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Review Article

Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases

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ABSTRACT

Hesperidin (Hsd) and its aglycone, hesperetin (Hst), are two flavonoids from citrus species that have various biological properties, particularly those for the prevention of cancer and cardiovascular diseases. Studies have shown both anti-cancer and cancer chemopreventive effects for Hsd and Hst. Cancer chemopreventive properties of Hsd and Hst are mainly associated with their antioxidant, radical scavenging and anti-inflammatory activities. In addition, Hsd and Hst interfere at different stages of cancer. Unlike conventional anti-cancer drugs, Hsd and Hst inhibit tumor growth by targeting multiple cellular protein targets at the same time, including caspases, Bcl-2 (B-cell lymphoma 2) and Bax (Bcl-2 associated X protein) for the induction of apoptosis, and COX-2 (cyclooxygenase-2), MMP-2 (matrix metalloproteinase-2) and MMP-9 for the inhibition of angiogenesis and metastasis. The results of the recent basic and clinical studies revealed the beneficial effects for Hst, Hsd and their derivatives in the treatment of heart failure and cardiac remodeling, myocardial ischemia and infarction, and hypertension. In addition, the valuable effects of Hst and Hsd in the treatment of diabetes and dyslipidemia with their anti-platelet and anti-coagulant effects make them good candidates in the treatment of various cardiovascular diseases. In this review, new findings regarding the molecular targets of Hsd and Hst, animal studies and clinical trials are discussed.

Contents

Introduction

Flavonoids are a large group of phenolic compounds that are widely distributed in plants. To date, a large number of these compounds have

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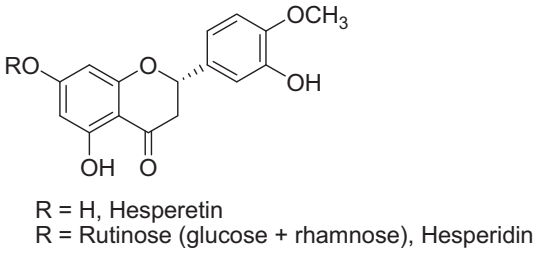

Fig. 1. The chemical structures of hesperidin and hesperetin.

been evaluated both in their free state and as glycosides. In addition to this work, several biological properties have been reported from flavonoids, including antioxidant, anticancer, cancer chemopreventive, and anti-inflammatory properties [29,67]. Hesperidin (Hsd) is a flavanone glycoside (a subclass of flavonoids) that is found abundantly in citrus fruits. Its aglycone form is called hesperetin (Hst). Hsd was first isolated from citrus peel by the French chemist Lebreton. Because of its various biological activities, Hsd is also called a bioflavonoid. Hsd is a β-7-rutinoside of Hst because it consists of an aglycone, Hst, and a disaccharide, rutinose (Fig. 1).

Both Hsd and its aglycone Hst have shown various biological activities [24]. For example, Hsd possesses vitamin-like activity and can decrease capillary permeability (vitamin P), leakiness and fragility. It also showed antioxidant, anti-inflammatory, anticarcinogenic and antiallergic properties [24]. The biological activities of Hsd together with its physicochemical properties were reviewed in a paper published by Garg et al. [24]. However, a large number of studies have been published since then describing its new pharmacological activities, molecular targets and mechanisms of action. For example, the effects of Hsd on the central nervous system have been a topic of research during the past decade, while they have not previously been investigated [21, 74]. New findings also revealed that the antioxidant activity of Hsd was not only limited to its radical scavenging activity, but it augmented the antioxidant cellular defenses via the ERK/Nrf2 signaling pathway as well [10,20].

This review addresses the biological and pharmacological properties of Hsd and Hst that have been reported since 2001. Additionally, the current paper provides a deeper insight into the mechanisms of action and molecular targets of Hsd and Hst and shows the gaps in our knowledge about Hsd, which deserve further research.

All of the relevant databases were searched for the terms “hesperidin”, “hesperetin” and “citrus flavonoid” without limitation from 2001 to 30th June 2014. Information on Hsd and Hst was collected via electronic search by using Pubmed, Scopus, Web of Science and ScienceDirect.

Anticancer and cancer chemopreventive properties

There is a noticeable body of evidence that concerns Hsd and Hst actions against tumors. Promising results of these in vivo and in vitro studies have been mostly justified by antioxidant properties of these compounds. Table 1 summarizes the main features of published investigations that focus on the chemopreventive and chemotherapeutic properties of Hsd and Hst.

The two following in vivo studies exhibited promising antineoplastic effects of Hsd.

Kamaraj et al. observed that while the total body weight was decreased in tumor-bearing mice, pre- and post-treatment with Hsd resulted in a significant increase in the body weight and also significantly decreased the lung weight and tumor incidence. In addition, lung tumor caused an increase in lipid peroxides, AHH (aryl hydrocarbon hydroxylase), γ-GT (gamma glutamyl transpeptidase), 5′-ND (5′-nucleotidase) and LDH (lactate dehydrogenase), and decreased enzymatic and non-enzymatic antioxidant activities, which were altered to almost the normal state by Hsd pre- and post-treatment [41].

It was shown that Hsd (30 mg/kg body weight for 45 days) treatment had antineoplastic and antigenotoxic effects due to the modulation of the energy reservoir of the cell and oxidative phosphorylation. In addition, Hsd inhibited enzyme leakage by maintaining the integrity of the lysosomal membrane [60].

One of the main characteristics of Hsd is its radical scavenging property, which results in normalization of the redox profile of treated cells. In this regard, Hsd-treated cells showed less ROS and improved the antioxidant system.

While not being effective at low concentrations (1–10 μM), Hst at higher doses (50 and 100 μM) decreased the development of vessel-like tube structures and PECAM mRNA expression (a vascular marker), thus having anti-angiogenic properties. On the other hand, in the presence of H_2O_2, Hst (50 and 100 μM) scavenged ROS, and at 100 μM concentration, it reduced the lipid peroxidation biomarker and 8-iso-prostaglandin F2α. It is worth mentioning that in contrast to other flavonoids that possess prooxidant properties, Hst even at the highest dose did not cause acute cell damage or cytotoxic effects but instead induced a mild oxidative stress [14].

In the model of rat colon carcinogenesis that is induced by 1,2-dimethylhydrazine (DMH), oral administration of Hst significantly decreased intestinal tumor incidents, which was proposed to be mainly due to the enhancement of the antioxidant defense. During the initiation, post-initiation and entire period phases, Hst brought the liver and colon lipid peroxidation profiles back to normal levels. While DMH treatment decreased the catalase (CAT) and superoxide dismutase (SOD) activities, Hst significantly reversed this trend and potentiated the colon and liver antioxidant system. In addition, Hst caused no toxicity to the main organs [5].

It was shown that benzo(a)pyrene [B(a)P] treatment weakened the antioxidant system in lung mitochondria regarding superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, reduced glutathione, vitamin E, and vitamin C. These factors were back to being almost normal following pre- and post-treatment with Hsd. A similar observation was recorded regarding the levels of mitochondrial ATP levels in the lungs. Furthermore, Hsd preserved mitochondrial integrity and saved it from damage, which suggests its usage as a chemopreventive agent [40].

Cytotoxic effects of Hsd on breast (MCF-7), larynx (HEp-2) (with the least IC_{50}), cervix (HeLa) and liver (HpG-2) carcinoma cell lines were proposed to be related to its antioxidant capacity [4].

Diet supplementation with Hsd (30 mg/kg b.w.) for rats bearing 7,12-dimethybenz(a) anthracene-induced breast cancer resulted in reduced lipid peroxidation and reversing the marker enzymes to normal levels. In addition, cell structure and integrity were recovered via an increase in the total protein and nucleic acid content, which was mainly mediated by the radical scavenging effects of Hsd [61].

There are some studies that concern the pharmacodynamic and pharmacokinetic interactions of Hsd and chemotherapeutic agents.

Cyclophosphamide (CP) administration for the treatment of colon carcinoma resulted in a significant decrease in the WBC (white blood cells) count on days 4, 7, 10 and 14. Hsd treatment increased the WBC count on days 4 and 7, but it had no effect on the counts on days 10 and 14. The co-administration of Hsd and CP reduced the CP effects on tumor growth, which is hypothesized to be due to either its antioxidant effect or its interaction with CP metabolism in the liver [31].

In addition, the effect of Hsd on the multidrug-resistant human leukemia cell line P-gp showed that Hsd increased doxorubicin toxicity toward the cell line due to the decreased P-gp activity [19].

Alteration of inflammatory responses

It was shown that Hsd modifies the production of cytokines and enzymes that are involved in inflammation. This interaction with inflammatory processes could play a crucial role in the anti-cancer effects of Hsd.

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