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FISETIN: A PHYTOCHEMICAL WITH VARIOUS PHARMACOLOGICAL ACTIVITIES

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Abstract

Flavonoids are the plant secondary metabolites which work as growth hormone as well as defence mechanism for the plants. These are well known for their antioxidant properties and are part of our daily food. Fisetin is one of the polyphenolic flavonol, present in various fruits and vegetables. Fisetin is reported to have various pharmacological properties. Strawberries have the maximum concentration of fisetin. Despite having various pharmacological properties, low oral bioavailability and high lipophilicity meared its use. In this review we tried to collect the information regarding the various pharmacological properties and its developed formulations to improve its bioavailability.

***Keywords*:** Fisetin, Flavonoids, Polyphenols, Antioxidant, Plant hormone

Abbreviations used: ALT: alanine aminotransferase, AST: aspartate aminotransferase, MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, ROS: Reactive oxygen species, Nf-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, TNF: Tumour necrosis factor, IL-6: Interleukin 6, GABA: Gamma-Aminobutyric acid, i.p: Intra-peritoneal, p.o: par oral, COX: Cyclooxygenase, iNOS: Inducible nitric oxide synthase, MAPK: Mitogen-activated protein kinases, SOD: Superoxide dismutase, CAT: Catalase.

Introduction

Flavonoids are the one of the important class of the chemicals which are available from the plants. Basically they are secondary metabolites of the plants and have polyphenolic basic structure. Flavonoids are abundantly found in various fruits, vegetables etc. They are also an integral part of various nutraceutical, pharmaceutical cosmetic and medicinal products because of their health promoting activity. Flavonoids are reported to help in the treatment of various diseases related to nervous and cardiovascular system. Flavonoids are extracted from the various plant parts depending on their concentration in different parts of the plant. In plants they are used as growth hormones and as defence mechanism **(Panche *et al*., 2016).**

Fisetin is one of the flavonol bioactive molecules. It is present in various fruits and vegetables like: apple, strawberry, persimmon, grape, onion and cucumber etc. The concentration of fisetin in fruits and vegetables varies from 2 to 160 µg/g (Figure 1). It is reported that strawberries have the maximum concentration of fisetin that is 160 µg/g. From last few year fisetin becomes an interesting drug molecule for research because of its presence in human food and also because of its various pharmacological reported activities like: antioxidant, anti-diabetic etc. **(Arai *et al*., 2000)**

Physicochemical Properties of fisetin:

Chemical name : 3, 3', 4', 7 – tetrahyroxyflavone

Molecular weight : 286.26 g/mol

Colour : Pale yellow

Melting point : 330 ºC

Solubility : Soluble in methanol, acetone, and acetic acid, very slightly soluble in water

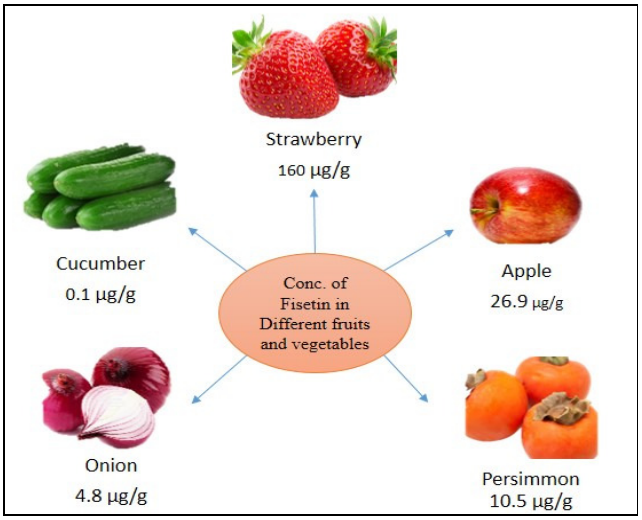

Fig. 1 : Fisetin concentration in different fruits and vegetable

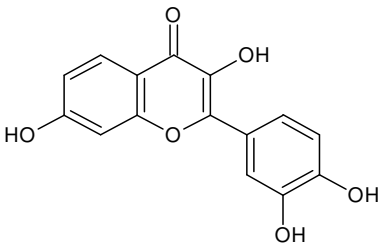

Fig. 2 : Structure of Fisetin

Antioxidant properties of fisetin

Fisetin was reported as a good antioxidant molecule as it is its inherent properties because of a flavonoid molecule. It acts as antioxidant by different activities like:

Scavenging the ROS/RNS free radicals: For a flavonoid molecule free radical scavenging activity is of great importance. In this process flavonoid transfer an electron from the hydroxyl radical to their nucleus and produces less reactive radicals. Fisetin found to have good free radical scavenging activity in 1,1–diphenyl-2-picrylhydrazyl (DPPH) and 2,2'–azino-bis (3-ethyl-benzothiazoline-6-sulfonic acid) (ABTS) assays. In these tests, fisetin inhibit 90.61% and 84.57% of DPPH and ABTS respectively, which reveals that fisetin have a strong free radical scavenging property (Ghosh *et al*., 2016; Prasath *et al*., 2013).

Restrain oxidant enzymes: Fisetin is also able to modulate the production of ROS by affecting the activity of oxidant enzymes like xanthine oxidase. Xanthine oxidase highly activate during the reperfusion (re-oxygenation) phase and produces superoxide. It has been reported that fisetin was able to reduce the production of superoxide ions by inhibiting the activity of xanthine oxidase or by scavenging the superoxide radicals (Cos *et al*., 1998; Wang *et al*., 2006).

Alleviate oxidative stress induced by nitric oxide: It is reported that in a mouse model of convulsion, treated with fisetin there is a significant reduction of high level of brain NO and xanthine oxidase. It is also reported that with fisetin treatment the expression of iNOS and COX-2 get also decreased (Raygude *et al*., 2012; Seo & Jeong, 2015; Wang *et al*., 2006).

Reinforce intracellular antioxidants: It is reported that supplementation or treatment with fisetin in certain animal models of neurotoxicity (Prakash *et al*., 2013), hepatotoxicity (Koneru *et al*., 2016) nephrotoxicity (Sahu *et al*., 2014) and diabetes (Prasath and Subramanina, 2013) there is reversal of depleted level of enzymatic antioxidant like: catalase, superoxide dismutase and non-enzymatic antioxidants like: vitamin c, vitamin e and ceruloplasmin etc.

Chelate transitional metals: Flavonoids have the inherent properties to chelate transition metals including ferrous ion (Fe II), ferric ion (Fe III) and copper ions (Cu II). By chelating these ions flavonoids ultimately protects the cells from their toxic effects. Fisetin also have the ability to chelate these ions and it is reported that fisetin was a good chelator of iron (Kasprzak *et al*., 2015).

Act as a substrate for oxidoreductase activity: Erythrocytes have a plasma membrane bound oxidoreductase (PMOR) which uses the ascorbic acid as electron donor to maintain the reduced state of the plasma membrane. Fisetin along with some other flavonoids like myricetin and quercetin have the ability to penetrate the erythrocyte plasma membrane and can donate an electron to PMOR (Fiorani and Accorsi, 2005).

Interact with redox-related signalling pathways: It was reported that fisetin might be interacting with some of the redox signalling pathway like: Nrf2, MAPK, NF-κB and P13K/Akt. It was reported that fisetin modulate the keap-1 association with Nrf2 and facilitate Nrf2 translocation and enhancement in expression of the target gene. Production of antioxidant enzyme also increases with induction of the Nrf2 by fisetin (Zhang *et al*., 2013; Sandireddy *et al*., 2016).

Reported Pharmacological Activities of Fisetin

In last few years fisetin was investigated in number of diseases using *in vitro* and *in vivo* models (Table 1). These studies provide evidence in the favour of fisetin that it is antioxidant, anti-diabetic, neuroprotective, nephroprotective and hepatoprotective molecule. It was reported that with the treatment of fisetin the depleted level of antioxidant enzymes like superoxide dismutase, catalase get restored and level of free radicals get decreased like reduces the level of thiobarbituric acid reactive substances, superoxide anions (Sahu *et al*., 2014; Koneru *et al*., 2016). Following are the reported pharmacological activities of fisetin:

Anti-oxidant and Anti-inflammatory: As a fisetin is a natural flavonoid so it has antioxidant property. The antioxidant property of fisetin and its anti-inflammatory activity investigated by various researchers. (Gelderblom *et al*., 2012) reported that fisetin was able to reduce the lipopolysaccharide induced neurotoxicity by reducing the oxidative stress and by reducing the level of inflammatory mediators. In other study, (Sahu *et al*., 2014) reported that fisetin reduces the expression of apoptotic factors and reduces the level of inflammatory cytokines. (Guh *et al*., 2014) reported that fisetin reduces the Reduces airway hyper responsiveness, reduces NF-κB activity and reduces inflammatory cell recruitment and mucus production. (Maurya and Trigun, 2016) reported that fisetin was able to reduce oxidative stress along with improving the level of antioxidant enzymes (superoxide dismutase and catalase).

Antiepileptic and Anticonvulsant: In an electrical seizure model of epilepsy it was observed that fisetin has the ability to block the electrical seizures and also help to maintain the activity of ATPase (Das *et al*., 2017). In other studies it was also reported that fisetin reduces strychnine induced convulsions and increases the level of GABA and reduce the level of nitric oxide. (Raygude *et al*., 2012).

Nephrotoxicity: In a cisplatin induced rat model of nephrotoxicity model, it was observed that fisetin was able to reverse the toxicity induced by cisplatin by modulation the activation of Nf-κB and by improving the level of antioxidant enzymes. Level of TNF-α and IL-6 was also reduced by the treatment with fisetin (Sahu *et al*., 2014).

Neurotropic: When a compound helps in the growth and differentiation of the growing neuron cells, it is called as neurotropic activity / neurotropic compound. In an in vitro cell line study it was observed that fisetin helps in the differentiation of the nerve cells which represents that the fisetin molecule have the neurotropic activity (Mehar, 2006).

Anti-viral: Fisetin was evaluated in an in vitro study against dengue virus type-2 along with rutin and naringenin. It was observed that fisetin blocks the replication of the dengue virus, and this activity was more in fisetin when compared to rutin and naringenin (Zandi *et al*., 2011).

Anti-Parkinson's: Oxidative stress and accumulation of alfa synuclein protein are the hal mark of the Parkinson disease. In an in vitro study of MPTP induced Parkinson's cellular model it was observed that fisetin reduces the MPTP induced oxidative stress and also reduces the accumulation of alfa synuclein protiein in the nerve cells. This reveals that fisetin have the anri-parkinsonian activity, which further can be accessed by using in vivo parkinson's model (Patel *et al*., 2012).

Antidepressant: In reserpine induced depression model in mice it was observed that fisetin abolished the depressant effect of reserpine and also regulate the hypothermia. On the

other hand fisetin increase the level of serotonin and non-adrenaline (Zhen *et al*., 2012).

Hepatoprotective: Alcohol consumption is the main reason for hepatotoxicity. In an alcohol induced hepatotoxicity model in mice fisetin was employed to treat the hepatotoxicity. It was observed that fisetin reversed the toxic effect of alcohol on the liver. The increased level of ALT and AST get decreased with treatment of fisetin. The level of antioxidant enzymes (SOD and CAT) get improved (Koneru *et al*., 2016). In other study which is performed on hepatocellular carcinoma cell line it was observed that fisetin reversed the oxidative stress and improve the level of antioxidant enzymes. The level of TNF-α and IL-6 also get decreased (Maurya and Trigun, 2016).

Diabetic neuropathy: It is a condition in which there is nerve damage occurs in the presence of diabetes. There is continuous pain sensation occurs at the nerve endings. Oxidative stress is also a main cause of diabetic neuropathy. In a study it was reported that fisetin reduces the diabetic neuropathy induced hyperalgesia and improves the level of antioxidant enzymes. Fisetin also reduces the expression of NF-κB (Sandireddy *et al*., 2015).

Anti-Adipogenic: It was reported that fisetin inhibits the intracellular lipid accumulation and also reduce the expression of adipocyte protein 2 in in vitro study. But on the other hand in vivo study it was reported that fisetin has no effect on body weight and fat tissue (Yonesaka *et al*., 2014).

Ulcerative colitis: In study on ulcerative colitis, it was reported that fisetin inhibits the oxidative stress and reduces the expression of apoptotic factors as well as level of pro inflammatory cytokines. This ultimately leads to reduced inflammation of the colon (Sahu *et al*., 2016).

Table 1: Reported pharmacological activities of fisetin

S. No	Reported Activity	Type of Study	Dose	Results	Reference
1	Anti-inflammatory	*In vivo* and *In vitro* study	25 mg/kg, 50 mg/kg and 2.0 µl/ml	It reduces the infarct size and lipopolysaccharide induces neurotoxicity by reducing the inflammatory response.	Gelderblom *et al*., 2012
2	Antiepileptic	*In vivo*		Inhibited the electrical seizures and retain the activity of ATPase	Das *et a*l., 2017
3	Nephrotoxicity	*In vivo*	1.25 and 2.5 mg/kg	Level of antioxidant emzymes (catalase, superoxide dismutase) get improved	Sahu *et al*., 2014
4	Antidepressant	*In vivo*	5, 10 and 20 mg/kg p.o	Act as antidepressant, it reduces reserpine induced hypothermia, increase the level of serotonin and noradrenalin	Zhen at al., 2012
5	Neurotrophic	*In vitro*	5µM	Promote the differentiation of the nerve cell in the culture (Act as neurotrophic factor)	Maher, 2006
6	Against Ulcerative colitis	*In vivo*	0.625 and 1.25 mg/kg i.p	It act as antioxidant, reduced the expression of apoptotic factor and level of pro inflammatory cytokines. Ultimately reduces the inflammation of colon	Sahu *et al*., 2015
7	Anti-Viral	*In vitro*	0.00, 3.125, 6.25,12.50, 25.00, 50.00 µg/ml	Fisetin block the viral replicatin by making complex with RNA and hence produces anti-viral effect.	Zandi *et al*., 2011
8	Anti-Adipogenic	*In vitro* and *In vivo*	25, 50, 75 µM and 20 mg/kg	In *in vitro study* fisetin was reported to inhibit the intracellular lipid accumulation, reduce expression of adipocyte protein 2. But in case in vivo fisetin has not effect of body weight and fat tissue.	Yonesaka *et al*., 2014
9	Neuroprotective in Diabetic neuropathy	*In vivo*	5 and 10 mg/kg p.o	Reduces hyperalgesia an reduce oxidative stress, and reduce the expression of NF-κB	Sandireddy *et al*., 2015
10	Anti-Parkinson	*In vitro*	----	MPTP induced cytotoxicity get reduced	Patel *et al*., 2012
11	Hepatoprotective	*In vivo*	5 and 10 mg/kg	Alcohol induced increased level of AST and ALT get reduced. Level of antioxidant enzyme gets also improved.	Koneru *et al*., 2016
12	Anticonvulsant	*In vivo*	5, 10 and 25 mg/kg i.p	Found to be act as anticonvulsant in Pentylenetetrazole, strychnine, Isoniazid and increases the level of GABA and reduces the level of nitric oxide	Raygude *et al*., 2012
13	Hepatic cancer (Hepatocellular carcinoma rat moel)	*In vivo*	-----	Reverse the depletion of antioxidant enzymes along with TNF alfa and IL-6, improve the hepatic neoplastic lesions	Maurya and Trigun, 2016
14	Anti-inflammatory	*In vivo*	0.3, 1 and 3 mg/kg i.v	Reduces airway hyper responsiveness, reduces NF-κB activity and reduces inflammatory cell recruitment and mucus production	Goh *et al*., 2012

Pharmacokinetic properties of Fisetin

It was reported that upon administration fisetin rapidly and extensively biotranformed by conjugation mechanism especially sulfation and produces fisetin sulfates and fisetin glucuronides (Khan *et al*., 2013). Geraldol (3,4',7 trihydroxy-3-methoxyflavone) is an active metabolite of fisetin. Fisetin is methylated in the liver to form geraldol by methyltrasferases. The terminal plasma $t_{1/2}$ of fisetin was reported to be 3.1 h (Jo et al., 2016). Despite having various *in vivo* and *in vitro* pharmacological properties, fisetin is not in that much use for research work. The reason behind this is its low oral bioavailability (44.1%) and high lipophilicity (log P 3.2) and low water solubility (10.45µg/mL) (Bothiraja *et al*., 2014). Various researchers work in the direction to improve its oral bioavailability and to reduce its first pass metabolism by developing various kinds of formulations. The developed formulations are listed in the table 2.

Table 2: Reported formulation of Fisetin

Sr. No	Type of Formulation	Evaluated for	Outcomes	Reference
1	Liposome	Antitumor efficacy	Formulation shows 47 folds increase in bioavailability as compared to naïve fisetin, formulation also provides good antitumor effect at low dose as compared to naïve fisetin	Seguin *et al*., 2013; Mignet *et al*., 2012
2	Novel Polymeric nanoparticles	In vitro antioxidanr and alfa glucosidase inhibitor activity	Antioxidant activity and alfa glucosidase inhibition activity of fisetin get increased in formulation	Sechi *et al*., 2016
3	Nanoemulsion	Antitumor	When nanoemulsion administered intraperitoneal there is 24 fold increase in bioavailability as compared to naïve fisetin, and at low dose of fisetin in nanoemulsion produces good antitumor activity	Ragelle *et al*., 2012
4	Novel water soluble inclusion complexes using β-cyclodextrins	Solubility	With inclusion complexes the solubility of fisetin in water get increased by 2.8 folds	Zhang *et al*., 2015

Conclusion

Fisetin was reported to have various pharmacological activities but still it is not in the pipeline of clinical trials due to various reasons specifically its pharmacokinetic issues. So, it provides an opportunity for both the pharmacologist and well as formulation scientists to work on it so that in future we will see this compound in the clinical trial and ultimately in the market for the treatment of diseases.

Reference

Arai, Y.; Watanabe, S.; Kimira, M.; Shimoi, K.; Mochizuki, R. and Kinae, N. (2000). Dietary Intakes of Flavonols, Flavones and Isoflavones by Japanese Women and the Inverse Correlation between Quercetin Intake and Plasma LDL Cholesterol Concentration. J. Nutr. 130: 2243–2250.

Bothiraja, C.; Yojana, B.D.; Pawar, A.P.; Shaikh, K.S. and Thorat, U.H. (2014). Fisetin-loaded nanocochleates: formulation, characterisation, in vitro anticancer testing, bioavailability and biodistribution study. Expert Opin. Drug Deliv., 11: 17–29.

Das, J.; Singh, R. and Sharma, D. (2017). Antiepileptic effect of fisetin in iron-induced experimental model of traumatic epilepsy in rats in the light of electrophysiological, biochemical, and behavioral observations. Nutr. Neurosci., 20: 255–264.

Fiorani, M. and Accorsi, A. (2005). Dietary flavonoids as intracellular substrates for an erythrocyte trans-plasma membrane oxidoreductase activity. Br. J. Nutr., 94: 338–345.

Gelderblom, M.; Leypoldt, F.; Lewerenz, J.; Birkenmayer, G.; Orozco, D.; Ludewig, P. *et al*. (2012). The flavonoid fisetin attenuates postischemic immune cell infiltration, activation and infarct size after transient cerebral middle artery occlusion in mice. J. Cereb. Blood Flow Metab., 32: 835–843.

Ghosh, P.; Singha Roy, A.; Chaudhury, S.; Jana, S.K.; Chaudhury, K. and Dasgupta, S. (2016). Preparation of albumin based nanoparticles for delivery of fisetin and evaluation of its cytotoxic activity. Int. J. Biol. Macromol., 86: 408–417.

Goh, F.Y.; Upton, N.; Guan, S.; Cheng, C.; Shanmugam, M.K. and Sethi, G. *et al*. (2012). Fisetin, a bioactive flavonol, attenuates allergic airway inflammation through negative regulation of NF-κB. Eur. J. Pharmacol., 679: 109–116.

Jo, J.H.; Jo, J.J.; Lee, J.M. and Lee, S. (2016). Identification of absolute conversion to geraldol from fisetin and pharmacokinetics in mouse. J. Chromatogr. B Anal. Technol. Biomed. Life Sci., 1038: 95–100.

Kasprzak, M.M.; Erxleben, A. and Ochocki, J. (2015). Properties and applications of flavonoid metal complexes. RSC Adv., 5: 45853–45877.

Khan, N.; Syed, D.N.; Ahmad, N. and Mukhtar, H. (2013). Fisetin: A Dietary Antioxidant for Health Promotion. Antioxid. Redox Signal., 19: 151–162.

Koneru, M.; Sahu, B.D.; Kumar, J.M.; Kuncha, M.; Kadari, A.; Kilari, E.K. *et al*. (2016). Fisetin protects liver from binge alcohol-induced toxicity by mechanisms including inhibition of matrix metalloproteinases (MMPs) and oxidative stress. J. Funct. Foods, 22: 588–601.

Lisu Wang, Yi-Chen Tu, Tzi-Wei Lian, Jing-Ting Hung, Jui-Hung Yen, and Ming-Jiuan Wu, (2006). Distinctive Antioxidant and Antiinflammatory Effects of Flavonols. J. Agric Food Chem., 54 (26): 9798-804

Maher, P. (2006). A comparison of the neurotrophic activities of the flavonoid fisetin and some of its derivatives. Free Radic Res., 40: 1105–1111.

Maurya, B.K. and Trigun, S.K. (2016). Fisetin Modulates Antioxidant Enzymes and Inflammatory Factors to Inhibit Aflatoxin-B1 Induced Hepatocellular Carcinoma in Rats. Oxid. Med. Cell. Longev.

Mignet, N.; Seguin, J.; Romano, M.R.; Brullé, L.; Touil, Y.S.; Scherman, D. *et al*. (2012). Development of a liposomal formulation of the natural flavonoid fisetin. Int. J. Pharm., 423: 69–76.

Panche, A.N.; Diwan, A.D. and Chandra, S.R. (2016). Flavonoids: an overview. J. Nutr. Sci., 5

Patel, M.Y.; Panchal, H.V.; Ghribi, O. and Benzeroual, K.E. (2012). The neuroprotective effect of fisetin in the MPTP model of Parkinson's disease. J. Parkinsons. Dis., 2: 287–302.

Paul, C.; Li, Y.; Mario, C.; Jia, P.; Hu, K.C.; Bart, V.P. *et al*. (1998). Structure Activity Relationship and Classification of Flavonoids as Inhibitors of Xanthine Oxidase and Superoxide Scavengers. J Nat Prod., 61(1): 71-76.

Prakash, D.; Gopinath, K. and Sudhandiran, G. (2013). Fisetin Enhances Behavioral Performances and Attenuates Reactive Gliosis and Inflammation During Aluminum Chloride-Induced Neurotoxicity. NeuroMolecular Med., 15: 192–208.

Prasath, G.S.; Sundaram, C.S. and Subramanian, S.P. (2013). Fisetin averts oxidative stress in pancreatic tissues of streptozotocin-induced diabetic rats. Endocrine., 44: 359–368.

Prasath, G.S. and Subramanian, S.P. (2013). Fisetin, a tetra hydroxy flavone recuperates antioxidant status and protects hepatocellular ultrastructure from hyperglycemia mediated oxidative stress in streptozotocin induced experimental diabetes in rats. Food Chem. Toxicol. 59: 249–255.

Ragelle, H.; Crauste-Manciet, S.; Seguin, J.; Brossard, D.; Scherman, D.; Arnaud, P. *et al*. (2012). Nanoemulsion formulation of fisetin improves bioavailability and antitumour activity in mice. Int. J. Pharm., 427: 452–459.

Raygude, K.S.; Kandhare, A.D.; Ghosh, P.; Bodhankar, S.L. (2012). Anticonvulsant effect of fisetin by modulation of endogenous biomarkers. Biomed. Prev. Nutr., 2: 215–222.

Sahu, B.D.; Kalvala, A.K.; Koneru, M.; Kumar, J.M.; Kuncha, M. and Rachamalla, S.S. (2014). Ameliorative effect of fisetin on cisplatin-induced nephrotoxicity in rats via modulation of NF-??B activation and antioxidant defence. PLoS One 9.

Sahu, B.D.; Kumar, J.M. and Sistla, R. (2016). Fisetin, a dietary flavonoid, ameliorates experimental colitis in mice: Relevance of NF-κB signaling. J. Nutr. Biochem., 28: 171–182.

Sandireddy, R.; Yerra, V.G.; Komirishetti, P.; Areti, A. and Kumar, A. (2016). Fisetin Imparts Neuroprotection in Experimental Diabetic Neuropathy by Modulating Nrf2 and NF-κB Pathways. Cell. Mol. Neurobiol., 36: 883–892.

Sechi, M.; Syed, D.N.; Pala, N.; Mariani, A.; Marceddu, S. and Brunetti, A. *et al*. (2016). Nanoencapsulation of dietary flavonoid fisetin: Formulation and in vitro antioxidant and α-glucosidase inhibition activities. Mater. Sci. Eng., C 68: 594–602.

Seguin, J.; Brullé, L.; Boyer, R.; Lu, Y.M.; Ramos Romano, M.; Touil, Y.S. *et al*. (2013). Liposomal encapsulation of the natural flavonoid fisetin improves bioavailability and antitumor efficacy. Int. J. Pharm., 444: 146–154.

Seo, S.-H. and Jeong, G.S. (2015). Fisetin inhibits TNF-α-induced inflammatory action and hydrogen peroxide-induced oxidative damage in human keratinocyte HaCaT cells through PI3K/AKT/Nrf-2-mediated heme oxygenase-1 expression. Int. Immunopharmacol. 29: 246–253.

Zandi, K.; Teoh, B.; Sam, S.; Wong, P. and Mustafa, M.R. (2011). In vitro antiviral activity of Fisetin, Rutin and Naringenin against Dengue virus type-2. J. Med. Plants Res., 5: 5534–5539.

Zhang, J.; Jiang, K.; An, K.; Xie, X.; Jin, Y. et al. (2015). Novel water-soluble fisetin/cyclodextrins inclusion complexes: Preparation, characterization, molecular docking and bioavailability. Carbohydr. Res. 418: 20–28.

Zhang, M.; An, C.; Gao, Y.; Leak, R.K.; Chen, J. and Zhang, F. (2013). Emerging roles of Nrf2 and phase II antioxidant enzymes in neuroprotection. Prog. Neurobiol. 100: 30–47.

Zhen, L.; Zhu, J.; Zhao, X.; Huang, W.; An, Y.; Li, S. *et al*. (2012). The antidepressant-like effect of fisetin involves the serotonergic and noradrenergic system. Behav. Brain Res., 228: 359–366.