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


Introduction
Flavonoids are 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 – tetrahydroxyflavone
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

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 (Konuru et al., 2016) nephrotoxicity (Sahu et al., 2014) and diabetes (Prasath and Subramania, 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: Erythrocyes 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).

Antiepileptie 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 protein in the nerve cells. This reveals that fisetin have the anti-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

<table>
<thead>
<tr>
<th>S. No</th>
<th>Reported Activity</th>
<th>Type of Study</th>
<th>Dose</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anti-inflammatory</td>
<td><em>In vivo</em> and <em>In vitro</em> study</td>
<td>25 mg/kg, 50 mg/kg and 2.0 µl/ml</td>
<td>It reduces the infarct size and lipopolysaccharide induces neurotoxicity by reducing the inflammatory response.</td>
<td>Gelderblom et al., 2012</td>
</tr>
<tr>
<td>2</td>
<td>Antiepileptic</td>
<td><em>In vivo</em></td>
<td></td>
<td></td>
<td>Das et al., 2017</td>
</tr>
<tr>
<td>3</td>
<td>Nephrotoxicity</td>
<td><em>In vivo</em></td>
<td>1.25 and 2.5 mg/kg</td>
<td>Level of antioxidant enzymes (catalase, superoxide dismutase) get improved</td>
<td>Sahu et al., 2014</td>
</tr>
<tr>
<td>4</td>
<td>Antidepressant</td>
<td><em>In vivo</em></td>
<td>5.10 and 20 mg/kg p.o</td>
<td>Act as antidepressant, it reduces reserpine induced hypothermia, increase the level of serotonin and noradrenalin</td>
<td>Zhen et al., 2012</td>
</tr>
<tr>
<td>5</td>
<td>Neurotrophic</td>
<td><em>In vitro</em></td>
<td>5 µM</td>
<td>Promote the differentiation of the nerve cell in the culture (Act as neurotrophic factor)</td>
<td>Maher, 2006</td>
</tr>
<tr>
<td>6</td>
<td>Against Ulcerative colitis</td>
<td><em>In vivo</em></td>
<td>0.625 and 1.25 mg/kg i.p</td>
<td>It act as antioxidant, reduced the expression of apoptotic factor and level of pro inflammatory cytokines. Ultimately reduces the inflammation of colon</td>
<td>Sahu et al., 2015</td>
</tr>
<tr>
<td>7</td>
<td>Anti-Viral</td>
<td><em>In vitro</em></td>
<td>0.00, 3.125, 6.25,12.50, 25.00, 50.00 µg/ml</td>
<td>Fisetin block the viral replicatin by making complex with RNA and hence produces anti-viral effect.</td>
<td>Zandi et al., 2011</td>
</tr>
<tr>
<td>8</td>
<td>Anti-Adipogenic</td>
<td><em>In vitro</em> and <em>In vivo</em></td>
<td>25, 50, 75 µM and 20 mg/kg</td>
<td>In <em>in vitro study</em> 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.</td>
<td>Yonesaka et al., 2014</td>
</tr>
<tr>
<td>9</td>
<td>Neuroprotective in Diabetic neuropathy</td>
<td><em>In vivo</em></td>
<td>5 and 10 mg/kg p.o</td>
<td>Reduces hyperalgesia an reduce oxidative stress, and reduce the expression of NF-κB</td>
<td>Sandireddy et al., 2015</td>
</tr>
<tr>
<td>10</td>
<td>Anti-Parkinson</td>
<td><em>In vitro</em></td>
<td>----</td>
<td>MPTP induced cytotoxicity get reduced</td>
<td>Patel et al., 2012</td>
</tr>
<tr>
<td>11</td>
<td>Hepatoprotective</td>
<td><em>In vivo</em></td>
<td>5 and 10 mg/kg</td>
<td>Alcohol induced increased level of AST and ALT get reduced. Level of antioxidant enzyme gets also improved.</td>
<td>Koneru et al., 2016</td>
</tr>
<tr>
<td>12</td>
<td>Anticonvulsant</td>
<td><em>In vivo</em></td>
<td>5, 10 and 25 mg/kg i.p</td>
<td>Found to be act as anticonvulsant in Pentylenetetrazole, strychnine, Isoniazid and increases the level of GABA and reduces the level of nitric oxide</td>
<td>Raygude et al., 2012</td>
</tr>
<tr>
<td>13</td>
<td>Hepatic cancer (Hepatocellular carcinoma rat model)</td>
<td><em>In vivo</em></td>
<td>----</td>
<td>Reverse the depletion of antioxidant enzymes along with TNF alfa and IL-6, improve the hepatic neoplastic lesions</td>
<td>Maurya and Trigun, 2016</td>
</tr>
<tr>
<td>14</td>
<td>Anti-inflammatory</td>
<td><em>In vivo</em></td>
<td>0.3, 1 and 3 mg/kg i.v</td>
<td>Reduces airway hyper responsiveness, reduces NF-κB activity and reduces inflammatory cell recruitment and mucus production</td>
<td>Goh et al., 2012</td>
</tr>
</tbody>
</table>
Pharmacokinetic properties of Fisetin

It was reported that upon administration fisetin rapidly and extensively biotransformed 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 methyltransferases. The terminal plasma t½ 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

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Type of Formulation</th>
<th>Evaluated for</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Liposome</td>
<td>Antitumor efficacy</td>
<td>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</td>
<td>Seguin et al., 2013; Mignet et al., 2012</td>
</tr>
<tr>
<td>2</td>
<td>Novel Polymeric nanoparticles</td>
<td>In vitro antioxidant and alfa glucosidase inhibitor activity</td>
<td>Antioxidant activity and alfa glucosidase inhibition activity of fisetin get increased in formulation</td>
<td>Sechi et al., 2016</td>
</tr>
<tr>
<td>3</td>
<td>Nanoemulsion</td>
<td>Antitumor</td>
<td>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</td>
<td>Ragelle et al., 2012</td>
</tr>
<tr>
<td>4</td>
<td>Novel water soluble inclusion complexes using β-cyclodextrins</td>
<td>Solubility</td>
<td>With inclusion complexes the solubility of fisetin in water get increased by 2.8 folds</td>
<td>Zhang et al., 2015</td>
</tr>
</tbody>
</table>

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


Fisetin: A phytochemical with various pharmacological activities