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Review

Molecular and Therapeutic Effects of Fisetin Flavonoid in Diseases

Ezgi Nur Sari[1], **Yasemin Soysal**[1]

[1]Dokuz Eylül University Department of Molecular Medicine, Izmir, Turkey

Address for Correspondence: Yasemin Soysal, **E-mail:** yasemin_soysal@yahoo.com
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ABSTRACT

Chronic inflammation is defined as a prolonged and impaired immune response leading to a wide range of physiological and pathological conditions, for instance; abnormalities in nervous system, heart diseases, diabetes, obesity, lung diseases, immunological diseases, and cancer. In order to suppress chronic inflammatory diseases, inflammation should be prevented and treatments without side effects are needed at this time.

Traditional medicine and dietary restriction have been used in treatment by people for ages. Today, the WHO (the World Health Organization) data reveals that approximately 60% of the world's population and about 80% of the population of the developing countries have turned to herbal medicines. In this context, nutraceuticals attract attention because of their being safe, economical, easily accessible and in low toxicity, and their usages are gradually increasing.

Recently, fisetin, a new flavonoid among nutritional supplements, has attracted considerable attention. Fisetin, a bioactive flavonol found in fruits and vegetables, has chemo-preventive, anti-metastatic, neuroprotective, antioxidant, and anti-inflammatory effects. It is known that the concentration of fisetin is mainly high in strawberries, apples and dates. Studies conducted in cell culture and animal models have shown that fisetin has potential healing effects on diseases by affecting various signal pathways.

The effects of fisetin, which is a natural nutritional compound with promising potential, on obesity, cancer, neurological diseases, diabetes and cardiovascular diseases are presented to the attention of researchers with this review in the light of current studies.

Keywords: fisetin, flavonoid, nutraceuticals, polyphenols, therapeutic effects

INTRODUCTION

Inflammation, a strong, complex and pliable component of the immune response, not only helps to regenerate damaged tissue, but also defends against pathogens, dead cells, and harmful chemical or physical stimuli. Inflammatory response pulls phagocytic cells, such as neutrophils, monocytes and macrophages, to the inflammation site, thereby creating a physical barrier to destroy pathogens, limit their spread and prevent tissue damage. It is known that inflammatory mediators, cytokines and pro-inflammatory transcription factors manage the inflammation process by producing inflammatory regulators and recruiting inflammatory cells into the site (1). Following a prolonged chronic inflammation, heart diseases, diabetes, obesity, lung diseases, immunological diseases, cancer as well as various life-threatening inflammatory diseases and abnormalities in nervous system may occur. Therefore, the target of modulating the inflammatory response is of great interest for prevalence and therapeutic approaches. Steroidal anti-inflammatory drugs (SAID) and non-steroidal anti-inflammatory drugs (NSAIDs) which are used in the treatment of chronic inflammatory conditions for a long period of time have been associated with serious adverse effects. More and more studies are presenting that long-running use of non-steroidal anti-inflammatory medicine causes serious adverse effects in the gastrointestinal tract, as well as liver toxicities. Therefore, it is important to treat chronic diseases associated with inflammation without any side effects (2, 3).

Potentially, bioactive dietary agents (i. e. nutraceuticals) found in various fruits, vegetables, legumes, cereals, fibers and some spices may prevent or turn-around various chronic diseases associated with inflammatory responses and chronic inflammation. Nutraceuticals containing natural anti-inflammatory agents are widely used as dietary supplements or functional foods thanks

to their potential nutritional values, low toxicity, low costs, bioavailability by mouth, and protective/remedial impacts (4, 5).

Flavonoids, which are abundant in plant foods, are the most consumed polyphenols in the diet. The healing effects of flavonoids due to many biological functions such as enzyme modulation, gene transcription, and antioxidant activity have recently increased its popularity (6).

Fisetin (3,3′,4′,7-tetrahydroxyflavone), whose chemical formula was described by Josef Herzig in 1891, is a flavonoid that has long been used as a phyto-medical compound (3). Fisetin is found in various fruits such as strawberries, apples, dates, mangoes, kiwi, grapes, in vegetables such as tomatoes, onions, cucumbers, nuts, wine, and in various trees and shrubs of the *Fabaceae* and *Anacardiaceae* family, and in *quebracho colorado* and *pinophyta* species. Fisetin's highest concentration is in strawberries (160 µg/g), apples (26.9 µg/g) and dates (10.5 µg/g) respectively. Daily intake is 0.4 mg on average. Also, It is known to be used as a coloring agent (7–9). Moreover, fisetin has chemo-preventive, anti-metastatic, antioxidant, and anti-inflammatory effects (6, 10). Fisetin has two aromatic rings that are linked through a three-carbon oxygenated heterocyclic ring in its structure, and is complemented with four hydroxyl group substitutions and one oxo group (Figure 1). In addition, its water solubility and consequently its bioavailability is low. Fisetin's biological activity stems from the presence of hydroxyl groups at the 3, 7, 3′, 4′ positions and oxo group at the 4 position with double bond between C2 and C3 (11). Fisetin partly dissolves in the aqueous buffer solution. In ethanol, fisetin's solubility is averagely 5 mg/ml whereas in DMSO it is notably soluble, about 30 mg/ml, at 25°C and emits yellow color (3).

The aim of this review is to draw a general framework on the molecular effects of flavanol, a bioactive compound, in common chronic diseases and to contribute to the literature in this area.

FISETIN and CANCER

Cancer is a disease involving uncontrolled cell proliferation, morphological cellular transformation, deregulation of apoptosis, invasion, angiogenesis and metastasis (12). According to 2018 data by GLOBOCAN, 18.1 million new cancer cases and 9.6 million deaths from cancer were reported from 185 countries (13). Even though the advancement of diagnostic tools, improved treatment methods and cancer awareness programs have led to a noteworthy decrease in mortality rates of cancer, cancer prevalence is constantly increasing (14). The reason for this may be external factors such as smoking habits, infectious organisms, alcohol consumption, sedentary life, stress and unhealthy diet, and internal factors such as hereditary genetic mutations, hormones and immunity (14, 15). The most common cancers include lung, breast and colorectal cancers. Cancer-related causes of death include lung, liver and stomach cancers (16). Different therapeutic methods are available for the treatment of cancer, inclusive of surgical operation, radiation therapy, immunotherapy, chemotherapy and targeted therapy (11).

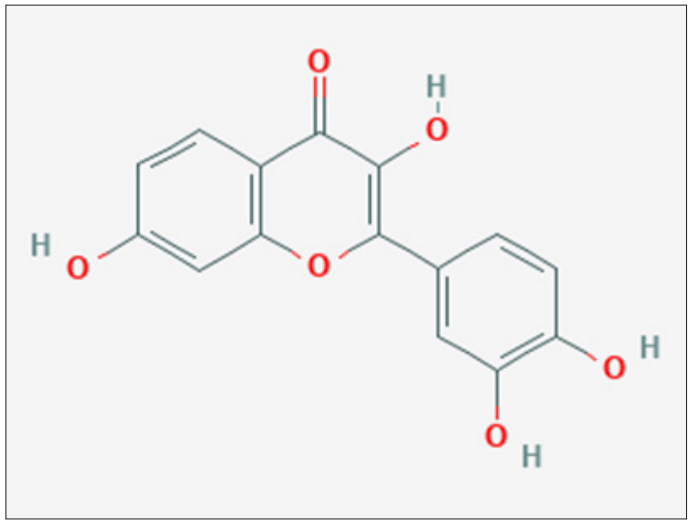

Figure 1. Chemical Structure of Fisetin (11)

While these treatment methods destroy cancer cells, they also harm healthy cells and cause serious side effects in the human body. For this reason, nutritional supplements come to the fore in order to prevent cancer and to minimize the treatment-based side effects during the treatment of the disease (17). Recently, fisetin (3,3′,4′,7-tetrahydroxyflavone), a flavonoid among these nutritional supplements, has been dwelled on.

Conducted studies show that the use of fisetin together with cancer treatments shows synergistic effect, increases apoptosis in cancer cells, suppresses invasion together with metastasis, and causes autophagic cell death thanks to its pleiotropic pharmacological effect (18).

It is expected from an ideal chemotherapeutic agent to target and exterminate tumor cells without showing cytotoxic effects on normal cells (18). It has been shown that besides its antioxidant activity, fisetin, as an ideal chemotherapeutic agent, has a strong anticancer activity in many different types of cancer by playing an important role in regulating significant signal pathways such as AMP (5′-Adenosine monophosphate-activated protein) kinase, ERK (extracellular signal-regulated protein kinase) 1 and 2, p53 and nuclear factor kappa B (NFκB) (19).

Oral doses in the literature for fisetin range from 5 to 25 mg/kg in animals, while intraperitoneal doses are between 0.3–3 mg/kg in the presence of a chemical carrier (Dimethyl sulfoxide). Commercially used doses for people are at the lower limit of this range and 100–200 mg daily for the oral compound (20). As a result of *in vivo* studies on fisetin toxicity, it has been reported that rodents do not show signs and symptoms such as decreased body weight, restlessness, respiratory distress, diarrhea, contractions and coma (21, 22). Fisetin has not shown measurable signs of toxicity at doses up to 2 g/kg in the acute toxicity analysis; in addition, no signs of toxicity has been found in the pathological evaluation of vitals as the heart, stomach, kidneys, intestines, liver, spleen, lungs and reproductive organs (23).

In a study of prostate cancer cells, fisetin has been shown to be a new regulator of the rapamycin complex 1 (mTORC1) signal and causes autophagic cell death induction (24). The most important signal pathway for the pathogenesis and progression of prostate cancer is the androgen receptor (AR) signal pathway. The key enzyme 5a-reductase in the AR signal is the catalysor for the conversion of testosterone to stronger androgen dihydrotestosterone, which is a process that increases the androgenic response and is related to the development of prostate cancer in people. Surprisingly, fisetin has been shown to have a higher affinity for AR than dihydrotestosterone, and AR interacts with the ligand binding domain. As a result, AR-mediated transactivation of target genes is suppressed, including prostate-specific antigen (PSA), which is used as a marker for prostate cancer. In another study, it was observed that fisetin significantly suppressed tumor growth in athymic nude mice which CWR22Rv1 prostate cancer cells were transplanted to, and therefore serum levels of PSA decreased significantly, marking an effect specific to AR (25).

In an *in vivo* study that fisetin has been shown to protect against benzo (a) pyrene-induced lung carcinogenesis, fisetin treatment has been reported to significantly reduce the degree of histological lesions and restore lipid peroxidation and antioxidants in benzo (a) pyrene-induced mice (26). In another *in vivo* study on lung cancer, fisetin treatment has been shown to have anti-angiogenic effects, reduce micro-vascularization, and also significantly reduce tumor volume when administered with cyclophysophamide (25).

Colorectal cancer ranks third among the most common cancers in both men and women (27). Studies with HT29 and HCT-116 human colon cancer cell lines have shown that fisetin inhibiting the actions of cyclin-dependent kinases stops the cell cycle. Additionally, fisetin has been shown to induce apoptosis in HT-29 cells that over-express COX2 (cyclooxygenase2), reduce the level of protein expression in COX2 without any effect on COX1 and inhibit prostaglandin E2 secretion. In addition, fisetin has been reported to inhibit Wnt signal by reducing the expression of β-catenin and T cell factor 4 activity and to reduce the expression of target genes such as cyclin D1 and MMP-7 (matrix metalloproteinase-7). Researchers have also reported that treatment of HT29 and HCT-116 cells with fisetin inhibits the activation of the epidermal growth factor receptor and NFκB pathways (28). In the research conducted by Lu et al. in 2005, it was shown that fisetin induced apoptosis by activating the death receptor and mitochondrial pathways in HCT-116 colon cancer cells. As a result of induction by p53, apoptosis occurs with Bax being translocated to the mitochondria followed by the activation of the caspase cascade (29). Fisetin has poor water solubility, and it is a difficult compound to administer intravenously. For this reason, a new approach has been adopted by using nano-assemblies of polymeric micelles that can encapsulate fisetin. The polymeric micelle encapsulation presented a retained and extended *in vitro* release, intensified cytotoxicity, cellular uptake, and apoptosis. This method, which was first developed in colon cancer, was found to suppress proliferation, trigger apoptosis and increase anti-angiogenesis activity in colon cancer cells. Accordingly, fisetin is thought to be a promising agent in the treatment of colon cancer (30).

Breast cancer comes second following the lung cancer as the reason of mortality rates related to cancer for women (27). In a 2012 research, the cytotoxic and apoptotic impacts of fisetin on MCF-7 and MDA-MB-231 breast cancer cells were examined thoroughly and it was determined that fisetin showed anticancer activity in caspase-3 deficient MCF-7 cells. Fisetin started a new atypical apoptosis form in MCF-7 cells and initiated rupture in plasma membrane, depolarization in mitochondria, activation of caspase-7, 8 and 9 and PARP (Poly (Adp-Ribose) Polymerase) cleavage. Those atypical characteristics of apoptosis were because of caspase-3 deficiency in MCF-7 cells. It has also been seen in this study that fisetin inhibits autophagy, supporting cell death in MCF-7 cells (27). Those preceding studies showed that the bioactive effects of fisetin were promising for the treatment of breast cancer.

Cervical cancer is one of the chief reasons of woman mortality, with approximately 12900 new cases and 4100 deaths each year (27). Studies conducted via *in vivo* tumor xenograft models indicated that fisetin notably curtailed tumor growth (31).

Recently, the promising potential of fisetin in combined therapies is a very popular research topic (18). Conducted studies demonstrated that fisetin with sorafenib as a novel drug combination showed significant antitumor effect on cervical cancer cell lines both *in vivo* and *in vitro*. *In vivo* studies with HeLa xenograft model showed that a combined treatment of fisetin and sorafenib was more effective than sorafenib treatment alone. That combined treatment induced apoptosis via activation of caspase-3 and 8 in HeLa cells, and caused loss of mitochondrial potential. In the light of these data, the combined application of fisetin and sorafenib reveals a new therapeutic strategy for advanced cervical cancer (32).

In another study of the combined administration of fisetin, it has been shown that the combined administration of hesperetin inhibits proliferation in HL-60 human acute promyelocytic leukemia cells, induces apoptosis, disrupts mitochondrial potential and induces cell cycle arrest at G2/M. Moreover, fisetin has been reported to induce PI3K/AKT signal pathway, cell cycle control pathways, JAK/STAT and MAPK signal paths. Based on these data, the combination of fisetin and hesperetin in the treatment of acute promyelocytic leukemia offers a new perspective (33).

FISETIN and ANTIAGING FEATURES

Senescence, a suppressor mechanism for tumor, is activated to inhibit the reproduction of defective DNA in stressed cells. Senescent cells are proven to have a causal part in triggering aging and age-related diseases. When the senolytic activities of flavonoids were investigated, fisetin was shown to be the compound with the strongest senolytic activity among the 10 flavonoids tested. In this study, fisetin applied to elderly mice acutely or intermittently suppressed the aging markers in more

than one tissue. Administrating fisetin to wild mice in a later stage in their lives recovered tissue homeostasis, decreased pathology related to age, and prolonged their lifespans. In addition, fisetin suppressed the aging of cells in rat and human adipose tissues. Being a natural product, fisetin showed seno-therapeutic activity both in mouse and human tissues and supported further studies. The question of whether fisetin could be utilized to lower senescent cell burden and improve dysfunction in older individuals has evoked clinical research. (34).

FISETIN and NEUROLOGICAL DISEASES

Many neurological pathologies such as stroke, trauma, Alzheimer and Parkinson's disease are associated with the death of nerve cells from oxidative stress. Epidemiological and experimental studies demonstrated that flavonoids had the capacity to safeguard the brain thanks to their abilities to support cellular survival and modulate intracellular signals (3).

It has been shown that fisetin protects nerve cells derived from central nervous system (HT-22 cells) and primary neurons of rats from glutamate toxicity, hypoglycemia and oxidative damage, improving glutathione (GSH) metabolism. Besides, fisetin has been shown to block hydrogen peroxide and to induce neuronal death by clearing reactive oxygen species (ROS) (35). It is known that the administration of fisetin reduces the neurotoxicity created by aluminum and increases the production of endogenous antioxidants, for instance Superoxide Dismutase, Catalase, and Glutathione S-Transferase, and escalates GSH levels in mice's brain tissues (cortex and hippocampi) (3).

A significant improvement in learning and memory was observed as a result of feeding rats with a fisetin-containing (500 mg/kg food) diet for 10 months compared to the mice fed a fisetin-free diet (36). In a study where a diet containing strawberry extract was fed to rats, evidence was provided that rats could keep spatial information (hippocampal-mediated behavior) better in comparison to the control group. Moreover, fisetin has been shown to have the potential to protect and increase nerve cell survival, cause differentiation, and increase long-term memory (3). Administration of 5, 10 and 20 mg/kg of fisetin to male mice through gavage has showed anti-depressant effects. As a result of neurochemical studies, fisetin has been shown to increase the production of serotonin and noradrenaline in the frontal cortex and hippocampus, and inhibit monoamine oxidase activity (37).

It was observed during a clinical examination that as a result of a 6-month administration of a diet which was rich in fisetin and hexacosanol and low in animal fat, the clinical symptoms of the Parkinson's disease, such as rigidness, bradykinesia, tremor, and dystonia improved (38).

According to a current study, it has been found that fisetin may improve mitochondrial enzyme activity and help prevent the disease as a result of administering different dose fisetin doses (10 mg/kg and 20 mg/kg) to the rats with Parkinson's disease model (39). In a study, fisetin treatment has been shown to significantly reduce ROS production while not affecting the macrophage cell viability, and it has been found that fisetin is the most effective neuroprotective flavonoid (40).

FISETIN and DIABETES

Diabetes mellitus (DM) which is distinctive with permanent hyperglycemia associated with the destruction in pancreatic beta cells or acquired insulin resistance in peripheral cells is a common chronic disease. It is thought that fisetin might have a part in managing diabetes as a natural option with less side effects compared to available diabetes treatments. Studies have shown that fisetin has several potential roles in the modulation of DM (3).

It has been found that in diabetic animal models fisetin lowers plasma glucose levels by increasing glycolysis and glycogen storage, inhibiting gluconeogenesis. As a result of administration of oral fisetin to diabetic rats for one month, it was demonstrated that blood sugar levels decreased, insulin increased, and red blood cell glycosylation decreased significantly (21, 41).

When fisetin was administered to rats orally, similar metabolic changes occurred to gliclazide, which is a recognized oral hypoglycemic agent. Fisetin caused those effects by modulating enzymes that play a role in carbohydrate metabolism. The activity of glycolytic pathway enzymes such as hexokinase, pyruvate kinase and lactate dehydrogenase in liver and kidney tissues were improved with the fisetin supplementation. Also, the activities of gluconeogenic enzymes glucose-6-phosphatase, fructose-1.6 bisphosphatase and glucose-6-phosphate dehydrogenase were inhibited by fisetin administration. Treatment with fisetin affected intrahepatic glycogen metabolism of diabetic rats by increasing glycogen concentration, glycogen synthase activation and inhibition of glycogen phosphorylase (21).

Studies suggest that fisetin may play a role in regulating inflammatory responses due to hyperglycemia. Under hyperglycemic conditions, natural and secondary immune system cells synthesize and secrete inflammatory cytokines. Histone acetylation, NF-κB activation and pro-inflammatory cytokine (IL-6 and TNF-α) released from human monocytic (THP-1) cells are significantly induced in hyper-glycemic (HG, 20 mmol/L glucose) conditions. Treatment of fisetin in THP-1 cells suppresses NF-κB activation and translocation and cytokine release. Fisetin demonstrates the anti-inflammatory effects by epigenetic regulation. Alterations in the inflammatory cytokine expression result from a decline in histone acetylation by histone acetyltransferases inhibition. The CBP/p300 protein is known as the NF-κB coactivator. Fisetin treatment significantly reduces the levels of acetylation and HAT activity of this protein. In addition, fisetin administration also significantly reduced CBP/p300 gene expression. These results indicate that fisetin inhibits hyperglycemia–induced cytokine production in monocytes, through epigenetic changes involving NF-κB (42).

Along with the pro-inflammatory cytokine modulation, it was found that fisetin lowered hyperglycemic vascular inflammation. Current studies have shown that fisetin could affect a variety of pathophysiological processes such as leukocyte adhesion associated with vascular inflammation, vascular permeability, migration and reactive oxygen species (ROS) formation. According to the data obtained from *in vivo* studies, it is thought that increases in vascular permeability of albumin due to hyperglycemia can be prevented by the pre-administration of fisetin. Additionally, pre-administration of fisetin has inhibited intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and hyperglycemia-induced overexpression of E-selectin in endothelial cells. This reduced the adhesion of monocytic THP-1 cells to human umbilical vein endothelial cells (HUVEC) activated by hyperglycemia (43). Vascular inflammation increases atherosclerosis and thrombosis in diabetic patients. It is thought that fisetin administration may be an appropriate option to decrease the potential of cardiovascular sequels (3).

Fisetin may contribute to easing known complications in DM. There is a rooted connection between DM and lipoprotein metabolism abnormalities. A new research has shown that fisetin administration to rats with diabetes induced by streptozotocin draws serum LDL and VLDL levels within the usual spectrum. This study has also showed that HDL levels in fisetin-treated rats have increased in comparison to the control group (41).

OBESITY, CARDIOVASCULAR DISEASES and FISETIN

It has been suggested that dietary obesity pathogenesis can be reduced by various mechanisms via the fisetin treatment. Studies show that supplementation of fisetin can mitigate the risk of obesity development by inhibiting the differentiation and proliferation of adipocytes. When fisetin was applied to 3T3-L1 undifferentiated fibroblast cells, it was observed that differentiation reduced in adipocytes. *In vivo* experiments also confirmed that in mouse models where a high-fat diet was given, supplementation of fisetin inhibited mTORC1 signal and the differentiation of preadipocytes, reducing weight gain and accumulation of white adipose tissue (44, 45).

It has been reported that by suppressing mitotic clonal expansion, fisetin treatment lowers adipocyte differentiation and proliferation. Fisetin treatment has curtailed the expression of some important cell cycle promoters, containing cyclin A, cyclin D1, and cdk4. Moreover, fisetin has induced the cell cycle inhibitor p27 expression by continuously supporting the G_0 phase (45).

Obesity is an accountable reason for cardiovascular complications such as hypertension, atherosclerosis and heart failure. Obesity-related cardiomyopathy is a critical cause of mortality and morbidity in diabetes and metabolic syndrome. Insulin resistance and inflammatory response are accounted for pathologies underlying metabolic disorders. Chronic over-nutrition, such as a high-fat diet, causes insulin resistance in a variety of tissues, including the heart. The progress of insulin resistance causes abnormal lipid accumulation in the heart, liver and kidneys. The protective effects of fisetin compound, which has the potential to alleviate obesity-related metabolic syndrome, on cardiac dysfunction in mice fed a high-fat diet have been investigated. In this study, it has been found that fisetin alleviates the metabolic disorder triggered by the high-fat diet lowering body weight, pre-prandial blood glucose and insulin levels, as well as insulin resistance. Fisetin has notably reduced dyslipidemia, stimulated by metabolic stress, in the hearts and cardiomyocytes of mice. Treatment with fisetin has suppressed the TNF receptor-1/TNF receptor-related factor-2 (Tnfr-1/Traf-2) signal, eliminating the inflammatory response caused by the high-fat diet in the heart tissues. Nevertheless, fisetin has neutralized the transforming growth factor (TGF) –β1/Smads/Erk1/2 signal, causing a drastic decrease in the fibrosis-related gene expressions. These results have showed that for the treatment of obesity and obesity-related heart damage, fisetin could also be a encouraging therapeutic strategy (46).

In a study on diabetic cardiomyopathy, the protective effects of fisetin have been examined. Fisetin has suppressed oxidative stress in the hearts of diabetic rats, prevented inflammation and apoptosis, and also increased antioxidant defense. It has been suggested that fisetin compound, which has been proven to prevent hyperglycemia-induced cardiomyopathy, may be a treatment option for humans in diabetic cardiomyopathy (47).

CONCLUSION

Herbal supplements have been used for centuries to improve human health and wellfare. Due to its anti-inflammatory, antioxidant and anti-tumorigenic properties, fisetin as a natural polyphenol has been reported to be utilized in the treatment in a variety of diseases, primarily of cancer, neurological, and cardiovascular diseases. Fisetin provides various neurological benefits to animals by improving the learning ability, behavior and memory. With these features, fisetin has the potential to be a part of the treatment for neurological diseases like Alzheimer's and Parkinson's in the future. The fact that fisetin affects cancer formation mechanisms, induces natural cell death, inhibits vascularization and metastasis in tumor demonstrates its chemotherapeutic potential and gives hope for cancer treatment. Other chronic diseases such as diabetes, obesity, atherosclerosis, and dyslipidemia are serious diseases in terms of incidence and treatment costs, and their treatment requires alternative adjuvants and monotherapies. Fisetin is an adjuvant that has a great potentiality for preventing inflammation in *in vitro* systems and animal models, and further studies should investigate the biological activities of fisetin and its various conjugates, and evaluate the short and long-term safety and effectiveness of the mentioned phytochemical in animal models. Preclinical *in vitro* and *in vivo* studies on the pharmacological features of fisetin show that clinical studies are applicable for humans, too. Studies that have been conducted so far guide us by presenting various perspectives on the potential of fisetin, which is a promising natural compound.

Table 1. Clinical studies on Fisetin (18, 48, 49)

Product	Condition or disease	Intervention/treatment	Phase	Identifier	Sponsor
Dietary supplement	Frail Elderly Syndrome	Oral; 20/mg/kg/day for 2 consecutive days, for 2 consecutive months	II	NCT03430037	Mayo Clinic
Dietary supplement	Diabetic kidney disease	Oral; 20/mg/kg/day for 2 consecutive days	II	NCT03325322	Mayo Clinic
Dietary supplement	Mild cognitive impairment	4 Soft-gels/day for 18 months	-	NCT02741804	Cedars-Sinai Medical Center
Dietary supplement	Gulf War Illness	Oral; 200–800 mg capsule/day	-	NCT02909686	University of Alabama, England
Dietary supplement	Brain Ischemic Stroke	Oral; 100 mg fisetin daily for a period of 7 days	II	-	No financial support for the research
Dietary supplement	Colorectal Cancer Patients	Oral; 100 mg capsule/day	-	IRCT2015110511288N9	Nutrition Research Center of Tabriz University
Dietary supplement	Healthy	Oral; 20 mg/kg/day for three consecutive days	II	NCT04313634	Mayo Clinic

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