THINK INDIA Journal

ISSN:0971-1260
Vol-22-Issue-16-August-2019

Reported Pharmacological Actions and Formulations of Fisetin: A Brief Review

Gunjal Pradnya Machhindra, Sachin Kumar Singh*,Monica Gulati, Rajan Kumar

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara – 144411, Punjab, India

* Corresponding Author: Name: Sachin Kumar Singh; Address: School of Pharmaceutical Sciences, Lovely Professional University, Phagwara - 144411, Punjab, India. Tel.: +918699267353; Fax: +91 1824501900; E-mail address: singhsachin23@gmail.com; sachin.16030@lpu.co.in

Abstract

Fisetin (3, 3, 4, 7-tetrahydroxyflavone) is a flavonoid found in various vegetables, fruits, nuts, teas and derived products. Fisetin possesses excellent neuroprotective, antioxidant, anti-inflammatory, anticancer, hepatoprotective and anti-diabetic effect through various molecular mechanisms. Fisetin has limitations in clinical application because of its physicochemical properties i.e. low water solubility, low physical and chemical stability that possesses dissolution rate-limited oral bioavailability. To overcome this limitation various novel drug delivery systems of fisetin was developed such as such as liposomes, nanoparticles, micelles, self-nano emulsifying drug delivery system, nanoparticles, solid lipid nanoparticles, cyclodextrin complexes and nanoemulsion. In this present review we tried to summarize the information available regarding fisetin related to its pharmacological activities and reported formulations.

Introduction

Fisetin

Fisetin (Fig. 1) (3, 3, 4, 7-tetrahydroxyflavone) is a flavonoid found in various vegetables, fruits, nuts, teas and derived products and their concentration such as Lotus root 5.8µg/g, onion 4.8µg/g, grape 3.9µg/g, kiwi 2.0µg/g, peach 0.6µg/g, cucumber 0.1µg/g, tomato 0.1µg/g, strawberry 160µg/g, apple 26.9µg/g, persimmon 10.6µg/g[1]. 2µg/g to160µg/g of flavanol presents in various fruits and vegetables. In humans the regularday-to-dayconsumption of fisetin

ISSN:0971-1260
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is 0.4 mg[2, 3]. It is synthesized from various source such as senegalia berlandieri (*Acacia berlandieri*), senegalia greggii (*Acacia greggii*) belonging to Fabaceae family[4].

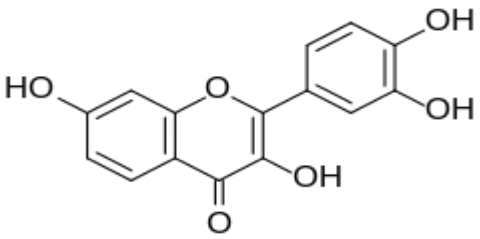

Figure1. Structure of fisetin

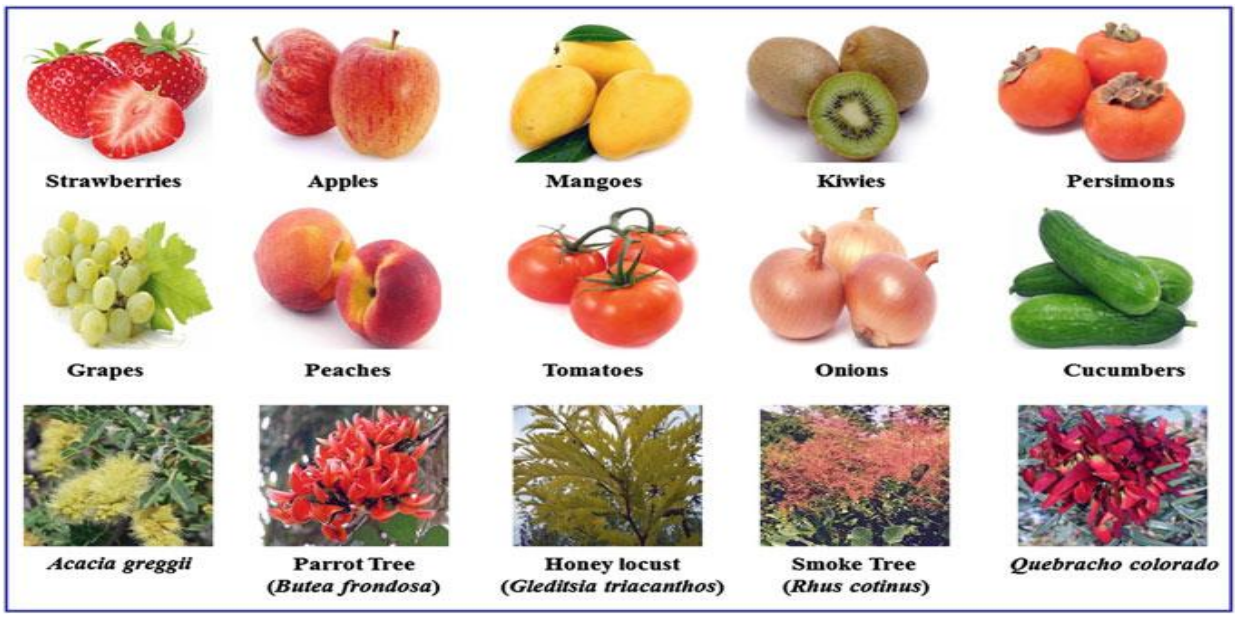

Figure 1 Sources of fisetin

Fisetin has limitations in clinical application due to low water solubility, low physical and chemical stability, poor oral bioavailability and high lipophilicity. Thus, the fisetin formulated by using various formulation strategies such as nanoemulsion, nanoparticles, spherical crystals, transethosomes, liposomes, self-nano emulsifying drug delivery system, lipid vesicles, and solid lipid nanoparticles [5-10].

Pharmacological activities and molecular targets of fisetin

Neurological diseases

Alzheimer's disease is characterized by cognitive deterioration, behavioral disturbances functional impairment and memory loss due to progressive degeneration in hippocampal functions. Alzheimer's disease diagnosed in two ways i.e., clinically and pathologically by

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dementia and two cardinal lesions such as senile plaques and neurofibrillary tangles initiated due to the extracellular assertion of amyloid-beta fibrils and intracellular aggregation of tau protein. Oxidative stress and cholinergic dysfunction increases at the beginning and involved in the progression of the disease. Fisetin reverses synaptic dysfunction, prohibited neuroinflammation, and improves memory and absence of plaque deposition in the C57BL/6N transgenic mouse model[11]. In another research, fisetin has been used in many disease conditions such as Alzheimer's disease it increases extracellular receptor kinase phosphorylation, decreases protein carbonylation, reduces levels of p25 which deregulate the CDK5 activity, which protect from neurodegeneration[12]. In addition, induction of lipopolysaccharide activates the gliosis and produces the neuroinflammation and neurodegeneration associated with AD and PD. Fisetin treatment inhibits the stimulation of Iba-1 and GFAP,TLR4/NFKB, CD14, TLR4, p-IKKβ, p-NFKB, TNF-α, cyclooxygenase (COX) 2, and interleukin-1 (IL1) – β in the mouse's hippocampus.Fisetin treatment produces a protective effect against lipopolysaccharide mediated apoptotic neurodegeneration, synaptic and memory dysfunction; it also increased the level of pre and postsynaptic protein such as SNAP-23, PSD-95 and p-GluR1[13]. In this study reported that, oxidative stress causes various neurogenerative disorders such as AD, PD which is characterized by impairment of balance, it also causes tremor, rigidity, bradykinesia, sensory, psychiatric, autonomic disturbances. In Parkinson's disease mainly cause due decrease the level dopamine and imbalance the dopamine metabolism in the substantia nigra. In Huntington's disease genetically degeneration of neurons which cause brain loss and muscle failure, it caused by an expansion of CAG trinucleotide in the Huntington gene. The naturally occurring flavonoid fisetin plays a major role in treatment of neurogenerative disorders it reduces the oxidative stress and maintains the neurological function[14]. It is reported that fisetin act as a ligand, it interacts with multiple target proteinslike MAO-A, MAO-B, COMT and hydroxylase of tyrosinewhich involved in dopamine degradation and dopamine metabolism. Fisetin may enhance the impaired function of Parkinson's disease, due to its antioxidant and neuroprotective activities [15]. In depression, fisetin activates Kinase B (TrkB) tropomyosin receptor signal pathway to produce antidepressant effects[16]. Epilepsy is a condition in which episodes of recurring seizures cause brain trauma. Fisetin produces an anti-epileptic effect in iron induces traumatic epilepsy, it inhibited the Na+, K+-ATPaseactivity and electrical activity of the brain which responsible for

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hyperexcitability in animal models and reduced lipid peroxide formation[17]. Administration of fisetin reduced the level of nitric oxide, xanthine oxidase and significantly increased the level of gamma-aminobutyric acid to produce the anticonvulsant effect and inhibit the oxidative injury[18]. In another research, fisetin is used to treat aluminum chloride-induced neurotoxicity. Aluminum chloride activates the Astrocyte, microglia and other inflammatory mediators which cause neurogenerative disorders. Fisetin treatment decreases the activities and levels of SOD, CAT, GST, AChE, GSH, LPO, and reactive gliosis and improves the behavioral performance, gait performance, neuromuscular strength, motor coordination, reduce the MDA level, enhances the antioxidant level and regulate the cholinergic function [19].

Anti-inflammatory effect

Inflammation produces by the immune system which necessary for the repairs of tissue homeostasis, makes sure the endurance during infection and tissue injury. Inflammation produces the adaptive response which is important to balance the normal functions of the cells. Inflammatory mediators, including chemokine, TNF, IL-1 and IL-6produced due to activation of pathogen-specific receptors which causes inflammation[20]. The anti-inflammatory activity of fisetin is not clearly understood. Fisetin produces anti-inflammatory effect in lipopolysaccharide to treatgingival fibroblasts cells in the gum tissue. Lipopolysaccharide activates the mitogen-activated protein kinase and nuclear factor kappa-beta which induces the expression of inflammatory mediators. Fisetin inhibits the stimulation of MAPK and NFkB without affecting cell viability and reduced the synthesis of prostaglandin E2[21]. In another research paper, fisetin inhibits the mRNA level which produces nitric oxide, p65, NFkB regulatory protein, tumor necrosis factor, cyclooxygenase in RAW264.7 cells. The activationNFkB due to a phosphorylation event that consists of Src, Syk, and IkBa was also suppressed by fisetin[22]. In another research paper, UV-B radiation produces inflammation, DNA damage, and mutation of p53 which causes skin cancer. Fisetin inhibits the PI3K, AKT phosphorylation, and NFkB signaling pathway in mice and reduces the cutaneous inflammation[23].

Anti-oxidant effect

Natural flavonoid fisetin produces an anti-oxidant effect by scavenging free radicals, decreases the lipid peroxidation and clear hydrogen peroxide through the non-enzymatic pathway which causes the oxidative stress and responsible for many diseases[24]. It is reported that, fisetin

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shows 61.6% anti-oxidant activity and 76 % anti radical activity.Because of the presence of the C3 hydroxyl group fisetin responsible for inhibiting oxidation of heterogeneous β-carotene and linoleic cycle[25]. Fisetin contains several phenolic hydroxyl groups which possess antioxidant and anti-proliferative effect. The biological activity relates to the interaction and localization of molecules in dipalmitoylphosphatidylcholine bilayers[26].

Anti-diabetic effect

Impairment of metabolism of amino acids, carbohydrates, lipids, and fatty acids causes chronic hyperglycemia which causes diabetes mellitus. It is a metabolic syndrome which always categorized by a deficiency in secretion and response of insulin. Diabetes mellitus distinguished by two typesi.e. type 1 which depend on insulin/ immune mediated/ idiopathic DM and most common type 2 DM which is non-insulin dependent which causes hyperglycemia, deficiency and resistance to insulin synthesis. Gestational diabetes mellitus (GDM) type of DM which is not related to pathophysiologic condition develop during gestation period[27]. Fisetin is used to treat the streptozotocin-induced hyperglycemia. Fisetin increases the level of plasma insulin and reduces the oxidative stress by increasing the antioxidant activity in pancreas and plasma of diabetic rats. *In-vitro* fisetin downregulates the glycogenolysis and gluconeogenesis cycle pathway and inhibits the NF-kB signaling pathway, IL-1β, and nitric oxide synthesis. Anti-diabetic activity produced due to the renewal of pancreatic β cells by oral administration of fisetin[28]. In another research paper, fisetin improves the anti-oxidant activity and elevate the level of glutathione in diabetic rat. Fisetin also decreases the level of hemoglobin A1C and plasma glucose; and increases the secretion of plasma insulin in diabetic rats[29]. It is reported that, fisetin used to treat diabetic neuropathy which affects the peripheral nerves of a diabetic patient. Fisetin decreases the level of IL-6 and TNF-α in sciatic nerves of streptozotocin-induced diabetes in rats[30]. Furthermore, fisetin produces an antidepressant effect to treat neuropathic pain associated with diabetic mice. Also, reduces higher oxidative stress which causes hyperglycemia by inhibiting the activity catalase of dorsal root ganglion, spinal cord, and sciatic nerve.Neuropathic hyperalgesia and allodynia decreases in type 1 diabetic mice[31]. Fisetin produces a protective effect against diabetic cardiomyopathy throughdecreasing oxidative stress, preventing inflammation and programmed cell death which causes due to hyperglycemia and

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hyperlipidemia. Also decreases the ROS, regulate the appearance of antioxidant genes and restore in structural and functional property of mitochondria in cardiac injury [32].

Hepatotoxicity

Hepatic steatosis, hepatic fibrosis, and hepatic cirrhosis caused due to excessive intake of alcohol. It also causes the generation of reactive oxygen speicies and oxidative degradation resulting increased oxidation and acute injury to the liver. Treatment of fisetin produces an anti-oxidant effect which decreases oxidation, inhibit the activity of NFkB, matrix metalloproteinases, specific inflammatory mediators include TNF-α, IL-6 and protect the liver from toxicity caused due to excessive alcohol consumption[33]. It is reported that, consumption of alcohol causes accumulation of lipids in the liver and elevates the level of plasma alanine aminotransferase, aspartate aminotransferase. Fisetin treatment decreases the level of AST, ALT, hepatic NADPH oxidase 4, plasma H_2O_2, hepatic superoxide and 4-hydroxynonenal levels[34].

Anticancer effect

Effect of fisetin on colon cancer

Fisetin shows cytotoxic activity and apoptosis in different colon cancer cell lines by inhibiting COX2 without any effect on COX1, Wnt-signaling activity, stimulation of EGFR, nuclear-kappa factor B (NF-kB) and prostaglandin E2 in HT29 colon cancer cells[35]. In another research paper reported that fisetin induced apoptosis, inhibit PI3K, AKT and mTOR pathways in *PIK3CA*-mutant and *PIK3CA*cancer cells[36]. It is reported, that fisetin activates caspase-3, 7, 9 and PARP protein; induce apoptosis and cause condensation of DNA in HCT-116 cell line. Fisetin decreases the level of antiapoptotic protein such as Bcl-xL,Bcl-2and elevates the level of apoptotic protein like Bak and Bim. Fisetin also elevates the level of p53 protein level which responsible for initiation of apoptosis in colon cancer cells. Administration of fisetin also contribute in translocation of protein by mitochondria, increases the mitochondrial membrane penetrability, cytochrome *c*release, improves the rate of protein inducing ligand in Caspase-8, and apoptosis associated with TNF [37]. Fisetin prevents the synthesis of DNA and HT-29 colon cancer cell development. Fisetin therapy arrests the G1, G2/M phases of the cell. Cyclin-dependent kinases activities in CDK-2, CDK-4, cyclin E, and D reduces by direct effect of fisetin on cell cycle HT-29 cell line of colon cancer[38]. Furthermore, fisetin increases the cytotoxicity,

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induces apoptosis, elevates the cellular uptake, defeat tumor growth and rises the cellular proliferation in CT26 cell line in colon cancer[39].

Effect of fisetin on breast cancer

Breast cancer characterized by four receptors fails to express such as receptors of estrogen, progesterone receptors and receptors of human EGF-2. Fisetin uses to treat triple-negative cancer of breast which is destructive and increases the risk of relapse. Fisetin produced an apoptotic effect, impedes the cell growth of MDA-MB-231, MDA-MB-468 and estrogen receptor-bearing cells with MCF-7 breast cancer [40]. In another research paper reported that proliferation of MCF-7 cell was inhibited in breast cancer after administration of fisetin, also they produce a greater inhibitory effect on endothelial cells as compared to fibroblast and keratinocytes[41]. Furthermore, fisetin produced the anti-invasive effect by inhibiting the matrix metalloproteinase expression in MCF- breast cancer cell. It also inhibits the activation of reactive oxygen species, NF-kB, p38 MAPK andERK1/2 signaling pathways in breast cancer cells [42].

Effect of fisetin on prostate cancer

The PI3K / Akt, MMP-2, MMP-9 and JNK signaling pathways are blocked by fisetin which stops the proliferation and metastasis in prostate cancer cells. It impedes cell adhesion, cell invasion and produced a cytotoxic effect on PC-3 cell line [43]. In another research paper, fisetin prevents the expression the both PI3K/Akt and mTOR pathways [44]. In addition, fisetin inhibits the overexpression of LNCaP, CWR22Ry1 and PC-3 cell line, arrests the G1 phase in the cell, induce apoptosis, reduces the cleavage of PARP protein zin in prostate cancer[45]. Fisetin inhibits the NF-kB, TRAIL cytotoxicity and causes stimulation ofcaspase 3, 8 and 9 in LNCaP, DU145, and PC3 prostate cancer cell lines[46].

Effect of fisetin on lung cancer

Lung cancer caused due to phosphorylation and overexpression pathways such as mTOR and phosphoinositide 3-Kinase in human non-small lung cancer cell. Fisetin treatment inhibits the phosphorylation and overexpression activities of mammalian target of rapamycin and phosphoinositide 3-Kinase signaling pathways in A549 and H1792 cell lines[47]. In recent study, fisetin inhibit the migration, adhesion, invasion of cell and the phosphorylation of ERK1/2 which responsible for metastasis in the A549 cell line[48]. It is reported thatmixture of paclitaxel and fisetin produces a synergistic activity on non-small cell lung cancer. It induces mitotic failure

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and autophagic death of cells; also inhibits the overexpression of caspase-3, LC3-II, Bax, Bcl-2 protein in A549 cell line[49].

Effect of fisetin on human leukemia cells

Accumulation of granulocyte in bloodstream and bone marrow leads to acute myeloid leukemia. In recent study, reported that fisetin induces an anti-proliferative and apoptotic effect on the HL-60 cell line. Fisetin arrests the G2/M phases in the cell, alters the mitochondrial translocation, elevates the activity of caspase-3 and inhibits the MAPK, ID, JAK/STAT signaling pathways in HL-60 leukemia cell[50]. In addition, fisetin used to treat chronic myeloid leukemia which causes due to translocation of various genes in chromosomes 9 and 22. Fisetin inhibits the translocation of genes and cell growth; induce apoptosis, increases caspase-3 activity, arrest S and G2/M phase in the cell in the K562cell line[51].

Effect of fisetin on human osteosarcoma cells

Human osteosarcoma characterized by bone tumors with a high level of cell invasion and metastasis. Fisetin induces apoptosis in malignant U-2-OS osteosarcoma cell lines. Fisetin treatment inhibits the MAPK and phosphoinositide 3-Kinase signaling pathways, elevates the activity of caspase-3, 8, 9 and protein like Bax and Bad in U-2-OS cell line. It also decreases the activity of Bcl-xL, Bcl-2 protein and inhibits the mitochondrial translocation[52].

Effect of fisetin on glioma cells

Gliomas are the frequently characterized primary adult malignant brain tumors, and glioblastoma average survival is about 12 to 15 months. Fisetin produced anti-metastatic, anti-invasive activity on GBM8401 cells. Administration of fisetin also inhibit the protein ADAM9 and mRNA expression which involved in development of glioma cancer [53]. In another study, fisetin produced anti-proliferative and anti-apoptotic effect on T98G cell. It enhanced the expression of BAK, caspase 3, 9 and 8 in cancer cells [54].

Effect of fisetin on cervical carcinoma

It most commonly occurs in women, it is a type of cancer which causes malignancy in which the prognosis is very low. Fisetin treatment induces apoptosis which causes the cell death of various tumor cells such as the in-vitro and in-vivo cell line of HeLa. It also causes activation of the protein caspase 3, 8 and phosphorylation of the ERK1/2 signaling pathway[55]. In another research paper, it decreases the phosphorylation of p38 MAPK, suppresses the urokinase

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plasminogen activator, inhibits the cell invasion, NF-κB Signaling Pathway and stimulates apoptosis in cells of cervical cancer [56].

Effect of fisetin on skin cancer

Melanoma is skin cancerless popular but most lethal form.In this study researcher reported that fisetin is used to treat the melanoma. Administration of fisetin inhibits the cell growth 451Lu melanoma cell line associated with microphthalmia-associated transcription factor and Wntsignaling pathway which causes in the progression of melanoma [57]. Furthermore, fisetin produce the anti-proliferative effect on melanomal cell line by inhibiting the proteinsmTOR, AKT and p70S6K phosphorylation [58]. It is also reported that fisetin produced anti-metastatic effect on A375 and 451Lu cell line by increasing the strain on endoplasmic reticulum. Fisetin therapy for 2-D cultures of melanoma resulted in the multifunctional AMPK-activated protein kinase (AMPK) phosphorylation and activation which involved in regulating various cellular processes, including autophagy and apoptosis [59].

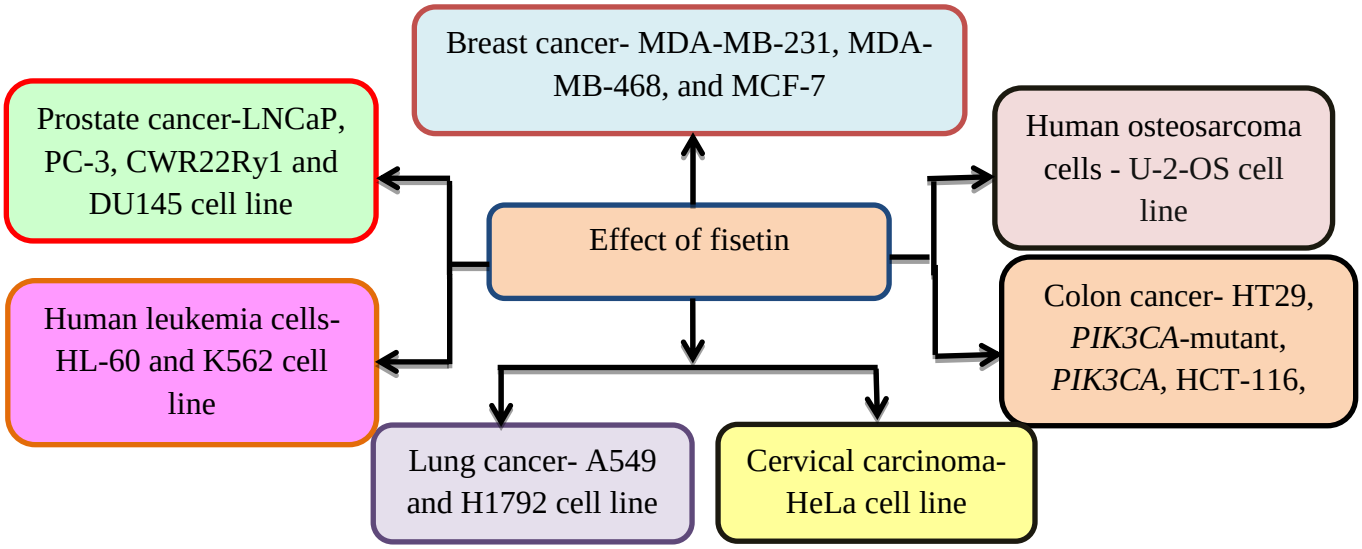

Figure 3.Effect of fisetin on different types of cancer cell line

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Table 1.1 Effect of fisetin on molecular targets in different cancer cell lines

SN	Targets	Cell line	Effect of fisetin	Ref
1.	Apoptosis	MCF-7	Impede the growth of MDA-MB-231 and 468 cells and estrogen receptor-bearing breast cancer cell line.	[40]
			Inhibit the proliferation of MCF-7 cells and greater inhibitory effect on endothelial cells as compared to fibroblasts .	[41]
		HL-60	Causes rapid induction of caspase 3/CPP32 activity and exhibit anticancer activity.	[60]
			Inhibit cell proliferation, arrest G2/M phases in the cell cycle, activate caspase 3, alteration of MAPK, ID, JAK/STAT signaling pathways	[50]
		SHEP	In neuroblastoma inhibit alteration of neuronal characteristics and does not express the nerve growth factor receptor.	[41]
		U-2 OS	Inhibit the MAPK and phosphoinositide 3-Kinase pathways and induce apoptosis in cancer cell	[52]
		HCT-116	Induce p53 which produce an apoptotic effect, decrease the is Bcl-xL and Bcl-2, induced the translocation by mitochondria, increases the penetrability of the mitochondrial membrane, releases cytochrome *c*, rises apoptosis inducing ligand level the caspase-8, Fas ligand, and TNF.	[37]
			Inhibit the HSF-1 factor which increases the existence of cancer cells, decreases the protein level like such as Bcl-2, Bcl-xL, and Mcl-1.	[61]
		HT29	Induces apoptosis in colon cancer via COX2,prostaglandin E2, Wnt-signaling activity, activation of EGFR and (NF-kB) inhibition.	[35]
		LNCaP, DU145 And PC3	Inhibition of Nf-kB, TRAIL cytotoxicity and caspase 3, 8 and 9 activation.	[46]
		K562 CML	Inhibit cell proliferation due to depolarization of mitochondrial membrane, initiate programmed cell death, activate caspase 3, alter JAK/STAT and KIT signaling pathways.	[51]
		CCA cell line	Causes phosphorylation of extracellular receptor kinase and AKT pathways, induce apoptosis in CCA cell lines and decreases the cell proliferation.	[62]
		SK-HEP-1	Activate the caspase 3 and induces the p53 protein and elevate the p21 protein in SK-HEP-1 protein.	[63]
		NCI-H460	Induce apoptosis, produce reactive oxygen species, activate caspase 3, and 9, elevate the expression of Bcl-2 and causes mitochondrial depolarization.	[64]

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	COLO205	Induce apoptosis and cytotoxicity in the presence of HSP90 inhibitors,[65] elevate the activities of caspase-3 and PAPR protein.
	U937 cell line	Induce apoptosis by TNF-α and activate the caspase-3 in leukemia cells [66]
	Human Burkitt's lymphoma Raji cells	Inhibit the mammalian target ofphosphatidylinositol-3-kinase[67] rapamycin which involves in development of cancer.
2. Antimetastasis		
	NSCLC A549 and H1299 cell line	Inhibit EMT which induce tumor to cells,interfere with tumorto [68] cells,interfere with migration and invasion in NSCLC and block β-catenin, EGFR, STAT-3signaling pathways.
	PC-3 cell line	Inhibit the MMP 2, 9, phosphoinositide 3-Kinase and JNK signaling[43] Pathways which stops the proliferation and metastasis in prostate cancer cells.
	HT-1080 and HUVECs cell line	Inhibit the gene expression of MMP-14, 1, 3, 7 and 9gene[69] genewhich causes invasion of tumor cells and formation of the tube by endothelial cells leads to metastasis cancer.
	MLNM-FT-A375, A375 cell lines	Inhibits the cell invasion, ERK1/2 phosphorylation, [70] NFkBsignaling pathway, stimulate epithelial transformation mesenchymal in melanoma cells which reduces the level of N-cadherin, fibronectin and elevate the level of epithelial markers such as E-cadherin and desmoglein.
	GBM8401 cell line	Inhibit migration of cell, expression of ADAM9 protein which causes [53] glioma cancer and also prevents the phosphorylation of ERK1/2.
	A549 cell line	Inhibit the cell migration, cell adhesion, cell invasion and impede the [48] phosphorylation of ERK1/2 which responsible for metastasis.

Formulation strategies for improving the bioavailability of fisetin

The use of fisetin is limited in the industry due to low water solubility and oral bioavailability of fisetin. The log P 3.2 indicates that fisetin has higher lipophilicity that why the dissolution rate of fisetin in the gastrointestinal tract is lower. That's why the fisetin is formulated in various novel systems for drug delivery such as liposomes, nanoparticles, micelles, self-nano emulsifying drug delivery system, nanoparticles, solid-lipid nanoparticles, cyclodextrin complexes, nanoemulsion[71].

Liposomes

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Liposomal formulation increases the bioavailability of fisetin and it improves the antitumor activity. The 1,2- dioleoyl-sn-glycerol-3-phosphocholine (DOPC) and dioctadecyldimethylammonium chloride (DODA)-PEG2000 used for preparation of liposomes. The diameter of liposomes within nanometer range possesses 173.5 ± 2.4 nm, index of polydispersity 0.181± 0.016 which shows a higher homogeneity and 58% fisetin is encapsulated in liposomes. The lower dose of fisetin liposomes shows the antitumoral activity relative to free form of fisetin in mice tumor cells. Further, fisetin and cyclophosphamide combination increases the antitumoral activity of fisetin liposomal formulation[5].In another research paper, the liposomal formulation was prepared by using P90G and DODA (1,2-dioleoyl-sn-glycerol-3-phosphocholine)-GLY-PEG2000 which solubilized the fisetin. The diameter of liposomes in the nanometer range possesses 175 nm, polydispersity index 0.12 which shows a high homogeneity and 73% fisetin is encapsulated in liposomes. This liposomal formulation shows the antiangiogenic and anticancer activity in tumor cells of mice[72].

Nanoemulsion

Fisetin shows the higher antitumor activity but the oral administration of fisetin is complicated due to poor water solubility. Nanoemulsion formulation of fisetin increases the pharmacokinetics and therapeutic efficacy in anti-tumor. The nanoemulsion developed with Miglyol812 N, Labrasol, Tween80, Lipoid E80 and water with composition 10%, 10%, 2.5%, 1.2%, and 76.3%. The oil droplet diameter of nanoemulsion of fisetin is 153 ± 2 nm, and the zeta potential was found to be -28.4 ± 0.6 mV and index of PDI is 0.129 which shows the high homogeneity. Nanoemulsion of fisetin administered intraperitoneally shows the antitumor activity in mice with low dose lewis lung carcinoma 36.6 mg/kg in comparison with the free form fisetin 223 mg/kg.The stable fisetin formulationof nanoemulsion formulation increases its relative bioavailability and activity of antitumor [6].

Nanoparticle

Fisetin shows anticancer activity MCF-7 cell line.Fisetin shows low aqueous solubility that affects the bioavailability. Fisetin nanoparticles were prepared to increases the oral bioavailability of fisetin. The fisetin encapsulation was done by poly-lactide-co-glycolic acid nanoparticles and the inclusion complex formation with the help of hydroxyl propyl beta-cyclodextrin (HPβCD). FST-HPβCD showed anticancer activity in MCF-7 cell line. Pure fisetin

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and FHIC-PNP bioavailability were determined after oral administration in C57BL6 mice[7]. Fisetin encapsulated into PLA nanoparticles which increases the water solubility and therapeutic activity of fisetin against in vitro HCT116 cancer cell line and in vivo antitumor effect.The nanoparticle diameter around 226.85 ± 4.78 nm and fisetin encapsulated 90.35% in nanoparticles[73].

Solid lipid nanoparticles

To achieve the simultaneous delivery of multi-agents is encapsulated into solid lipid nanoparticles. Fisetin packed in matrix of phosphatidylcholine i.e cetyl palmitate in combination with the photosensitizer-780 form of indocyanine. The solid lipid nanoparticle prepared by using a high-pressure homogenization method. The SLP polydispersity index below 0.3 which shows high homogeneity [74]. In another research paper, nanoparticles of solid lipid filled with cyanine form IR-780 which act as a diagnostic agent.Fisetin loaded in cyanine type IR-780 which the help of solvent diffusion method which helps the delivery of the drug into cancer cells. At lower dose SLP of fisetin reduces tumor growth and toxicity. This SLP stabilized with the help of various concentrations of Phospholipon 90G and solid matrix applied by using cetyl palmitate[75].

Polymeric micelles

Polymeric micelles developed when fisetin-loaded in D-α-tocopheryl glycol polyethylene 1000used to treat the cells with MCF-7 breast cancer. Free FIS and FIS-TPN shows the toxic effect and greater cellular uptake in the MCF-7 cell line. The cytotoxic effect was increased when fisetin loaded in the nanocarrier. In a normal group, both free FIS and FIS-TPN induced the apoptosis 11% and 20%.In treated group free FIS and FIS-TPN induced 30% and 42% apoptosis in breast cancer cells; also the migration of BCC inhibited after administration of FIS-TPN [76]. In another research paper, intravenous administration of fisetin is difficult due to the low water solubility.To overcome thisnanoassemblies are developed with the help of self-assembly procedure in that fisetin loaded in monomethyl poly (ethylene glycol)-poly(ε-caprolactone) copolymer. The prepared micelles particle size are 22±3 nm, the polydispersity index is 0.163 ±0.032 which shows high homogeneity, the encapsulation and drug loading efficacy of fisetin found to be 98.53±0.02% and 9.88±0.14%. Fisetin micelles showed the controlled and repeated activity *in vitro* release behavior of drugs as compared to the free fisetin

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which increases the cytotoxic effect, cellular absorption and enhanced the apoptosis in CT26 cancer cell line. The *invivo* studies of fisetin micelles suppresses cell proliferation, enhanced the induction of apoptosis and anti-angiogenesis [39].

Transethosomes

Transethosomal formulation is developed for the dermal delivery of fisetin. The transethosomes optimization was done by using Box–Behnken design. To develop the transethosomes the Lipoid S-100, cholate with sodium and ethanol were used as independent variables. The evaluation of formulation carried out by using parameters such as vesicle size, drug entrapping effectivenessof and in vitro skin penetration study of transethosomes. Transethosomes vesicle length is 74.21 ± 2.65 nm and 11.0 mV zeta potential. The entrapping efficiency of fisetin is 68.31 ± 1.48%. Rhodamine B loaded fisetin transethosomes were developed that show the better penetration of fisetin through rat skin that determined by using the confocal study. Additionally, the dermatokinetic study showed the fisetin transethosomes gel has better penetration across the rat's skin as compared to fisetin conventional gel [10].

Self-nano emulsifying drug delivery system (SNEDDS)

To overcome poor oral bioavailability, fisetin self-nano emulsifying drug delivery system (SNEDDS) has formulated. Prepared SNEDD composition includes castor oil-0.1 mL, Lauroglycol FCC-0.1 mL, Tween 80-0.4 mL, Transcutol P-0.6 mL, and 5 mg fisetin. Box Behnken Model has been used to refine the preparation. The SNEDDS droplet size was 154 nm and the negative zeta p was found negative zeta potential −37 mV. As compared to unprocessed fisetin the dissolution of fisetin SNEDDS increased significantly $p < 0.05$. The fisetin SNEDDS has high cell viability 89.05% and unprocessed form has 10.8% cell viability which is revealed by toxicity study [77].

Cyclodextrin complex

An inclusion complex for fisetin wasdeveloped by loading fisetin in β-cyclodextrin and γ-cyclodextrin. The cyclodextrin inclusion complexes showed high cytotoxicity in Hela and MCF-7 cell lines of the breast cancer relative to free fisetin[52]. In another research paper, fisetin combined in the β-cyclodextrin and hydroxyl propyl-β-cyclodextrin complex showed the

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cytotoxic effect on B164A5 murine melanoma cell line. The characterization of fisetin cyclodextrin complex was done by using SEM, DSC, and X-ray diffraction of the powder[78].

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Table 1.2 Animal studies of different fisetin formulations

S.N	Disease	Formulation	Animal model	No of animals	Dose (mg/kg)	Duration	Results	Cell line study	Reference
1.	Tumor	Liposomes	C57BL/6J mice	5	21 mg/kg	9 days	Liposomal formulation increases the bioavailability and delay the tumor growth in Lewis lung carcinoma	-	[5]
2.	Breast cancer	Nanoparticle	C57BL6 mice	27	10 mg/kg	24 hours	Induce apoptosis, anti-proliferative and cytotoxic effect on MCF-7 cell line	MCF-7 cell line	[7]
3.	Colon	Micelles	BALB/c mice	6	50 mg/kg	21 days	Increases cytotoxicity, cellular uptake, cancerinhibits the tumor growth in CT-26 cell line	CT26 cell[39]	
4.	Lewis lung carcinoma	Nanoemulsion	C57BL/6J mice	4	36.6 mg/kg	12 days	Suppress the tumor growth in lung carcinoma	-	[6]
5.	Colon and Breast Cancer	Nanoparticle	Balb/C mice	10	40 mg/kg	Three weeks	Enhanced cytotoxic activity, inhibit ERK phosphorylation in colon and breast cancer cell line	HCT-116, 4T1	[73]

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Conclusion

It is clear from the studies described here that fisetin potential for treating different disorders is highly promising. Fisetin interact with various molecular targets in different types of cancer cell lines and produced the beneficial effect in treatment of various diseases such as neurological diseases, diabetes, hepatotoxicity, inflammation and cancer. The different formulation were developed such as nanoparticles, liposomes, self-nano emulsifying drug delivery system, inclusion complex etc., to overcome aqueous solubility and oral bioavailability related issues. The safety and effectiveness of most of the formulations mentioned in the article is demonstrated through studies on in-vitro cell line or through animal models.

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