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Review

The flavonoid fisetin as an anticancer agent targeting the growth signaling pathways

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ABSTRACT

Epidemiological studies show that consumption of diets rich in fruits and vegetables is associated with lower risks of cancer. This evidence has kindled interest into research on bioactive food components and has till date resulted in the identification of many compounds with cancer preventive and therapeutic potential. Among such compounds is fisetin (3,7,3,4-tetrahydroxyflavone), a flavonol that is commonly found in many fruits and vegetables such as apples, persimmons, grapes, kiwis, strawberries, onions and cucumbers. Fisetin has been shown to inhibit or retard the growth of various cancer cells in culture and implanted tumors *in vivo*. Fisetin targets many components of intracellular signaling pathways including regulators of cell survival and apoptosis, tumor angiogenic and metastatic switches by modulating a distinct set of upstream kinases, transcription factors and their regulators. Current evidence supports the idea that fisetin is a promising agent for cancer treatment. This review summarizes reported anticancer effects of fisetin, and re-emphasizes its potential therapeutic role in the treatment of cancer.

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Contents

1. Introduction

Chemotherapy is one of the principal modes of treatment for various cancers. However, many patients suffer major problems associated with cancer chemotherapy which include treatment-related adverse effects such as fatigue, nausea, vomiting, hair loss and cardiac toxicity (U.S. National Institutes of Health, 2015) or development of cancer drug resistance through various mechanisms (Niero et al., 2014). As such, alternative treatments such as herbal medicines have been used by patients to treat a variety of cancers, including breast, liver, testicular, esophageal, leukemia, lung, stomach, ovarian, cervical, colon and rectal cancer (Arjunan et al., 2014). Many of these herbs contain polyphenolic compounds known as flavonoids (Zhang et al., 2011) that are reported to have anticancer effects against various human tumor cell lines and xenograft tumors. These include apoptosis induction, cell cycle arrest, antiproliferative, antioxidative, antiangiogenic and

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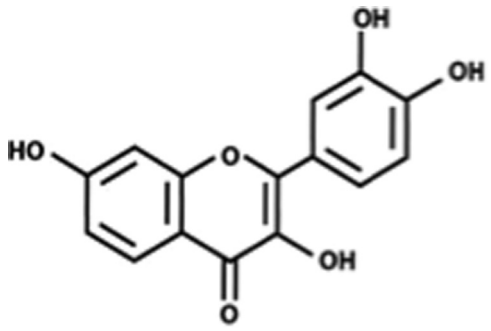

Fig. 1. Structure of fisetin.

antimetastatic effects (Mohammad et al., 2006; Huang et al., 2009; Auyeung and Ko, 2010; Deep et al., 2010; Meiyanto et al., 2012; Weng and Yen, 2012). A growing body of evidence also suggests that medicinal herbs or compounds may act as adjuvant to enhance the therapeutic efficacy of chemotherapeutic drugs, help overcome development of cancer drug resistance or reduce chemotherapy-induced side effects (Becker et al., 2014; Li and Leung, 2014; Li et al., 2015a).

Fisetin (3,7,3,4-tetrahydroxyflavone) (Fig. 1) is a naturally occurring flavonoid, commonly found in trees such as *Eudicotyledons*, *Acacia greggii, Acacia berlandieri, Butea frondosa* (parrot tree), *Gleditsia triacanthos* (honey locust) and *Quebracho coloradocs* (Manach et al., 2004). It is also widely distributed in fruits and vegetables such as strawberry, apple, persimmon, grape, onion and cucumber at concentrations of 2–160 μg/g (Arai et al., 2000). The average daily fisetin intake in the Japanese diet has been estimated to be 0.4 mg/day (Kimira et al., 1998). Toxicological studies on fisetin revealed no signs and symptoms of adverse effects such as reduction of body weight, restlessness, respiratory distress, diarrhea, convulsions and coma in rodents (Prasath and Subramanian, 2011; Touil et al., 2011) which are notable advantages of fisetin use in the treatment of diseases. This review discusses the available mechanistic data to support its potential use in cancer treatment. Emerging data on the potential therapeutic use of fisetin in combination with conventional chemotherapeutic agents are also presented.

1.1. Antioxidant and free radical scavenging activity

Cellular exposure to ionizing radiation causes oxidative stress due to high cellular levels of reactive oxygen species including superoxide anions, hydroxyl radicals and hydrogen peroxide (H_2O_2) (Nishikawa, 2008). The deleterious effect to irradiated cells in part reflects the macromolecular targets of reactive oxygen species – primarily DNA, lipids and proteins. Reactive oxygen species are also formed as normal by-products of cellular metabolism. At physiologically low levels, reactive oxygen species function as intracellular signaling messengers but induce oxidative stress that damages cell functions and structures at high concentrations (Bartosz, 2009; Sen et al., 2010), leading to conditions such as Alzheimer's disease, cancer, heart disease and chronic inflammation (Zhu et al., 2007; Khansari et al., 2009).

The human antioxidant defense system must therefore minimize the levels of reactive oxygen species while allowing their physiological roles to continue (Halliwell, 2011). The cellular redox homeostasis is maintained by several endogenous (eg., superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx], reduced glutathione [GSH], glutathione-S-transferase [GST]) and exogenous antioxidants (eg., vitamin A, vitamin C and vitamin E) that neutralize free radicals or superoxide radicals generated from many different sources (Sikora et al., 2008). Prasath and Sorimuthu (2013) showed that decreased levels of SOD, CAT, GPx, GSH and GST in liver and pancreatic tissues in streptozotocin-induced diabetic rats could be reversed by fisetin. Additionally, fisetin increased the levels of antioxidant enzymes in buccal mucosa and plasma of hamsters with oral cancer (Sathiyapriya et al., 2013a, 2013b) and rats induced with lung cancer (Ravichandran et al., 2011).

The mitochondrion is a potential source of reactive oxygen species and disruption of the mitochondrial membrane is a trigger for apoptosis whereby apoptotic factors are released from the damaged mitochondrion into the cytosol (Circu and Aw, 2010). Fisetin attenuated intracellular reactive oxygen species levels and DNA damage in Chinese hamster lung fibroblasts (V79–4) exposed to γ-irradiation and thereby protected the cells against membrane lipid peroxidation, DNA damage and protein carbonylation (Piao et al., 2013). Fisetin also protected these fibroblasts against H_2O_2-induced cell damage through modulation of GSH activity and decreased levels of reactive oxygen species (Kang et al., 2014). In addition, the expression of the cytoprotective enzyme, heme-oxygenase-1 (HO-1) is induced by fisetin in human umbilical vein endothelial cells (Lee et al., 2011). HO-1 plays a role in the maintenance of homeostasis during oxidative injury whereby it prevents oxidative stress-induced cell death (Jang et al., 2009; Morse et al., 2009). Regulation of HO-1 expression is critical for differentiation of osteoclasts and suppression of HO-1 by receptor activator of nuclear factor kappa-B ligand (RANKL) is essential. Fisetin was able to prevent osteoclastogenesis in Balb/c mice bone marrow–derived macrophages via HO-1 upregulation and inhibition of RANKL-mediated reactive oxygen species production (Sakai et al., 2013). These findings suggest that as an antioxidant, fisetin could help reduce the adverse effects arising from elevated levels of free radicals in various diseases and the cellular protective effects occur partly via an HO-1-dependent mechanism.

1.2. Antiproliferative effect and cell cycle arrest

Cyclins and cyclin-dependent kinases (CDKs) are major controlling switches of the cell cycle. Cyclin D1, a component subunit of Cdk4 and Cdk6, is a rate-limiting factor in the progression of cells through the first gap (G1) phase of cell cycle. Cyclin E associates with cdk2 and this kinase complex is required for cell transition from G1 to S phase. Cyclin A controls the S phase in complex with Cdk2 or Cdk1 while cyclin B forms complex with Cdk1 to control the M phase (Lim and Kaldis, 2013). Dysregulation of cell cycle checkpoints and over expression of growth-promoting cell cycle factors such as cyclin D1 and cyclin E are associated with tumorigenesis (Bendris et al., 2015). Fisetin suppressed growth and proliferation of a wide variety of tumor cell lines of different tissue origins. It arrested HT29 colon cancer cells from G1 to S phase by inhibiting cyclin D1 and CDK4 expression (Lu et al., 2005). Cyclin D1 expression is regulated by nuclear factor kappa B (NF-κB) and suppression of NF-κB activity by fisetin down-regulated cyclin D1 in lung cancer cells (Sung et al., 2007). The NF-κB pathway was also inhibited in T24 and EJ bladder cancer cells and the fisetin-induced G0/G1 arrest was accompanied by p53 activation (Li et al., 2011). Fisetin also inhibited the proliferation of other cell types such as human A431 epidermoid carcinoma cells (Pal et al., 2013), KLE endometrial cancer cells (Wang et al., 2015) and 451Lu metastatic melanoma cells (Syed et al., 2011) through inhibition of CDK proteins. In A375 melanoma cells, fisetin arrested cell growth at G2 phase through dephosphorylation of the serine-threonine kinase, Akt, and inhibition of its downstream molecules (mammalian target of rapamycin [mTOR] and p70S6K) (Syed et al., 2014a). Retinoblastoma 1 (RB1), a major tumor suppressor of G1 to S progression, was also downregulated by fisetin in LNCaP and PC3 prostate cancer cells (Haddad et al., 2010).

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