flavonoid found in many fruits and vegetables that improves vascular function and reduces oxidative stress and inflammation in the cardiovascular system. The antioxidant properties of FTN help in heart protection. Cardiovascular diseases that include myocardial infarction, hypertension, and atherosclerosis are all brought on by oxidative stress. FTN, a free radical scavenger, neutralizes ROS and lowers oxidative damage to the cardiovascular system. FTN protects cardiovascular health, lipid peroxidation, and vascular endothelial cells by lowering oxidative stress. FTN reduces inflammation in the cardiovascular system due to its antiinflammatory effects. Cardiovascular conditions progress due to endothelial dysfunction, vascular inflammation, and the production of atherosclerotic plaque brought on by chronic inflammation. FTN reduces vascular inflammation and maintains vascular integrity by suppressing cytokines and other cardiovascular inflammatory mediators.<sup>38</sup>

FTN also facilitates vasodilation and endothelial function. One of the main features of cardiovascular disease is endothelial dysfunction, which lowers NO production and vasodilation. FTN improves blood flow and vascular tone by raising NO production, endothelial cell activity, and blood vessel relaxation.<sup>39</sup> Preclinical research using animal models demonstrated that FTN protects against cardiovascular illnesses such hypertension, atherosclerosis, and heart failure. Supplementing with FTN decreases blood pressure, prevents the formation of atherosclerotic plaque, and enhances cardiac function in models of cardiovascular disease. FTN is a promising cardioprotectant and disease preventer due to its anti-inflammatory, antioxidant, and vasoprotective properties. Clinical trials and more research are required to determine the safety, effectiveness, and therapeutic potential of FTN in patients with cardiovascular disease.<sup>38</sup> As a natural ingredient, FTN, might lessen cardiovascular events and enhance cardiovascular health.

# Anti-diabetic properties

FTN is a flavonoid found in fruits and vegetables that enhances insulin sensitivity and controls blood sugar. FTN alters insulin signalling pathways and glucose metabolism in diabetes treatment. Insulin sensitivity is improved by FTN, which enhances glucose absorption in peripheral tissues such as skeletal muscle and adipose tissue. By activating insulin signalling pathways like the IRS/PI3K/Akt pathway, it causes the glucose transporter protein (GLUT4) to migrate to the cell membrane and facilitates the uptake of glucose by cells.<sup>40</sup>

Moreover, FTN suppresses gluconeogenesis, the process by which the liver converts non-carbohydrate precursors into glucose. FTN inhibits gluconeogenesis enzymes such G6Pase and PEPCK, lowering blood sugar levels and the liver's synthesis of glucose.<sup>41</sup> FTN lowers inflammation and oxidative stress associated with diabetes. By diminishing pancreatic  $\beta$ -cell function, causing insulin resistance, and exacerbating problems, oxidative stress and inflammation exacerbate diabetes. FTN preserves function and insulin sensitivity and prevents the effects of diabetes by reducing oxidative stress and inflammation in pancreatic  $\beta$ -cells and peripheral organs.<sup>42</sup>

FTN has been demonstrated in preclinical studies to enhance insulin sensitivity and glycemic control in animal models of type 2 diabetes and its consequences. In diabetic mice, FTN treatment reduces fasting blood glucose, enhances glucose tolerance, and increases insulin signalling. FTN is a potentially effective treatment for diabetes due to its ability to control blood sugar, enhance insulin sensitivity, and lessen oxidative stress and inflammation. Research, including clinical studies, is necessary to determine the safety, effectiveness, and therapeutic potential of FTN in diabetics. Nonetheless, FTN, a naturally occurring substance, might enhance metabolic health and lessen the consequences of diabetes.<sup>26</sup>

# Skin protection

FTN is a flavonoid found in many fruits and vegetables that may shield skin from ageing and UV damage. Cancer, pigmentation issues, and skin ageing are all significantly influenced by UV radiation from the sun. FTN offers several advantages for skincare, such as anti-aging and UV protection. The antioxidant qualities of FTN shield the skin. Inflammation, DNA damage, and oxidative stress are all brought on by the ROS that UV light creates in the skin. FTN, a free radical scavenger, neutralizes ROS and lowers oxidative stress on the skin. FTN reduces the damage associated with oxidation and prevents the production of age-associated cutaneous symptoms such as liver spots, wrinkles, and fine lines due to photoaging.<sup>43</sup>

Also, FTN has an anti-inflammatory action that can reduce erythema and photo irritation due to UV light. Inflammation is needed for UV-induced skin damage, because it is linked with skin photoaging. FTN reduced proinflammatory mediators and cytokines in the skin, which protected against UV rayinduced damage.<sup>44</sup> FTN enhances the skin's UV protection, potentially offering photo-protective benefits. Studies show that FTN increases levels of SOD and catalase, two antioxidant enzymes present in the skin. These enzymes are crucial for eliminating free radicals and preventing UV-induced oxidative damage to skin cells. Due to its anti-aging and skin-protecting properties, FTN is a promising ingredient for skincare products. Incorporate it into your daily creams, serums, and lotions to help safeguard against UV damage and premature aging. FTN could enhance the antioxidant and photo protective qualities of sunscreen. However, additional research is needed to fully grasp the skincare benefits and photo protective advantages of FTN. Human clinical studies should assess the long-term efficacy, safety, and benefits of skincare formulations incorporating FTN. These skincare products should be both effective and visually appealing.<sup>45</sup>

FTN could be beneficial as a natural skincare ingredient for anti-aging and UV protection. Due to its anti-inflammatory,

Table 1: Pharmacological areas and uses of FTN		
SN	Therapeutic areas	FTN's Clinical Uses
1	Cancer Treatment	Strong anticancer properties stop tumor growth, trigger cell death, and slow tumor spread.
2	Neurodegenerative Diseases	Neuroprotective effects may help manage Parkinson's and Alzheimer's disease by reducing neuronal degeneration and damage.
3	Cardiovascular disorders	Cardioprotective effects may be useful in cardiovascular disease prevention and treatment because they maintain cardiovascular function, lower oxidative stress, and improve vascular health.
4	Inflammatory Conditions	By modifying inflammatory pathways, anti-inflammatory qualities offer treatment for ailments like inflammatory bowel illness and arthritis.
5	Antimicrobial Applications	Antimicrobial activity against bacteria, viruses, and fungi suggests potential as an antimicrobial agent for a variety of infections.
6	Diabetes Management	Anti-diabetic actions help to reduce inflammation and oxidative stress linked to diabetes, as well as blood sugar levels and insulin sensitivity.
7	Skin Protection	This technique has potential uses in skincare since it shields the skin from UV-induced damage, lowers oxidative stress, and enhances skin health.

photo protective, and antioxidant qualities, it is valuable in skincare formulations that promote skin health and protect against UV damage. Further research and clinical trials are necessary to optimize the use of FTN in skincare and create safe, effective products.

#### Safety and Side Effects

FTN is generally considered safe to consume in dietary quantities found in fruits and vegetables. However, limited toxicity studies have been conducted to evaluate its safety profile at higher doses or over prolonged exposure periods. Animal research indicates that FTN demonstrates minimal toxicity, with no significant side effects noted at doses above a specific threshold. Nevertheless, additional comprehensive toxicity studies are needed to assess the potential adverse effects of FTN at increased doses and extended durations of exposure in humans.<sup>46</sup>

Most people tolerate FTN well, but some may experience moderate side effects, particularly if they take large dosages or use it as a supplement. People frequently report experiencing gastrointestinal adverse effects like nausea, diarrhea, or abdominal pain. Although allergic reactions to FTN are uncommon, they can happen to those who are susceptible, resulting in symptoms including swelling, redness, or itching.<sup>47</sup> It is imperative that people get medical advice before beginning FTN supplementation, particularly if they are on medication or have any underlying medical issues.

Moreover, due to the limited safety data available on FTN supplements, it is advisable for pregnant women to be attentive and pursue medical advice before incorporating them. Consequently, while FTN appears to demonstrate favorable safety characteristics, additional research is imperative to grasp the potential side effects fully and ensure its safe use in clinical scenarios.<sup>48</sup>

## **Clinical Applications and Future Perspectives**

There are a limited number of clinical trials currently focused on exploring FTN in humans. However, ongoing studies are investigating its potential therapeutic advantages (Table 1) for various medical conditions including diabetes, cancer, neurological disorders, and inflammation.<sup>49</sup> To establish the safety, efficacy, and optimal dosage of FTN for humans, conducting clinical trials is crucial. The broad spectrum of pharmacological properties of FTN, such as anti-inflammatory, antioxidant, anticancer, neuroprotective, and cardioprotective effects, positions it as a promising therapeutic treatment. FTN may hold promise for treating and preventing several conditions, including diabetes, cancer, Parkinson's, Alzheimer's, as well as cardiovascular and inflammatory diseases.<sup>50</sup>

Further research on FTN's efficacy and safety profiles in humans should focus on elucidating its mechanisms of action, enhancing its formulation and administration methods, and conducting well-designed clinical trials. Understanding and utilizing FTN in clinical settings necessitate investigating potential synergies with other compounds, as well as exploring long-term effects and possible drug interactions. To optimize FTN's therapeutic efficacy and streamline its integration into clinical practice, additional studies on its pharmacokinetics, bioavailability, and tissue distribution are imperative.<sup>51</sup>

## CONCLUSION

This review has outlined the therapeutic efficacies of FTN. They have several beneficial characteristics: anti-inflammatory, neuroprotective, anti-cancer, antibacterial, cardioprotective, anti-diabetic, and skin-protective. Because FTN can remove free radicals and suppress inflammations, it may be a new path for attacking inflammatory diseases, tumors, as well some diseases caused by oxidation-stress. Moreover, FTN can be used in medicine to deal with a wide spectrum of chronic diseases: it treats what in practice are many unrelated problems very effectively. It has hypothesized effects on neurological diseases, with both its metabolically and clinically derived properties showing promise; cardiovascular pathologies such as the build-up of arterial plaque; microbial infections in cancers, sometimes those caused by viruses or bacteria and even diabetes metabolism problems themselves -- a crucial domain for this drug. We have arrived at the soma evaluation of fetal therapy. While results of preclinical trials are encouraging, further study is necessary to determine the safety, efficacy and potential clinical use of FTN in humans. Especially those implying the need for clinical trials. Taken together, FTN has potential as a natural substance with a variety of therapeutic purposes, creating opportunities for innovative medical interventions and disease management strategies.

## REFERENCES

- Chaachouay N, Zidane L. Plant-Derived Natural Products: A Source for Drug Discovery and Development. Drugs Drug Candidates. 2024; 3:184–207.
- Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K. Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. Int. J. Mol. Sci. 2018; 19:1578. Available from: doi.org/10.3390/ijms19061578
- Iqbal D, Pawar RK, Sharma RK. Physico-chemical Standardization of *Butea monosperma* (Lam.) Kuntze (Palasha): An Ayurvedic Drug. International Journal of Pharmaceutical Quality Assurance. 2010; 2(1): 49-51.
- Khurana N, Sharma RK, Bhaduria S. Microbiological Quality Assessment of Some Commercial Herbal Drugs. International Journal of Pharmaceutical Quality Assurance. 2011; 3(4):15-17.
- Wang H, Chen Y, Wang L, Liu Q, Yang S, Wang C. Advancing herbal medicine: enhancing product quality and safety through robust quality control practices. Front. Pharmacol. 2023; 14:1265178. Available from: doi.org/10.3389/fphar.2023.1265178
- Khan N, Syed DN, Ahmad N, Mukhtar H: Fisetin: A Dietary Antioxidant for Health Promotion. Antioxidants & Redox Signaling. 2013; 19(2). Available from: doi.org/10.1089/ ars.2012.4901
- Syed DN, Adhami VM, Khan N, Khan MI, Mukhtar H. Exploring the molecular targets of dietary flavonoid Fisetin in cancer. In Seminars in Cancer Biology. 2016; 40: 130–140.
- Bag S, Ghosal S, Karmakar S, Pramanik G, Bhowmik S. Uncovering the Contrasting Binding Behavior of Plant Flavonoids Fisetin and Morin Having Subsidiary Hydroxyl Groups (-OH) with HRAS1 and HRAS2 i-Motif DNA Structures: Decoding the Structural Alterations and Positional Influences. ACS Omega. 2023; 8(33): 30315–30329. Available from: doi.org/10.1021/ acsomega.3c03105
- Szymczak J, Cielecka-Piontek J. Fisetin-In Search of Better Bioavailability-From Macro to Nano Modifications: A Review. Int. J. Mol. Sci. 2023; 24: 14158. Available from: doi.org/10.3390/ ijms241814158
- Shia CS, Tsai SY, Kuo SC, Hou YC, Chao PDL. Metabolism and Pharmacokinetics of 3,3',4',7-Tetrahydroxyflavone (Fisetin), 5-Hydroxyflavone, and 7-Hydroxyflavone and Antihemolysis Effects of Fisetin and Its Serum Metabolites. Journal of Agricultural and Food Chemistry. 2009; 57(1):83-9. Available from: doi.org/10.1021/jf802378q
- Mehta P, Pawar A, Mahadik K, Bothiraja C. Emerging novel drug delivery strategies for bioactive flavonol Fisetin in biomedicine. Biomedicine & Pharmacotherapy. 2018; 106: 1282-1291. Available from: doi.org/10.1016/j.biopha.2018.07.079
- Liu H, Lu Q. Fisetin Alleviates Inflammation and Oxidative Stress in Deep Vein Thrombosis via MAPK and NRF2 Signaling Pathway. Int. J. Mol. Sci. 2024; 25: 3724. Available from: doi. org/10.3390/ijms25073724
- 13. Qaed E, Al-Hamyari B, Al-Maamari A, Qaid A, Alademy H,

Almoiliqy M, Munyemana JC, Al-Nusaif M, Alafifi J, Alyafeai E, Safi M, Geng Z, Tang Z, Ma X. Fisetin's Promising Antitumor Effects: Uncovering Mechanisms and Targeting for Future Therapies. Global Medical Genetics. 2023; 10(3): 205-220. Available from: doi.org/10.1055/s-0043-1772219

- Sundarraj K, Raghunath A, Perumal E: A review on the chemotherapeutic potential of Fisetin: *In vitro* evidences. Biomedicine & Pharmacotherapy. Biomed Pharmacother. 2018; 97:928-940. Available from: doi.org/10.1016/j.biopha.2017.10.164.
- Imran M, Saeed F, Gilani SA, Shariati MA, Imran A, Afzaal M, Atif M, Tufail T, Anjum FM. Fisetin: An anticancer perspective. Food Sci Nutr. 2021; 9:3–16. Available from: doi.org/10.1002/ fsn3.1872
- Wawre MB, Khobragade D, Mundhada D, Kayarkar H. Utilizing In-vitro Techniques to Evaluate the Antioxidant Potential of Vitex negundo Leaves Extract. International Journal of Pharmaceutical Quality Assurance. 2023; 14(4):1071-1074.
- Panche N, Diwan AD, Chandra SR. Flavonoids: An overview. Journal of Nutritional Science. 2016; 5-e47: 1-15. Available from: doi.org/10.1017/jns.2016.41
- Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bittol A. Oxidative Stress: Harms and Benefits for Human Health. Oxidative Medicine and Cellular Longevity. 2017; 8416763: 13. Available from: doi. org/10.1155/2017/8416763
- Park S, Kim BK, Park SK. Effects of Fisetin, a Plant-Derived Flavonoid, on Response to Oxidative Stress, Aging, and Age-Related Diseases in *Caenorhabditis elegans*. Pharmaceuticals. 2022; 15: 1528. Available from: doi.org/10.3390/ph15121528
- Kejik Z, Kaplanek R, Masarik M, Babula P, Matkowski A, Filipensky P, Vesela K, Gburek J, Sykora D, Martasek P *et al.* Iron Complexes of Flavonoids-Antioxidant Capacity and beyond. Int. J. Mol. Sci. 2021; 22: 646. Available from: doi.org/10.3390/ ijms22020646
- Sip S, Rosiak N, Sip A, Arowski ZM, Hojan K, Cielecka-Piontek JA. Fisetin Delivery System for Neuroprotection: A Co-Amorphous Dispersion Prepared in Supercritical Carbon Dioxide. Antioxidants. 2024; 13: 24. Available from: doi. org/10.3390/antiox13010024
- 22. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Reviews. 2010; 4(8):118-126.
- Park HH, Lee S, Oh JM, Lee MS, Yoon KH, Park BH, Kim JW, Song H, Kim SH. Anti-inflammatory activity of Fisetin in human mast cells (HMC-1). Pharmacological Research. 2007; 55(1): 31-37. Available from: doi.org/10.1016/j.phrs.2006.10.002
- 24. Sun Y, Qin H, Zhang H, Feng X, Yang L, Hou DX, Chen J. Fisetin inhibits inflammation and induces autophagy by mediating PI3K/ AKT/mTOR signaling in LPS-induced RAW264.7 cells. Citation: Food & Nutrition Research. 2021; 65: 6355. Available from: doi. org/10.29219/fnr.v65.6355
- Lee K, Seo I, Choi MH, Jeong D. Roles of Mitogen-Activated Protein Kinases in Osteoclast Biology. Int. J. Mol. Sci. 2018; 19: 3004. Available from: doi.org/10.3390/ijms19103004
- 26. Maher P, Dargusch R, Ehren JL, Okada S, Sharma K, et al. Fisetin Lowers Methylglyoxal Dependent Protein Glycation and Limits the Complications of Diabetes. PLoS ONE. 2011; 6(6): e21226. Available from: doi.org/10.1371/journal.pone.0021226
- Lee KH, Cha M, Lee BH. Neuroprotective Effect of Antioxidants in the Brain. Int. J. Mol. Sci. 2020; 21: 7152. Available from: doi. org/10.3390/ijms21197152

- 28. Su HS, Samanta S, Dash R, Karpinski TM, Habibi E, Sadiq A, Ahmadi A, Bungau S. The neuroprotective effects of Fisetin, a natural flavonoid in neurodegenerative diseases: Focus on the role of oxidative stress. Front. Pharmacol. 2022; 13:1015835. Available from: doi.org/10.3389/fphar.2022.1015835
- Zubcic K, Radovanovic V, Vlainic J, Hof PR, Orsolic N, Simic G, Jembrek MJ. PI3K/Akt and ERK1/2 Signalling Are Involved in Quercetin Mediated Neuroprotection against Copper-Induced Injury. Oxidative Medicine and Cellular Longevity. 2020; 9834742. Available from: doi.org/10.1155/2020/9834742
- 30. Tang X, Deng P, Jiang Y, Zhang L, He Y, Yang H. An Overview of Recent Advances in the Neuroprotective Potentials of Fisetin against Diverse Insults in Neurological Diseases and the Underlying Signaling Pathways. Biomedicines. 2023; 11: 2878. Available from: doi.org/10.3390/ biomedicines11112878
- Saraf A, Dubey N, Dubey N, Sharma M. Formulation and Optimization of Colon-Specific Nanoparticles Containing an Herbal Anticancer Agent. International Journal of Drug Delivery Technology. 2023; 13(2):591-596. Available from: doi. org/10.25258/ijddt.13.2.20
- Wang L, Chen N, Cheng H. Fisetin inhibits vascular endothelial growth factor induced angiogenesis in retinoblastoma cells. Oncology Letters. 2020; 20: 1239-1244. Available from: doi. org/10.3892/ol.2020.11679
- 33. Rahmani AH, Almatroudi A, Allemailem KS, Khan AA, Almatroudi SA. Recent strategies towards the surface modification of liposomes: an innovative approach for different clinical applications. 3 Biotech. 2020; 10(4):163. Available from: doi.org/10.1007/s13205-020-2144-3.
- Roya R, Tiwaria M, Donellib G, Tiwaria V. Strategies for combating bacterial biofilms: A focus on anti-biofilm agents and their mechanisms of action. Virulence, 2018; 9(1): 522–554. Available from: doi.org/10.1080/21505594.2017.1313372
- Musarra-Pizzo M, Pennisi R, Ben-Amor I, Mandalari G, Sciortino MT. Antiviral Activity Exerted by Natural Products against Human Viruses. Viruses. 2021; 13: 828. Available from: doi.org/10.3390/v13050828
- 36. Reis MPC, Carvalho CRC, Andrade FA, Fernandes OFL, Arruda W, Silva MRR. Fisetin as a promising antifungal agent against *Cryptocococcus neoformans* species complex. J Appl Microbiol. 2016; 121(2):373-9. Available from: doi.org/10.1111/ jam.13155.
- Vaou N, Stavropoulou E, Voidarou C, Tsigalou C, Bezirtzoglou E. Towards Advances in Medicinal Plant Antimicrobial Activity: A Review Study on Challenges and Future Perspectives. Microorganisms. 2021; 9: 2041. Available from: doi.org/10.3390/ microorganisms9102041
- Rodius S, Klein N, Jeanty C, Sanchez-Iranzo H, Crespo I, Ibberson M, Xenarios I, Dittmar G, Mercader N, Niclou SP, Azuaje F. Fisetin protects against cardiac cell death through reduction of ROS production and caspases activity. Scientific Reports. 2020; 10:2896. Available from: doi.org/10.1038/s41598-020-59894-4
- 39. Sun HJ, Wu ZY, Nie XW, Bian JS. Role of Endothelial Dysfunction in Cardiovascular Diseases: The Link between

Inflammation and Hydrogen Sulfide. Front. Pharmacol. 2020; 10:1568. Available from: doi.org/10.3389/fphar.2019.01568

- AL-Ishaq RK, Abotaleb M, Kubatka P, Kajo K, Busselberg D. Flavonoids and Their Anti-Diabetic Effects: Cellular Mechanisms and Effects to Improve Blood Sugar Levels. Biomolecules. 2019; 9: 430. Available from: doi.org/10.3390/biom9090430
- Prasath GS, Pillai SI, Subramanian SP. Fisetin improves glucose homeostasis through the inhibition of gluconeogenic enzymes in hepatic tissues of streptozotocin induced diabetic rats. Eur J Pharmacol. 2014; 740:248-54. Available from: doi.org/10.1016/j. ejphar.
- 42. Althunibat OY, Hroob AM, Abukhalil MH, Germoush MO, Jumah MB, Mahmoud AM. Fisetin ameliorates oxidative stress, inflammation and apoptosis in diabetic cardiomyopathy. Life Sci. 2019; 15:221:83-92. Available from: doi.org/10.1016/j. lfs.2019.02.017.
- Domaszewska-Szostek A, Puzianowska-Kuznicka M, Kuryłowicz A. Flavonoids in Skin Senescence Prevention and Treatment. Int J Mol Sci. 2021; 22(13):6814. Available from: doi. org/10.3390/ijms22136814.
- 44. Pal HC, Athar M, Elmets CA, Afaq F. Fisetin inhibits UVBinduced cutaneous inflammation and activation of PI3K/AKT/ NFκB signaling pathways in SKH-1 hairless mice. Photochem Photobiol. 2015; 91(1): 225–234. Available from: doi.org/10.1111/ php.12337.
- Yao K, Zhang L, Zhang YD, Ye PP, Zhu N. Flavonoids in Skin Senescence Prevention and Treatment. Molecular Vision. 2008; 14:1865-1871
- 46. Mirza MA, Padhi S, Mohapatra S, Mahmood S, Iqbal Z. Fisetin from Dietary Supplement to a Drug Candidate: An Assessment of Potential - A Review. Curr Pharm Biotechnol. 2024. Available from: doi.org/10.2174/0113892010304479240415074928.
- Duda-Chodak A, Tarko T. Possible Side Effects of Polyphenols and Their Interactions with Medicines. Molecules. 2023; 28: 2536. Available from: doi.org/10.3390/ molecules28062536
- Lorenzo GD, Scafuri L, Costabile F, Pepe L, Scognamiglio A, Crocetto F, Guerra G, Buonerba C. Fisetin as an adjuvant treatment in prostate cancer patients receiving androgendeprivation therapy. Future Sci. OA. 2022;8(3): Available from: doi.org/10.2144/fsoa-2022-0002
- Kumar RM, Kumar H, Bhatt T, Jain R, Panchal K, Chaurasiya A, Jain V. Fisetin in Cancer: Attributes, Developmental Aspects, and Nanotherapeutics. Pharmaceuticals. 2023; 16: 196. Available from: doi.org/10.3390/ ph16020196
- 50. VishwasS, Singh SK, Gulati M, Awasthi A, Khursheed R, Corrie LC, Kumar R, Collet T, Loebenberg R, Omji O, Gupta S, Jha NK, Gupta PK, Devkota HP, Chellappan DK, Gupta G, Adams J, Dua K. Harnessing the therapeutic potential of Fisetin and its nanoparticles: Journey so far and road ahead. Chemico-Biological Interactions. 2022; 356: 109869. Available from: doi.org/10.1016/j. cbi.2022.109869
- Rahmani AH, Almatroudi A, Allemailem KS, Khan AA, Almatroodi SA. The Potential Role of Fisetin, a Flavonoid in Cancer Prevention and Treatment. Molecules. 2022; 27: 9009. Available from: doi.org/10.3390/molecules27249009