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ORIGINAL ARTICLE

Protective effects of *Parinari curatellifolia* flavonoids against acetaminophen-induced hepatic necrosis in rats

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Abstract In the present study, we investigated the hepatoprotective potential of *Parinari curatellifolia* Planch (Chrysobalanaceae) in experimental rats in order to ascertain the validity of folkloric claims of its effectiveness in the treatment of hepatic-related disorders. Flavonoid extract of *P. curatellifolia* seed, PCF (10-, 20- or 30 mg/kg body weight) or silymarin (25 mg/kg), dissolved in corn oil, was administered by gavage to experimental animals once daily for 14 consecutive days before liver damage was chemically induced through the administration of acetaminophen (2 g/kg p.o.) on the 14th day. Hepatoprotection was assessed by analyzing liver homogenate and serum for markers of hepatotoxicity – alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) activities as well as prothrombin time (PT). Evaluation of biochemical indices of oxidative stress – level of lipid peroxides (LPO), activities of superoxide dismutase (SOD) and catalase, along with histological assessment of hepatic tissue sections were also carried out. Results revealed that all doses of PCF significantly ($P < 0.001$) and dose dependently prevented acetaminophen-induced increase in serum activities of hepatic enzymes (ALT, AST, GGT, LDH) and PT. Furthermore, PCF (10- and 20 mg/kg) significantly ($P < 0.001$) reduced lipid peroxidation in liver tissue and restored the activities of the antioxidant enzymes SOD and catalase toward normal levels. Histopathology of the liver tissue showed that PCF mitigated the toxicant-induced hepatocellular necrosis, reduced inflammatory cell infiltration and enhanced hepatocyte regeneration. The results indicated that *P. curatellifolia* flavonoids demonstrated remarkable hepatoprotective activity in acute liver injury caused by acetaminophen.
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1. Introduction

Drug-induced hepatotoxicity is a common cause of liver injury and accounts for approximately half of the cases of acute liver failure while mimicking all forms of acute and chronic liver diseases (Kaplowitz, 2004). Many prescription drugs currently

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in use have side effects. This contributes to hepatotoxicity which is becoming a serious health challenge since the liver is the major site of drug metabolism. Acetaminophen (paracetamol, N-acetyl-p-aminophenol) is a widely used over-the counter analgesic and antipyretic drug with only weak antiinflammatory property (Hinson et al., 2010). Acetaminophen could cause potentially fatal centrilobular hepatic necrosis. This occurs at high doses after its conversion by drug metabolizing enzymes to a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI) that covalently binds to proteins. At toxic doses, the metabolite suppresses the antioxidant defense system and the amount of covalent binding correlates with the relative hepatotoxicity (Jollow, 1973). Acetaminophen-induced liver injury is now a viable model of hepatotoxicity popularly employed by clinical researchers to investigate the beneficial effects of drugs (Olaleye et al., 2010a, 2010b; Pattanayak et al., 2011).

Finding sustainable therapeutic approach to minimizing liver damage is important owing to the prevalence of this condition. Medicinal plants used in the folkloric management of liver-related diseases or diseases related to other organs could be considered an alternative therapeutic approach (Salama et al., 2013). The use of herbal and dietary supplements in disease management dates back to thousands of years (Schuppan et al., 1999). The therapeutic value of medicinal plants is largely dependent on the constituent antioxidant phytochemicals, notably the phenolics. This stems from the role of oxidative stress in the etiology or progression of various diseases including hepatic-related ones. Flavonoids constitute a large subset and one of the most ubiquitous groups of plant phenolics (De Groot and Raven, 1998). They are the major active nutraceutical ingredients in plants (Tapas et al., 2008). Apart from their antioxidant property, flavonoids have been recognized to possess antiinflammatory, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities (Tapas et al., 2008). Silymarin, a standardized flavonoid extract from the seed of *Silybum marianum*, has been found to be highly effective as a hepatoprotective agent and is now widely used as a reference drug in hepatoprotective assessments (Gupta et al., 2011; Salama et al., 2013).

The seeds of *Parinari curatellifolia*, commonly called Mobola Plum, are widely employed in traditional medicine for the management of various diseases including hypertension (Olaleye et al., 2010a, 2010b), diabetes and liver-related illnesses (Ogbonnia et al., 2011). Phytochemicals in the seed include polyphenols, glycosides, alkaloids and anthraquinones (Ogbonnia et al., 2008) but none of these has been specifically correlated with hepatoprotection. Bearing in mind the role of oxidative stress in both hepatic and non-hepatic diseases, we presumed that the therapeutic efficacy of *P. curatellifolia* could be related to its antioxidant components. Since there is paucity of information in this regard, the present study was aimed at determining the possible effect of the flavonoid extract of *P. curatellifolia* seeds on acetaminophen-induced liver injury.

2. Materials and methods

2.1. Chemicals

Thiobarbituric acid (TBA), malonaldehyde bis-(dimethyl acetal) (MDA), Epinephrine, 5′,5′-Dithiobis-(2-nitrobenzoic acid) (DTNB) and hydrogen peroxide were purchased from Sigma Chem., Co. (London, UK). γ-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase and total protein kits were obtained from Randox Laboratories, UK. All other chemicals were of analytical grade and were obtained from British Drug Houses, (Poole, UK). The water used was glass distilled.

2.2. Plant material and preparation of crude extract

The seeds of *P. curatellifolia* were purchased at Oja-Oba in Akure, Nigeria, in the month of February, 2013. Botanical identification and authentication were carried out at the herbarium of the Forestry Research Institute of Nigeria (FRIN), Ibadan, Nigeria. The seeds were air dried, pulverized and stored in air-tight containers. The crude extraction of the seeds was carried out with 80% methanol (Komolafe et al., 2013) using a Soxhlet apparatus. The solvent was evaporated to dryness and the dried methanolic extract (ME) was stored in an airtight bottle at 4 °C until needed.

2.3. Preparation of flavonoid extract

A portion (3 g) of ME was dissolved in 20 ml of 1% H_2SO_4 in a standard flask and was hydrolyzed by heating on a water bath for 30 min. The resulting mixture was placed on ice for 15 min to allow for the precipitation of the flavonoid aglycone. The cooled solution was filtered and the solid on the filter (flavonoid aglycone mixture) was dissolved in 50 ml of warm 95% ethanol at 50 °C. The resulting solution was re-filtered into a 100 ml volumetric flask which was made up to mark with 95% ethanol. The filtrate finally collected was concentrated to dryness using a rotary evaporator (El-Olemy et al., 1994). A calculated mass of the dried extract was dissolved in an appropriate volume of corn oil to prepare various concentrations which were administered to experimental animals by oral gavage.

2.4. Animals

Adult male rats (Wistar strain) weighing 180–220 g, obtained from a private breeder and housed in the primate colony of the Department of Biochemistry, Federal University of Technology, Akure, Nigeria were used for this study. The animals were kept in wire mesh cages under controlled light cycle (12 h light/12 h dark), fed with commercial rat chow (Vital Feeds Nigeria Limited) ad libitum, and liberally supplied with water. All animal experiments were conducted according to the guidelines of National Institute of Health (NIH publication 85-23, 1985) for laboratory animal care and use.

2.5. Experimental design

Age-matched rats were divided into nine groups ($n = 6$) and treated as follows:

- **Group I (Control)** Corn oil (1 ml/kg).
- **Group II** Corn oil (1 ml/kg) + 2 g/kg Acetaminophen (ACE).
- **Group III** 10 mg/kg *P. curatellifolia* flavonoids (PCF) + 2 g/kg ACE.

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