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Original article

Antioxidant potential of hesperidin and ellagic acid on renal toxicity induced by mercuric chloride in rats

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ABSTRACT

The health effects of mercury are highly dependent on the different chemical forms of mercury. Inorganic mercury has a non-uniform distribution after absorption being accumulated mainly in kidney tissue causing acute renal failure. The purpose of this work was to study the influence of hesperidin and ellagic acid followed by mercuric chloride induced kidney damage. At sub-lethal dose of mercuric chloride (1.23 mg/kg B.W) was administrated in rats for 7 days. The results revealed that treatment of mercuric chloride caused marked enhanced level of lipid peroxidation (LPO) content and significantly decreased in the level of reduced glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) activities in the kidney tissue. Hesperidin is a natural flavonoid and a strong antioxidant helps to prevent oxidative damage. Ellagic acid has a chemo protective effect in cellular models by reducing oxidative stress. The treatment of hesperidin and ellagic acid (5 mg/kg B. W) in the kidney tissue shows a significantly decreasing in the level of oxidant content and simultaneously an enhanced level of antioxidant properties by the way of recovery in kidney tissues. Antioxidant and non-antioxidant enzymes (LPO, GSH, GPx, SOD, CAT) activities were also an enhanced to near normal level when compared to mercury treated group. These observations of the present experimental study demonstrated a preliminary protective effect of hesperidin and ellagic acid against mercuric chloride intoxicated rat kidney tissue.

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1. Introduction

Mercury is receiving considerable attention today because of its ubiquity as an environmental pollutant. Moreover, mercury pollution and poisoning have imposed a huge economic cost on environmental remediation and public health [1,2]. The toxicity of mercury exposure is in part a function of increased oxidative stress. The increase in oxidative stress is possibly from the depletion of thiol compounds, inhibition of antioxidant enzymes, or both [3,4] leading to cell injury damage to bimolecular and lipid peroxidation [5,6]. Mercury bound to SH group may result in decreased glutathione level leading to an increasing of reactive oxygen species like superoxide anion radical hydrogen peroxide and hydroxyl radical [3,7]. In fact, free radical formation and subsequent lipid peroxidation was reported as cays of cell death in the mercury induced nephrotoxicity [8,9]. Mercury salts are very toxic to the kidneys causing acute tubular necrosis immunological glomerulao nephritis or nephritic syndrome. Central neuropathy can also occur from mercury exposure [7].

Free radicals and oxidative stress have been found to play a key role in many diseases and in this content antioxidants have gained a lot of importance because of their potential as prophylactic and therapeutic agents in many diseases [10]. Mercury is accumulated and expresses toxicity primarily to the kidney acute renal failure is a dramatically clinical syndrome, it develops after exposure to high doses of Hg and is frequently fatal. Toxic effects caused by mercury itself and by numerous secondary reaction in the body, reflect many biochemical parameters in blood and kidney tissue, [5,11]. As an example mercuric chloride induced a nephropathy that is restricted primarily to the proximal tubule, at the lowest doses of mercury [11,12].

The kidneys excrete waste products of metabolism and play an important role in maintaining the homeostasis by regulating the body water and solute balance. In addition to the excretory function, the kidney tissues also act as a harbor of mercury and its compounds has been shown to accumulate in kidneys along with in other organs [13]. A specific concern associated with mercury exposure in humans is the need for effective therapy in dealing with intoxication. In this respect, chelating therapy is the most commonly used and seen as the least invasive [5].

Hesperidin is a flavonone glycoside is an inexpensive and abundant byproduct of citrus cultivation [14]. Hesperidin also exhibited a strong superoxide radical scavenging activity [15,16]. Taken

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together, hesperidin has potential as an antioxidant agent against free radicals and deserves clinical trial in the near future [17,18]. Mohammed et al. [19] have recently reported the structural activity effects of hesperidin on the antioxidative activities were investigated by using a simple free radical scavenging system including, reducing power, chelating activity on Fe^{2+} free radical scavenging, total antioxidant, superoxide radical scavenging, hydrogen peroxide scavenging and hydroxyl radical scavenging activities in an attempt to understand its mechanism of action which may pave the way for possible therapeutic applications [20,21]. A number of researchers have examined the antioxidant activity and free radical scavenging properties of hesperidin using a variety of assay systems [18].

Ellagic acid is pharmacologically active and has been found to control hemorrhage in animal tests suggest that red raspberry may reduce levels of glucose in animals and therefore may help in the management of diabetes [22]. Ellagic acid inhibits lipid peroxidation necrosis of skin flaps enhancing preservation of grafting procedures. Ellagic acid has a marked inhibitory effect on acid secretion and the occurrence of stress induced gastric lesions [23,24]. Ellagic acid has been shown to exert a potent scavenging action on super oxide anion and hydroxyl anion *in vitro*, as well as the protective effects against lipid peroxidation. The polyphenol compounds could have both antioxidant and prooxidant properties, depending on the concentration and free radical source [25].

In the present study was aimed to investigate the protective effect of hesperidin and ellagic acid as an oral supplement against mercuric chloride induced nephrotoxicity in rats.

2. Materials and methods

2.1. Test chemicals

Mercuric chloride ($HgCl_2$), hesperidin, ellagic acid and all other necessary reagents of analytical grade were purchased from Hi-Media laboratories Ltd, Mumbai, India.

2.2. Animals

Healthy male albino rats (150–200 g) were procured from the Central Animal House, Department of Experimental Medicin, Raja Muthiah Medical College and Hospital Annamalai University and maintained in an air condition room (25 ± 3 °C) with a 12-h light/12-h dark cycle. Feed and water were provided *ad libitum* to all the animals. The study protocols were approved by the Institutional Animal Ethics Committee of Rajah Muthiah Medical College and Hospital (Reg No.: 160/1999/CPCSEA, Proposal Number: 954), Annamalai University, Annamalainagar.

2.3. Experimental design

The animals were randomized and divided into six groups, each group containing six rats. The toxic dosage of mercuric chloride has been determined (sub-lethal dose of $HgCl_2$ 1.23 mg/kg body weight) from our previous study carried out in our lab. And it has sufficient to elicit mild or moderate oxidative stress in rats (Sankarsamipillai and Jagadeesan, in 2007):

- group I ($n = 6$): only vehicle (0.9% Nacl) was given to these animals (control);
- group II ($n = 6$): the animals were administered HgCl2 1.23 mg/kg body weight in 0.9% Nacl intraperitoneally for 7 days;
- group III ($n = 6$): the animals were administered orally hesperidin (5 mg/kg body weight) alone for 7 days;
- group IV ($n = 6$): the animals were administered hesperidin after the intoxication of mercuric chloride administration;
- group V ($n = 6$): the animals were administered orally ellagic acid (5 mg/kg body weight) alone for 7 days;
- group VI ($n = 6$): the animals were administered ellagic acid after the intoxication of mercuric chloride administration.

At the end of the experimental duration, the rats were anaesthetized with intramuscular injection of ketamine hydrochloride (24 mg/kg body weight) and sacrificed by cervical dislocation. The whole kidney tissue was isolated immediately from the animal and kept in an ice-cold saline and then used for estimation of oxidant and antioxidant properties and also for histological studies.

2.4. Estimation of lipid peroxidation (TBARS)

The concentration of TBARS in the kidney tissue was estimated by adopting the method of Nichans and Samuelsen [26]. Known amount of whole kidney tissue homogenate was prepared in Tris-HCl buffer (pH 7.5). One milliliter of the tissue homogenate was taken in a clean test tube and 2.0 mL of TBA-TCA-HCL reagent was added and then mixed thoroughly. The mixture was kept in a boiling water bath (60 °C) for 15 minutes. After cooling, the mixture was taken to read the absorbance of the chromophore at 535 nm against the reagent blank in a UV-visible spectrophotometer (Spectronic-20, Bausch and Lamb). 1, 1', 3, 3' tetra methoxy propane was used to construct the standard graph. Values were expressed as n moles of MDA released/100 mg.

2.5. Estimation reduced glutathione (GSH) activity

The level of reduced glutathione in kidney tissue was estimated by the method of Ellaman [27]. A known weight of tissue was homogenized in phosphate buffer (0.1 M. pH 7.0) and centrifuged at 2500 rpm for 5 minutes. Also, 0.2 mL of the sample (Supernatant) was taken in a clean test tube and 1.8 mL of EDTA solution was added. To this 3.0 mL of precipitating reagent was added and mixed thoroughly and kept for 5 minutes before centrifugation at 3000 rpm for 10 minutes. In a clean test tube, 2.0 mL of the content mixture was taken and to this 4.0 mL of 0.3 M disodium hydrogen phosphate solution and 1.0 mL of DTNB reagents were added. The appearance of yellow colour was read at 412 nm in UV-visible spectrophotometer (Spectronic-20, Bausch and Lamb). A set of standard solution containing 20–100 μg of reduced glutathione was treated similarly. Values are expressed as μg/100 mg protein.

2.6. Estimation of superoxide dismutase (SOD) activity

Superoxide dismutase in the kidney tissue was assayed by adopting the method of Kakkar [28]. The kidney tissue was homogenized with 2.0 mL of 0.25 M sucrose solution and the centrifuged the contents at 10,000 rpm for 30 minutes in a cold centrifuge. After completing the centrifugation, the supernatant was taken in a clean test tube and the content was dialysed against the Tris-HCl buffer and then mixed the contents thoroughly. The contents were centrifuged again at 3000 rpm for 15 minutes. The supernatant was taken in a clean test tube and then 1.2 mL of sodium pyrophosphate buffer, 0.1 mL of phenazine methosulphate and 0.3 mL of nitroblue tetrazolium reagents were added. The sample mixture (enzyme preparation) was kept in water bath at 30 °C for 90 seconds and appropriately diluted enzyme preparation in a total volume of 3 mL with double distilled water. The reaction was started by the addition of 0.2 mL NADH. After completing the incubation period, the reaction was stopped by the addition of 1 mL glaicial acetic acid. The reaction mixture was stirred vigorously and shaken with 4 mL n-butanol. The mixture was allowed to stand for 10 minutes and

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