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Review

A review on the chemotherapeutic potential of fisetin: *In vitro* evidences

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ABSTRACT

During the past five decades, cancer cell lines are being successfully used as an *in vitro* model to discover the anti-cancer potential of plant secondary metabolites. Fisetin – the most popular polyphenol from fruits and vegetables, exhibits a repertoire of promising pharmacological features. Such versatile properties make fisetin an excellent anticancer agent and its efficacy as a chemotherapeutic agent against tumor heterogeneity from *in vitro* studies are encouraging. Fisetin is like a Pandora's box, as more research studies are being carried out, it reveals its new molecules within the cancer cells as therapeutic targets. These molecular targets orchestrate processes such as apoptosis, autophagic cell death, cell cycle, invasion, metastasis and angiogenesis in cancer cells. Besides apoptotic elicitation, fisetin's ability to induce autophagic cell death in cancer cells has been reported. This review examines the various molecular mechanisms of action elicited by fisetin leading to apoptosis and autophagic cell death as evidenced from cancer cell lines. In addition, the increased bioavailability and sustained release of fisetin improved through conjugation and enhanced effect of fisetin through synergism on various cancers are also highlighted.

1. Introduction

The ever-increasing worldwide prevalence of cancer has been a major public health concern and one of the leading causes of death worldwide [1]. Research studies in the last few decades have identified numerous potential plant compounds as natural cancer preventive agents. An increased consumption of these plant compounds regularly in the human diet offer beneficial effects. One such group of compounds – flavonoids effectively enhance apoptotic signaling pathways and inhibit cancer cell proliferation. Being antiproliferative agents, they act against different types of cancer cells. Flavonoids potential to inhibit carcinogenesis make them prospective chemopreventive and chemotherapeutic agents [2–5]. Recent studies have identified molecular targets of flavonoids against various cancers.

Fisetin (3, 7, 3′, 4′ – tetrahydroxyflavone) is the most ubiquitous bioactive plant flavonol, a member of the polyphenols – flavonoid (Fig. 1), and is synthesized by the secondary metabolism in plants [6]. Fisetin is found abundantly in vegetables, fruits, teas (Fig. 2) and Anacardiaceae plants (*Rhus succedanea*) ranging from 0.1 to 539 μg/g concentrations [7–10]. It exhibits a broad spectrum of biological functions, including antioxidant, anti-inflammatory, neuroprotective and anticancer activities [11–13].

An active component of fisetin scavenges free radicals with the free hydroxyl groups (C-3, C-3′, C-4′, C-7) and a carbonyl group (C-4) present in the molecular structure [14]. B and C ring of fisetin have higher scavenging activity compared to A ring. An ortho-dihydroxy region of fisetin is the electron donor that participates in the electron delocalization. 3- and 5-hydroxyl groups of fisetin scavenge the free radicals, defend against reactive oxygen species (ROS) and inhibit low-density lipoprotein oxidation [15–17]. Fisetin has been exploited as an effective anti-inflammatory agent, which inhibit the release of lysosomal enzymes, cyclooxygenase enzymes and arachidonic acids [18,19].

Several *in vitro* studies reported that fisetin as a tremendous inhibitor of signaling pathways and multiple deregulated proteins, which mediate growth, proliferation, and survival of cancer cells [20]. Emerging data from *in vitro* experiments showed clear evidence that fisetin treatment possesses tumor growth suppression. Fisetin interferes with the apoptotic and autophagic cell death pathway to maintain energy homeostasis [21,22]. Among the 22 flavonoids, fisetin triggers apoptosis in cancer cells by inducing DNA fragmentation, activating caspase 3 and 8, and calpain [23]. In addition to apoptosis, fisetin is capable of directing cancer cells to autophagic cell death. Though fisetin has been widely reported as a potential anticancer agent, the difference in the mechanism of action in different cancers still remains to be the subject of rigorous research. In this present review, we discussed the recent reports on the induction of apoptosis and autophagic cell death by fisetin in various cancer cell lines (Fig. 3). We highlight

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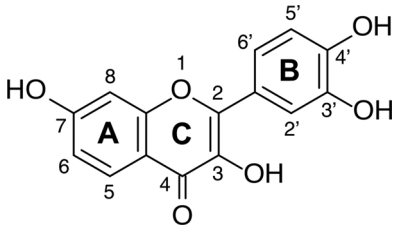

Fig. 1. Chemical structure of fisetin ($C_{15}H_{10}O_6$). Fisetin is an oxidation product of flavonols and a chromsene derivative. Fisetin is also called as 3-hydroxyflavone or 5-deoxyquercetin.

the multiple mechanisms of action, signaling pathways and cellular effects exhibited by fisetin. Table 1 summarizes the effect of fisetin on the different types of cancer cells targeting different proteins in the apoptotic and autophagy signaling pathways.

2. Anticancer potential of fisetin

2.1. Fisetin in colon cancer

A dietary polyphenol – fisetin altered the expression of cyclooxygenase 2 (COX2) thereby suppressed the secretion of prostaglandin E2 ultimately resulting in the inhibition of epidermal growth factor receptor (EGFR) and NF-κB in human colon cancer cells HT29 [21]. Furthermore, fisetin treatment inhibited the stimulation of Wnt signaling pathway via downregulating the expression of β-catenin and T cell factor (TCF) 4. Moreover, fisetin triggers apoptosis in U266 cells through multiple pathways: enhancing the activation of caspase-3 and PARP cleavage, decreasing the expression of anti-apoptotic proteins (Bcl-2 and Mcl-1_L), increasing the expression of pro-apoptotic proteins (Bax, Bim, and Bad), decreasing the phosphorylation of AKT and mTOR and elevating the expression of acetyl CoA carboxylase (ACC) [28]. Fisetin suppressed the proliferation of human colon cancer cells (HCT-116) with the ability to induce DNA condensations, PARP cleavage, caspase 9, 7, and 3 cleavages [51]. On fisetin treatment, anti-apoptotic proteins were downregulated with the upregulation of pro-apoptotic proteins and enhanced the mitochondrial membrane permeability to release the cytochrome *c* and Smac/Diablo into the cytosol. In addition, fisetin exhibited an increased level of cleaved caspase-8, Fas/Fas ligand, death receptor 5/TRAIL, and p53 levels in HCT-116 cells. Thus, apoptosis in HCT-116 cells was triggered through the activation of mitochondrial-dependent and death-receptor pathway and eventually by caspase cascade. Yu et al. [38] reported that fisetin treatment was much more effective in the suppression of securin expression in HCT-116 cells. Securin is a tumor transforming gene expressed highly in tumor cells and regulates the separation of sister chromatids, DNA repair mechanism and organ development. Securin gets degraded on exposure to fisetin in colon cancer cells. The depletion of securin increased the induction of apoptosis through the activation of p53, cleavage of PARP and procaspase-3, DNA fragmentation and DNA strand breakage. Further evidence of its anticancer activity was found against HT-29 cells [59]. Fisetin was shown to modulate the cell cycle regulatory proteins and play an imperative role in G2/M phase cell cycle arrest in HT-29 cells. The inhibition of cyclin-dependent kinases (CDK2 and CDK4) eventually decreased the cyclin E and cyclin D1 and increased $p21^{CIP1/WAF1}$. Further, fisetin decreased the expression of cell division cycle proteins (CDC2 and CDC25C), which resulted in the G1 arrest in the cell cycle. This finding reveals that fisetin suppresses the cell cycle progression and could serve as an anti-cancer agent against colon cancer.

The expression of the heat shock proteins (HSPs) is under the control of heat shock factor 1 (HSF1) – a transcription factor. HSPs are essential for the survival of colon carcinoma cells. In HCT-116 cells, the decreased expression of HSP79, HSP27, and Bcl-2-associated athanogene domain 3 (BAG3) was observed on fisetin treatment along with heat stress induction [22]. In the stressed state, HSP70/BAG3 complexes stabilize the anti-apotic Bcl-2 family proteins, thus prevents cancer cells from entering the apoptosis. Fisetin induced apoptosis as a result of the downregulation of HSP70 and BAG3 and the inhibition of Bcl-2, Bcl-x_L and Mcl-1. This study revealed the HSF1 inhibitory

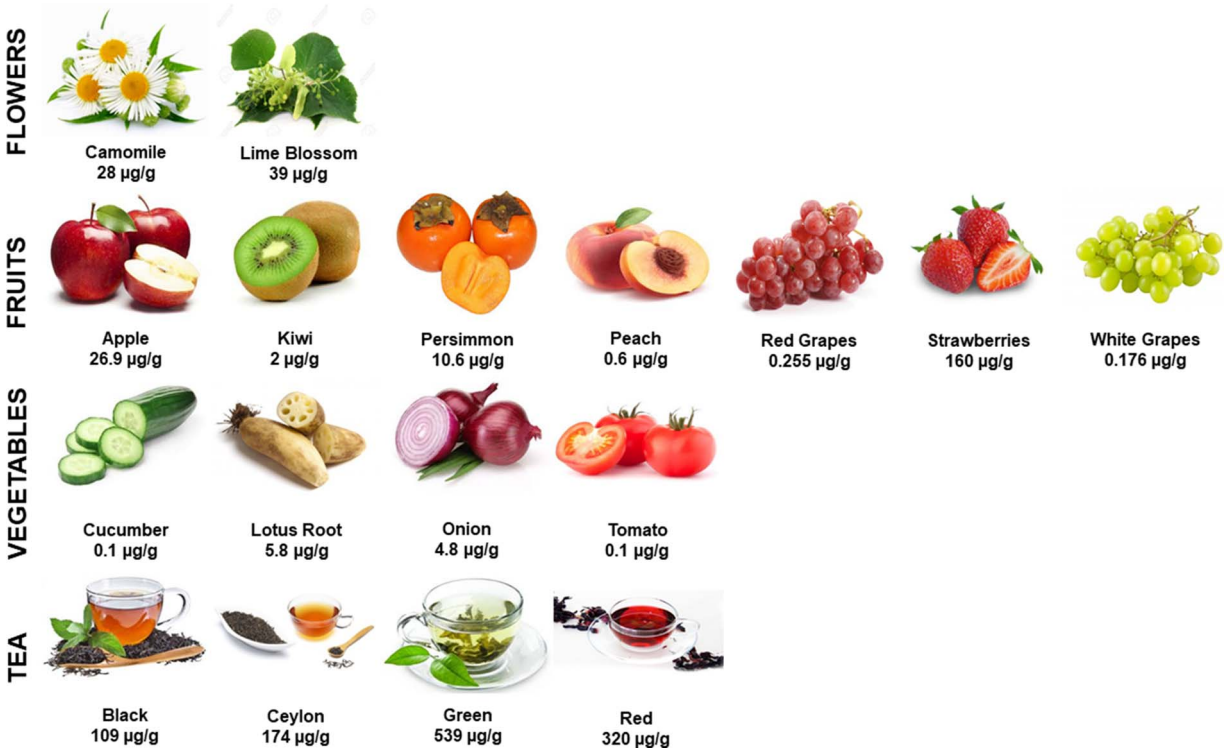

Fig. 2. Fisetin in flowers, fruits, vegetables and teas. The concentration of fisetin (µg/g) detected by high performance liquid chromatography/gas chromatography-mass spectrometry (HPLC/GC–MS) [17] and directly suspended droplet microextraction-gas chromatography-mass spectrometry (DSDME-GC–MS) [9].