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Hesperidin: A promising anticancer agent from nature

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A B S T R A C T

Cancer is major health problem in the worldwide which refers to a group of diseases caused by abnormal cell growth with invasive potentials. There are different environmental and genetic factors which cause cancers in human body such as smoking, diet, radiation, *etc.* In addition, oxidative stress plays a crucial role in the pathophysiology of different types of cancer. Therefore, much attention has been paid to antioxidants as novel therapeutic strategy for cancer. Flavonoids are important natural antioxidants in the nature which have potent anticancer effects under both *in vitro* and *in vivo* conditions. Hesperidin, an important bioflavonoid, is widely found in *Citrus* species and acts as potent antioxidant and anticancer agent. In present review, we summarize the scientific literature about anticancer effects of hesperidin with emphasis on its molecular mechanisms. We also discuss about chemistry, food sources, bioavailability, and clinical impacts of hesperidin.

Contents

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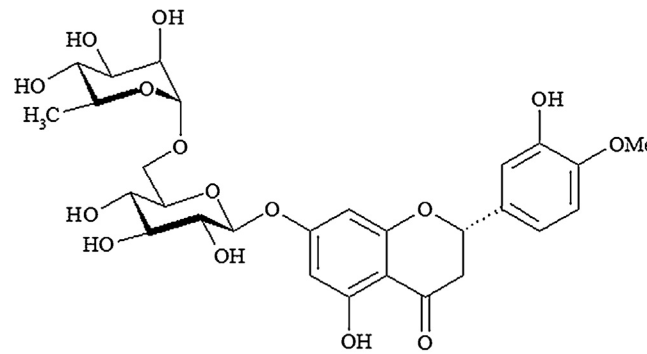
1. Introduction

Cancer is one of the most important global health problems which annually occurred in more than 12.7 million people in the world (Jemal et al., 2011). The term cancer refers to a group of disease caused by out-of-control cell growth with invasive behaviors (Dunn, 2012). Statistically, lung, prostate, colorectal and stomach cancers are the most common cancers among the men and breast, colorectal, lung, and cervical cancers are the most common cancers among the women (Jemal et al., 2011). Up to now, therapeutic strategies for cancer include combination of radiation therapy, chemotherapy, surgery, and targeted therapy (Curti et al., 2014; Demain and Vaishnav, 2011; Fulda, 2010; Mehta et al., 2010; Newman and Cragg, 2012; Tanaka et al., 2011). Recent research has been focused on the promising effects of antioxidants for the treatment of various diseases (Newman and Cragg, 2012; Gullett et al., 2010; Wang et al., 2012). Nowadays, much attention has been paid to natural antioxidants due to their high efficacy and low adverse effects in comparison with synthetic antioxidants (Alinezhad et al., 2013; Nabavi et al., 2012, 2015, 2014, 2013a,b). During past two decades, a plethora of scientific evidences showed that natural products especially plants and their polyphenolic compounds have different beneficial effects on human health (Del Rio et al., 2013; Pandey and Rizvi, 2009; Scalbert et al., 2005; Visioli et al., 2011). Among them, flavonoids known as the most important bioactive compounds which have beneficial effects on different cancerous tissues (Chahar et al., 2011; Nabavi et al., 2013a; Spatafora and Tringali, 2012). Several epidemiological studies indicate an inverse association between flavonoids intake in diet and risk of cancers (Romagnolo and Selmin, 2012; Somerset and Johannot, 2008). Hesperidin is a major dietary flavanone which is abundantly found in many citrus fruits like oranges and exhibits a wide range of biological properties. Moreover, hesperidin is one of the safest and important bioflavonoids which is found in *Citrus* genus (Rutaceae) (Roohbakhsh et al., 2014). Hesperidin has been recognized as a potent anti-inflammatory, anti-carcinogenic and anti-oxidant agent according to the data obtained from numerous *in vitro* and *in vivo* studies (Roohbakhsh et al., 2015). Until now, there are some scientific reports about anticancer effects of hesperidin and/or its aglycone, hesperetin, under both *in vitro* and *in vivo* conditions (Ghorbani et al., 2012; Roohbakhsh et al., 2015; Shahbazi et al., 2014; Yumnam et al., 2014). The aim of this paper is to critically review the available scientific reports on anticancer effects of hesperidin.

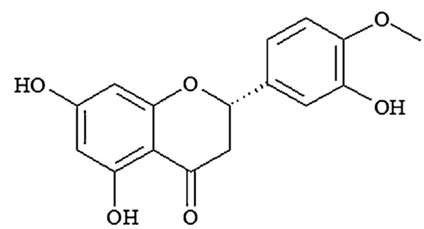
2. Chemistry of hesperidin

Chemical structure of hesperidin contains an aglycone, hesperetin (methyl eriodictyol) (Fig. 1) which is bonded to rutinose (Garg et al., 2001). Glycoside moiety of hesperidin is a disaccharide which contains rhamnose and glucose and presented in two isomeric forms including rutinose or neohesperidose (Garg et al., 2001). Rutinose is a disaccharide with chemical name 6-O-(α-L-Rhamnopyranosyl)-D-glucopyranose and/or 6-O-(α-L-Rhamnosyl)-D-glucose which is widely presented in the herbal sources (Garg et al., 2001; Konishi et al., 1983; Shimoda et al., 2008). Neohesperidose (2-O-alpha-L-Rhamnopyranosyl-D-glucopyranose) is also disaccharide and found in *Citrus* species as hesperetin 7-O-neohesperidoside (Bilbao et al., 2007).

In the chemical skeleton of hesperidin, glucose is bonded to aglycone based structure (hesperetin) and rhamnose is bonded to this structure from glucose moiety (Garg et al., 2001). The aglycone structure, hesperetin is a bioflavonoid with chemical name (*S*)-2,3-dihydro-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (Garg et al., 2001).



Hesperidin



Hesperetin

Fig. 1. Chemical structures of hesperidin and its aglycone, hesperetin.

Hesperidin is produced through alkaline hydrolysis of phloroglucinol and hesperetenic acid and it can convert in to the hesperetin, D-glucose and L-rhamnose during acid hydrolysis (Garg et al., 2001; Ranganna et al., 1983). It has been reported that disaccharide moieties in the chemical structure of *Citrus* bioflavonoids are responsible for their bitterness (Garg et al., 2001). For example, tasteless of *Citrus* species is due to the presence of rutinosides moiety and bitterness of *Citrus* species is due to the presence of neohesperidosides moiety (Garg et al., 2001). In nature, Hesperidin is widely found as the rutinoside form, which is non-bitter (such as orange) (Garg et al., 2001; Ooghe et al., 1994). However, in the grapefruit, hesperidin is presented as neohesperidosides form (Garg et al., 2001; Ooghe et al., 1994). It is well known that presence of hydroxyl moieties in the both aromatic and heterocyclic rings are responsible for biological activities of hesperidin (Garg et al., 2001). There is a close correlation between presence and number hydroxyl moieties with antioxidant capacities of hesperidin (Garg et al., 2001). In addition, hesperidin can penetrate into the blood–brain barrier and possesses neuroprotective actions (Garg et al., 2001; Mitsunaga et al., 2000).

3. Food sources

Hesperidin is widely found in epicarp, mesocarp, and endocarp of different *Citrus* species (Fig. 2) (Garg et al., 2001). In addition, *Citrus* juice is another source of hesperidin (Kanaze et al., 2003). It has been isolated at large scale from the rinds of *paradisi* Macfad., *Citrus sinensis* (L.) Osbeck, and *Citrus unshiu* Marcovitch. (Barthe et al., 1988; Inoue et al., 2010; Rouseff et al., 1987). It has also been reported from other *Citrus* species such as *Citrus aurantium* L. var. dulcis (sour oranges) and *Citrus reticulata* Blanco (tangerine or mandarin) (Rouseff et al., 1987). It has been demonstrated that the levels