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Review article

Fisetin: A bioactive phytochemical with potential for cancer prevention and pharmacotherapy

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ABSTRACT

A wide variety of chronic diseases, such as neurodegenerative and cardiovascular disorders, diabetes mellitus, osteoarthtitis, obesity and various cancers, are now being treated with cost effective phytomedicines. Since synthetic medicines are very expensive, concerted efforts are being made in developing and poor countries to discover cost effective medicines for the treatment of non-communicable diseases (NCDs). Understanding the underlying mechanisms of bioactive medicines from natural sources would not only open incipient avenues for the scientific community and pharmaceutical industry to discover new drug molecules for the therapy of NCDs, but also help to garner knowledge for alternative therapeutic approaches for the management of chronic diseases. Fisetin is a polyphenolic molecule of flavonoids class, and belongs to the bioactive phytochemicals that have potential to block multiple signaling pathways associated with NCDs such as cell division, angiogenesis, metastasis, oxidative stress, and inflammation. The emerging evidence suggests that fisetin may be useful for the prevention and management of several types of human malignancies. Efforts are being made to enhance the bioavailability of fisetin after oral administration to prevent and/or treat cancer of the liver, breast, ovary and other organs. The intent of this review is to highlight the in vitro and in vivo activities of fisetin and to provide up-to-date information about the molecular interactions of fisetin with its cellular targets involved in cancer initiation, promotion and progression as well as to focus on strategies underway to increase the bioavailability and reduce the risk of deleterious effects, if any, associated with fisetin administration.

1. Introduction

Despite longstanding efforts in the development of anticancer chemotherapeutic drugs, some cancers still remain incurable and kill millions of people each year all over the world [1]. Prevention of this devastating disorder is certainly more convenient and prudent approach than elusive cancer cure. Therefore, strategies to reduce the incidence and risk of cancer through education will be even more important for primary health care in the future. Unfortunately, according to the International Agency for Research on Cancer, the incidence of cancer cases is projected to increase with the number of new cases expected to rise to 25 million over the next two decades, compared to 14.1 million in 2012 [1]. Consumption antioxidant-containing fruits and vegetables has been associated with decreased susceptibility to different NCDs, including malignant neoplasms [2]. However, the exact mechanisms of action of anticancer bioactive compounds derived from plants still remain to be established [3–5]. Fisetin (3,7,3′,4′-tetrahydroxyflavone) is one of the major polyphenolic flavonoids found in various fruits and vegetables such as apples, grapes, persimmons, strawberries, cucumbers, and onions [6–11]. The levels of this natural flavonol products range from 2 μg/g to 160 μg/g in different fruits and vegetables and the average daily intake of fisetin is estimated to be around 0.4 mg in humans [2]. It has been reported that fisetin can exert numerous beneficial biological activities, including antioxidant, anti-inflammatory, antiangiogenic, hypolipidemic, neuroprotective, and antitumor effects [12–17]. Fisetin can block multiple signaling pathways such as the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) and p38, mitogen-

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Table 1
Physicochemical properties of fisetin.

IUPAC name	2-(3,4-Dihydroxyphenyl)-3,7-dihydroychromen-4-one
Chemical formula	$C_{15}H_{10}O_6$
CAS number	528-48-3
Melting point	330 °C
Molar mass	286.239 g/mol
λ_{max} (ethanol)	252, 320, 360 nm
Solubility	Alcohol, acetone, acetic acid. Solution of fixed alkali hydroxide, DMSO; practical insoluble in water, ether, benzene, chloroform and petroleum ether

activated protein kinases (MAPK)-dependent nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling which playing a central role in various cellular processes contributing to the malignancy [16–19]. In this review article, we have focused on the biochemical activities of fisetin in various cancer cell lines and a few available in-vivo model systems used for investigating its action at the molecular level. We have also pondered to highlight the potential anticancer properties of this promising molecule as a possible novel compound useful either alone as anticancer substance or as an adjuvant agent in combination with radiation therapy and conventional chemotherapeutic drugs used in treating cancer patients.

2. Biosynthesis and chemistry of fisetin

Fisetin is a bioactive flavonol and has diphenylpropane structure (Table 1) which contains two aromatic rings linked through a three carbons-oxygenated heterocyclic ring, which is supplemented with four hydroxyl group substitutions and one oxo group [20,21] (Fig. 1). It is naturally synthesized in strawberries, apples, persimmons, onions, and cucumbers, and also serves as a coloring agent in plants [22]. Fisetin also found in various acacia trees and shrubs (Table 2) belonging to *Fabaceae* family, such as *Acacia greggii*, *Acacia berlandieri* and *Gleditschia triacanthow*; *Anacardiaceae* family members, such as the parrot tree (*Butea fronds*) and the honey locust (*Gleditsia triacanthos*); *Quebracho colorado*, *Rhus cotinus*, lac tree (*Rhus vemiciflua* Stokes), smoke tree (*Cotinus coggygria*) and *Pinopyta* species, such as *Callitropsis nootkatensis* (yellow cypress) [21].

The biosynthesis of fisetin in plants remains unknown. Stahlhut et al. [23,24] have proposed the biosynthetic pathway for fisetin production by using *E. coli* as microbial strain. This procedure as illustrated in Fig. 2 involves conversion of *p*-coumaroyl-CoA (i) and 3-malonyl-CoA (ii) into isoliquiritigenin (iii) using chalcone synthase (CHS), chalcone reductase (CHR) and nicotinamide adenine dinucleotide phosphate (NADPH). The isoliquiritigenin (iii) is converted to liquiritigenin (iv) by chalcone isomerase (CHI) followed by the formation of garbanzol (v) from liquiritigenin (iv) using flavanone 3-hydroxylase (F3H), *α*-ketoglutarate (*αKG*) and O_2. The garbanzol (v) is converted to resokaempferol (vi) by the action of flavonol synthase (FLS), *α*-ketoglutarate (*αKG*) and O_2 followed by the conversion of resokaempferol

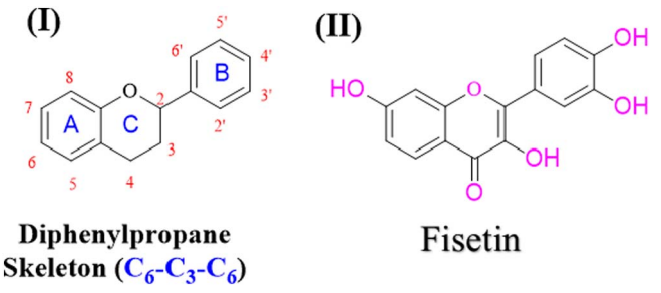

Fig. 1. Chemical structures of diphenylpropane skeleton (I) and fisetin aglycone (II). The basic diphenylpropane skeleton is common in both chemical structures.

Table 2
Various dietary sources of fisetin and its concentrations measured by dry weight basis method after acidic hydrolysis of parent glycosides into the respective aglycone [22].

Food source	Fisetin conc. (μg/g)
Strawberry (*Fragaria* sp.)	160
Apple (*Malus* sp.)	26.9
Persimmon (*Diospyros* sp.)	10.6
Lotus root (*Nelumbo* sp.)	5.8
Onion (*Allium* sp.)	4.8
Grape (*Vitis* sp.)	3.9
Kiwi (*Actinidia* sp.)	2.0
Peach (*Prunus* sp.)	0.6
Cucumber (*Cucumis* sp.)	0.1
Tomato (*Solanum* sp.)	0.1

(vi) into desired fisetin compound by action of flavonoid 3′-monooxygenase (FMO), cytochrome P450 reductase (CPR), NADPH and O_2 [23,24].

Chemically, fisetin can be synthesized by two methods, namely Kostanecki's method and Allan & Robinson's method. Kostanecki's method involves the formation of chalcone by reaction of 2-hydroxy-4-ethoxyacetophenone and 3,4-dimethoxybenzaldehyde in the presence of NaOH. The cyclization of chalcone into the respective substituted chroman-4-one was carried out by H_2SO_4 and C_2H_5OH. The treatment of substituted croman-4-one with *n*-amylnitrite and H_2SO_4 followed by hydroiodic acid results in the hydroxylation at C_3 with generation of hydroxyl groups at 7, 3′, 4′ and double bond between C_2–C_3 [25] (Fig. 3). Allan & Robinson's method involves the reaction of ω-methoxyresacetophenone, veratric anhydride and potassium veratrate for 4.5 h in an oil-bath at 175–180 °C followed by the treatment with hydroiodic acid [ref. 26] (Fig. 4).

Although fisetin is a potent bioactive phytoconstituent, whereas it exhibits low aqueous solubility and poor absorption from the gut and hence small bioavailability. A number of investigators have reported that the solubility and bioavailability of fisetin can be improved by co-crystallization with caffeine, isonicotinamide and nicotinamide [27,28], complexation with cyclodextrins and encapsulation with nanoparticles [29–31]. These modifications result in the enhancement of solubility, stability and biological activities of fisetin. The biological activity of fisetin depends up on the presence of hydroxyl groups at 3, 7, 3′, 4′ positions and oxo group at 4 position with double bond between C2 and C3. The hydroxyl group at C-7 and the double bond between C2 and C3 are essential for its antioxidant activity. Additionally, the presence of a hydroxyl group at C3′ in the ring B and at C3 is associated with its high antioxidant activity [32,33]. Awad et al. proposed the possible quinone/quinine methide structures (vii–ix) of fisetin (Fig. 5). The 2′-glutathionylfisetin formed by addition of glutathione to fisetin quinone occurs in the C ring at position 2 as a major product [34]. Fisetin is o-hydroquinone electrophilic compound form and acts as the neuroprotectant and antioxidant by activating the nuclear factor erythroid 2–related factor 2/antioxidant response element (Nrf2/ARE) pathway [25–37].

3. Anticancer effects of fisetin

3.1. Apoptosis activation

Induction of physiological or programmed cell death in tumor cells is a common mechanism of anticancer medications [38]. Numerous studies in the last few decades have determined the apoptotic activity of various plant-derived molecules, such as ursolic acid [39], quercetin [3], kaempferol [40] and cordycepin [41]. It has been observed that fisetin invokes antitumor activity through the activation of both intrinsic and extrinsic pathways of apoptosis determined in multiple in vitro and in vivo studies (Fig. 6). For instance, proapoptotic and