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Quercetin protects against acetaminophen-induced hepatorenal toxicity by reducing reactive oxygen and nitrogen species

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Abstract

High or toxic doses of acetaminophen (APAP), a mild analgesic and antipyretic drug, can cause life-threatening hepatic and renal dysfunction. This study is designed to investigate the potential protective role of quercetin to attenuate the hepatorenal toxicity induced by a high single oral dose (3 g/kg) of APAP in rats. Three main groups of Sprague-Dawley rats were used: quercetin, APAP and quercetin plus APAP-receiving animals. Corresponding control animals were also used. Interestingly, oral supplementation of quercetin (15 mg/kg/day) prior to APAP intoxication dramatically reduced APAP-induced hepatorenal toxicity as evidenced by measuring serum lipid profile, total protein, urea, creatinine, ALT, AST, ALP, G-GT and liver tissue content of TC and TG. Quercetin treatment markedly prevented the generation of TBARS and PCC with substantial improvement in terms of GSH and activities of antioxidant enzymes in both liver and kidney homogenates. The relationship between quercetin and NO levels which is still a matter of debate, was also investigated. NO levels in serum, liver and kidney tissues were significantly inhibited in quercetin pre-treated animals. Furthermore, quercetin administration significantly inhibited the reduction of liver and kidney contents of ATP parcels associated with this hepatorenal toxicity. These results suggest that the protective role of quercetin in the prevention of APAP-induced hepatorenal toxicity in rats was associated with the decrease of oxidative and nitrosative stress in hepatic and renal tissues as well as its capacity to improve the mitochondrial energy production. However, clinical studies are warranted to investigate such an effect in human subjects.
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Keywords: Acetaminophen; Hepatorenal; Nitric oxide; Quercetin; Rat

1. Introduction

N-acetyl-p-aminophenol (acetaminophen; APAP) is an effective over-the-counter analgesic and antipyretic drug. It is primarily metabolized by the liver and excreted by the kidneys [1]. Therapeutic doses of APAP are generally considered safe. Conversely, overdosing or chronic use can result in both hepatotoxicity and nephrotoxicity, although the latter's toxicity is less common and independent of APAP-induced hepatotoxicity. APAP is considered as the most frequent cause of acute liver failure in many countries [2–4]. APAP toxic metabolite, N-acetyl-para-amino-benzoquinone imine (NAPQI), is thought to be

Abbreviations: ALP, alkaline phosphatise; ALT, alanine transaminase; APAP, acetaminophen; AST, aspartate transaminase; ATP, adenosine triphosphate; G-GT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NAPQI, N-acetyl-para-amino-benzoquinone imine; NO, nitric oxide; NOS, nitric oxide synthase; PCC, protein carbonyl content; ROS, reactive oxygen species; TBARS, thiobarbituric acid reacting substances; TC, total cholesterol; TG, triglycerides.

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responsible for APAP-induced hepatorenal toxicity. NAPQI is produced in excessive amounts through cytochrome P450 system in APAP overdose, and only part of it can be detoxified by conjugation with reduced glutathione (GSH). The remaining part of NAPQI binds to cellular proteins and induces oxidative stress, which initiates cell death [5–7]. Besides, mitochondrial dysfunction observed after APAP overdose is due to covalent binding of NAPQI to mitochondrial proteins, which consequently inhibits mitochondrial respiration leading to ATP depletion [8,9].

The flavonol quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a polyphenolic compound found in substantial amounts in vegetables, fruits, herbs, leaves, seeds, tea and coffee. It has been reported to exhibit cell protection owing to its antioxidant, antinociceptive, and anti-inflammatory actions [10,11]. Nevertheless, quercetin is still a subject of various re-assessment studies concerning its hepatic and renal protective effect due to the comparative little information available.

In view of this, an experimental study was designed to investigate whether oral supplementation of quercetin protects against APAP-induced hepatorenal toxicity, and if so, what is the mechanistic basis of such protective effects in this toxicity paradigm.

2. Materials and methods

2.1. Chemicals

APAP and quercetin were purchased from Sigma–Aldrich Corp (St. Louis, MO, USA). All other chemicals used were of the highest available commercial grade.

2.2. Animals

Forty male Sprague-Dawely rats, weighing 160–180 g, were obtained from the animal facility of the Faculty of Pharmacy at Al-Azhar University, Cairo, Egypt. The animals were fed a standard chow (El-Nasr Company, Abou-Zaabal, Cairo, Egypt) with free access to water, and kept in wire-floored cages under standard laboratory conditions at room temperature (25 ± 2 °C), and a 12-h light/12-h dark cycle. The animal experiments were conducted according to the guidelines for the care and use of laboratory animals stated by College of Pharmacy, Al-Azhar University, Cairo, Egypt.

2.3. Experimental design

Animals were randomized and divided into four groups of ten animals each. One group received quercetin (15 mg/kg), suspended in arabic gum 1%, by gavage for twenty-one consecutive days [12,13]. The second group received a vehicle (arabic gum 1% suspension) by the same route of administration for twenty days and on the twentieth first day, a single dose of APAP (3 g/kg) suspended in arabic gum 1% was orally administered [14]. The third group received quercetin (15 mg/kg) for twenty-one days and on the last day, they received the single dose of APAP (3 g/kg) 1 h before quercetin. Last group of rats served as control and received only vehicle (arabic gum 1% suspension) along the experiment.

After the end of the specified period of the experiment, fasting blood samples were obtained from abdominal aorta under light ether anesthesia and used for determination of lipid profile, total protein, urea, creatinine, ALT, AST, G-GT, ALP, and NO levels. All animals were then euthanized by cervical dislocation. The liver and both kidneys from each rat were quickly removed, rinsed in ice-cooled physiological saline, blotted dry on filter paper, weighed, and then 10% (w/v) homogenate of the kidney was made in ice-cold 0.15 M KCl solution using a Potter–Elvehjem homogenizer. Aliquots of the homogenates were used for determination of tissue contents of TBARS, GSH, PCC, ATP and NO. The enzyme activities of GPx, GR and catalase were also carried out in liver and kidney homogenates. Total protein content of homogenates was determined to ascertain particular tissue parameters.

2.4. Biochemical analysis

Serum urea and serum creatinine were assayed according to the methods of Patton and Crouch [15] and Bonsnes and Taussky [16] respectively. The method of Fossati and Prencipe [17] was used to determine TG. TC was assayed according to the method of Roeschlau et al. [18]. HDL-C was determined following the method of Warnick et al. [19]. LDL-C was then calculated according to the equation of Friedewald et al. [20]: LDL-C = TC − HDL-C − TG/5. AST and ALT activities were determined according to the method of Reitman and Frankel [21]. The activities of ALP and G-GT were determined following the methods described by Bessey et al. [22] and Teitz [23] respectively. TG and TC of liver homogenate were determined following the same methods as for serum determination after lipid extraction. To extract lipids, aliquots of the liver homogenate were extracted with chloroform–methanol followed by separation and evaporation of the chloroform–methanol layer [24]. Liver and kidney homogenates were used for determination of lipid peroxides expressed as TBARS [25], PCC [26] and GSH [27]. Glutathione related enzymes: glutathione reductase, glutathione peroxidase and catalase were determined in the tissue homogenates following the methods of Pinto and Bartley [28], Rotruck et al. [29] and Aebi [30] respectively. Kidney and liver ATP contents were determined according to the method of Adams [31]. Serum and tissue concentrations of NO were measured spectrophotometrically as its stable metabolites, nitrate and nitrite, by the Griess et al.'s reaction [32]. The protein concentration of the collected serum and tissue samples were measured by the method of Lowry et al. [33].

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