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Protective effects of hesperidin on oxidative stress, dyslipidaemia and histological changes in iron-induced hepatic and renal toxicity in rats

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ABSTRACT

The present study was to evaluate the protective role of hesperidin (HDN) against iron-induced hepatic and renal toxicity in rats. Administration of iron (30 mg/kg body weight) intraperitoneally for 10 days, the levels of serum hepatic markers, renal functional markers, lipid profile, lipid peroxidation markers and iron concentration in blood were significantly ($p < 0.05$) increased. The toxic effect of iron was also indicated by significant ($p < 0.05$) decrease in the levels of plasma, liver and kidney of enzymatic and non-enzymatic antioxidants. Administration of hesperidin at different doses (20, 40 and 80 mg/kg body weight) significantly ($p < 0.05$) reversed the levels of serum hepatic markers, renal functional markers, lipid profile, lipid peroxidation markers, restored the levels of hepatic, renal enzymatic antioxidants and non-enzymatic antioxidants with decrease in iron concentration in blood. Hesperidin at a dose of 80 mg/kg body weight exhibits significant protection on hepatic and renal when compared with other two doses (20 and 40 mg/kg body weight). All these changes were corroborating by histological observations of liver and kidney. This study demonstrated the protective role of hesperidin in reducing toxic effects of iron in experimental rats.

1. Introduction

Heavy metals can be classified as potentially toxic (arsenic, cadmium, lead, etc.), probably essential (vanadium, cobalt) and essential (copper, zinc, iron, manganese, etc.). Toxic elements can be very harmful even at low concentration when ingested over a long time period [1]. They might come from the soil, environment, fertilizers and/or metal-containing pesticides, introduced during the production process or by contamination from the metal processing equipment. Food consumption had been identified as the major pathway of human exposure to toxic metals, compared with other ways of exposure such as inhalation and dermal contact [2].

Humans are constantly exposed to hazardous pollutants in the environment-for example, in the air, water, soil, rocks, diet or workplace. Trace metals are important in environmental pathology because of the wide range of toxic reactions and their potential adverse effects on the physiological function of organ systems. Exposures to toxic trace metals have been the subject of numerous environmental and geochemical investigations, and many studies have been published on the acute and/or chronic effects of high-level exposures to these types of agents; however,

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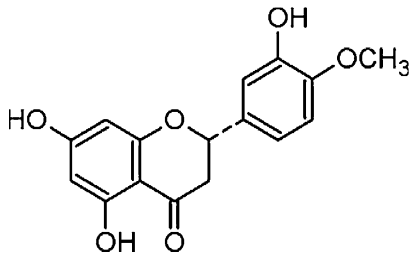

Fig. 1. Structure of hesperidin.

much fewer data are available concerning the health effects of low-dose chronic exposure to many trace metals [3].

Iron is an important trace element of the body, being found in functional form in hemoglobin, myoglobin, cytochrome enzymes with iron sulphur complexes [4]. Liver is one of the largest organs in the human body and the main site for intense metabolism and excretion [5]. Hepatotoxicity is the most common finding in patients with iron overloading as liver is mainly the active storage site of iron in our body [6]. Hydroxy radical may form due to excess iron concentration in kidney that leads to progression of tubular injury. Clinical evidence showed that iron deposition in kidney associated with the anemia during kidney diseases [7].

Although an optimum level of iron is always maintained by the cells to balance between essentiality and toxicity, in some situations it is disrupted, resulting in iron overload which is associated to the oxidative stress induced disorders including anemia, heart failure, hepatocellular necrosis and cirrhosis [8]. In iron overload-induced diseases, iron removal by iron chelation therapy is an effective life-saving strategy. Iron overload increases the formation of reactive oxygen species (ROS) which involves the initiation of lipid peroxidation, protein oxidation and liver fibrosis. However, excess iron is stored as Fe^{3+} in ferritin and iron overload sustains for long period and released depends on the efficiency of iron chelating drugs [9]. The currently available iron-chelating agents used clinically are deferoxamine, 1,2-dimethyl-3-hydroxypyrid-4-one (deferiprone, L1), and deferasirox [10]. The body lacks to excrete excessive iron and therefore the interest has been focused to develop the potent chelating agent capable of complexing with iron and promoting its excretion.

Flavonoids are phenolic compounds abundantly distributed in plants. It has been reported that most of them are effective antioxidants [11]. They were suggested to present a good scavenger to iron ions [12]. Hesperidin (3,5,7-trihydroxy flavanone-7-rhamnoglucoside) is a pharmacologically active bioflavonoid found in citrus fruits, with good free radical scavenging as well as anti-lipid peroxidation properties in biological membranes [13]. Hesperidin (Fig. 1) possesses highest reducing power, chelating activity on Fe^{2+}, hydrogen radical scavenging and hydrogen peroxide scavenging activities when compared with natural and synthetic antioxidants such as α-tocopherol, ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and trolox [14]. Clinical and experimental data showed the antihypertensive, lipid-lowering, insulin-sensitizing, antioxidative and anti-inflammatory properties of hesperidin [15]. However, the protective role of hesperidin against iron-induced liver and kidney injury has not been investigated. Hence we proposed to investigate whether administration of hesperidin offers protection against iron-induced liver and kidney injury.

2. Materials and Methods

2.1. Chemicals and drugs

Hesperidin (PubChem CID: 10621); ferrous sulfate (PubChem CID: 24393); 2-thiobarbituric acid (PubChem CID: 2723628); butylated hydroxytoluene (PubChem CID 31404); reduced glutathione (PubChem CID:745); 2,2′-dipyridyl (PubChem CID: 1474); xylenol orange (PubChem CID: 73041); 2,4-dinitrophenylhydrazine (PubChem CID:CID: 3772977); γ-glutamyl-*p*-nitroanilide (PubChem CID: 3772977); 5,5′-dithiobis(2-nitrobenzoic acid) (PubChem CID: 6254); trichloroacetic acid (PubChem CID: 6421); phenazine methosulfate (PubChem CID 9285); nitroblue tetrazolium (PubChem CID: 9281); reduced nicotinamide adenine dinucleotide (PubChem CID: 439153); 1-chloro-2,4-dinitrobenzene (PubChem CID: 6) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). The rest of the chemicals were obtained from S.D. Fine Chemicals Mumbai, India and were of analytical grade.

2.2. Experimental animals

Adult male albino rats of Wistar strain (200–220 g) were used for the experiment. The animals were housed in polypropylene cages and maintained in 12-h light/12-h dark cycle, 50% humidity and 25 ± 2 °C. The animals had free access to standard pellet diet (M/S. Pranav Agro Industries Ltd., Bangalore, India) and water ad libitum. This study was approved (Vide. No. 644, 2009) by Institutional Animal Ethics Committee of Annamalai University and the study conducted in accordance with the "Guide for the Care and Use of Laboratory Animals".

2.3. Experimental design

Ferrous sulfate (30 mg/kg body weight) was dissolved in isotonic saline and injected intraperitoneally (i.p). Hesperidin powder was dissolved in 0.1% carboxy methyl cellulose and each rat received daily 1 ml at a dose of 20, 40 and 80 mg/kg body weight orally by intragastric tube throughout the experimental period.

The animals were randomly divided into six groups of six rats in each group.

Group I: served as control (isotonic saline).

Group II: animals were orally administered with hesperidin alone (80 mg/kg body weight).

Group III: animals received ferrous sulfate (30 mg/kg body weight).

Group IV–VI: animals were treated with ferrous sulfate (30 mg/kg body weight) following oral administration of hesperidin (20, 40, 80 mg/kg body weight) for 10 days.