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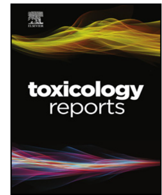

Hepato- and neuro-protective effects of watermelon juice on acute ethanol-induced oxidative stress in rats

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ABSTRACT

Chronic and acute alcohol exposure has been extensively reported to cause oxidative stress in hepatic and extra-hepatic tissues. Watermelon (*Citrullus lanatus*) is known to possess various beneficial properties including; antioxidant, anti-inflammatory, analgesic, anti-diabetic, anti-ulcerogenic effects. However, there is a lack of pertinent information on its importance in acute alcohol-induced hepato- and neuro-toxicity. The present study evaluated the potential protective effects of watermelon juice on ethanol-induced oxidative stress in the liver and brain of male Wistar rats. Rats were pre-treated with the watermelon juice at a dose of 4 ml/kg body weight for a period of fifteen days prior to a single dose of ethanol (50%; 12 ml/kg body weight). Ethanol treatment reduced body weight gain and significantly altered antioxidant status in the liver and brain. This is evidenced by the significant elevation of malondialdehyde (MDA) concentration; depletion in reduced glutathione (GSH) levels and an increased catalase (CAT) activity in the brain and liver. There was no significant difference in the activity of glutathione peroxidase (GPX) in the liver and brain.

Oral administration of watermelon juice for fifteen (15) days prior to ethanol intoxication, significantly reduced the concentration of MDA in the liver and brain of rats. In addition, water melon pre-treatment increased the concentration of GSH and normalized catalase activity in both tissues in comparison to the ethanol control group. Phytochemical analysis revealed the presence of phenol, alkaloids, saponins, tannins and steroids in watermelon juice. Our findings indicate that watermelon juice demonstrate anti-oxidative effects in ethanol-induced oxidation in the liver and brain of rats; which could be associated with the plethora of antioxidant phyto-constituents present there-in.

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1. Introduction

Excessive acute or chronic alcohol consumption poses a serious health hazard and can result into several metabolic disorders in hepatic and extra-hepatic diseases [1]. Alcohol is a commonly used hepatotoxin in experimental hepatopathy. Although the pathogenesis of alcohol-induced liver disease is not clearly defined, there is evidence that ethanol-induced liver injury is due to oxidative stress that leads to fibrosis and impaired liver functions [2,3]. Alcohol overuse is also characterized by central nervous system (CNS) intoxication symptoms, impaired brain activity, poor motor coordination, and behavioral changes [4]. Additionally, there are reports that ethanol exposure and metabolism results in cellular oxidative stress in the brain [5].

Excessive alcohol consumption commonly causes hepatic, gastrointestinal, nervous and cardiovascular injuries leading to physiological dysfunctions [6]. Cellular disturbances resulting from excessive alcohol consumption results in increased formation of oxidative stress biomarkers such as malondialdehyde (MDA); reduction in the level of reduced glutathione level and a decrease in the activities of antioxidant enzymes [7,8].

There is an increasing global interest concerning the use of medicinal plants in the prevention and treatment of different pathologies [9,10]. The beneficial effects of plants are attributed

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to the presence of secondary metabolites such as polyphenols, tannins, terpenoids, alkaloids, flavonoids [11]. Considering the central role played by free radicals in the initiation and progression of many diseases, the use of natural products with antioxidant constituents has been proposed as an effective therapeutic and/or preventive strategy against diseases and the search for potent and cost-effective antioxidants of plant origin has since increased [12]. The protective effects of antioxidant rich natural compounds against different toxicant mediated tissue injury has been identified in many studies [13–15]. In specific, numerous studies have demonstrated the protective effects of antioxidants such as pumpkin oil [16], resveratrol [17], curcumin [18], quercetin [19] and epigallocatechin-3-gallate [20] against alcohol induced tissue injury.

Watermelon (Citrullus lanatus) is one of such medicinal plant that has attracted scientific interest due to its bioactivities [21]. *C. lanatus* sp. is a natural source of antioxidants such as beta carotene [22], vitamin C [23], citrulline [24]. Watermelon with red flesh is also an excellent source of lycopene [25]. The tissue protective effects of watermelon juice have been reported [26,27]. Furthermore, the protective effects of watermelon juice against hepatotoxins such as carbon tetrachloride (CCl_4) and paracetamol has been demonstrated [23,28]. The anti-inflammatory, antioxidat, anti-ulcerogenic and anti-diabetic effects of watermelon have also been documented [29–31]. However, there is limited information on the neuroprotective and hepatoprotective effects of watermelon juice in acute ethanol-induced oxidative stress in rats.

The constituents of watermelon juice are known for their free radical scavenging activities and antioxidat effects. In the present study, the implication of oxidative stress in alcohol induced tissue damage, led to the hypothesis that watermelon juice which contains a mixture of antioxidants could be effective in ameliorating these effects. The present study evaluated the antioxidant effects of watermelon juice pre-treatment on acute ethanol-induced oxidative stress in the brain and liver of rats.

2. Materials and Methods

2.1. Chemicals

Glutathione (GSH), 5′,5′-dithiobis-2-nitrobenzene (DTNB), 2-thiobarbituric acid (TBA) and hydrogen peroxide (H_2O_2) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Sodium hydroxide (NaOH), copper(II) sulfate pentahydrate ($CuSO_4{\cdot}5H_2O$) and potassium iodide (KI) were obtained from the British Drug Houses (Poole, Dorset, UK). All other reagents were of analytical grade.

2.2. Preparation of watermelon juice

Watermelon fruits (green skin, red flesh) were procured from a fruit vendor in a local market in Iwo, Osun state, Nigeria. Watermelon skin was peeled and the seeds removed. The mesocarp of the ripe fruit was chopped into thin slices and crushed to juice with a blender. The watermelon juice obtained was filtered through a fine m̂esh muslin cloth to get the fresh watermelon fruit juice. Watermelon juice was prepared fresh daily throughout the treatment period.

2.3. Experimental design

A total of 24 (twenty-four) Wistar albino rats (100–150 g) were procured from the Central Animal House, College of Medicine, University of Ibadan, Nigeria for the study. The rats were initially acclimatized for a period of 2 weeks after their purchase. They were housed in wooden cages placed in a well ventilated rat house. Rats were provided with rat pellets and unlimited supply of water and subjected to natural photoperiod of about 12 h light:12-h dark throughout the study period. All the animals received humane care according to the criteria outlined in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institute of Health.

Rats were divided into 4 groups of 6 animals each. Watermelon juice was administered orally for fifteen (15) days before administration of a single oral dose of ethanol as presented below:

Group 1 (*C*): Control rats administered water (4 ml/kg body weight) only for 15 days.

Group II (*C* + *W*): Rats treated with watermelon (4 ml/kg body weight) only for 15 days

Groups III (*E*): Rats treated with a single dose of 50% ethanol (12 ml/kg) only

Group VI (*E* + *W*): Rats were pre-treated with watermelon (4 ml/kg body weight) for 15 days, followed by a single dose of 50% ethanol (12 ml/kg).

The dose of ethanol used in the present study is well documented to induce tissue toxicity and oxidative damage in rats [32]. All animals in each group were weighed before and after the experiment. At the end of the treatment, all rats were fasted for 12 h and then sacrificed by cervical dislocation. Liver and whole brain organs were excised, weighed and homogenized in 50 mmol/l Tris–HCl buffer (pH 7.4) and then centrifuged at $5000 \times g$ for 15 min for biochemical analysis. Supernatants were immediately kept frozen until needed.

2.4. Determination of protein concentration

The protein concentration of the various samples was determined by means of the Biuret method described by Gornal et al. [33] using bovine serum albumin (BSA) as the standard.

2.5. Phytochemical analysis

The analyses for phytochemical constituents (tannins, saponins, alkaloids, phenols and steroids) were performed using standard methods [34–36].

2.6. Assessment of lipid peroxidation

Lipid peroxidation was determined according to the method of Varshney and Kale [37] based on the reaction between 2-thiobarbituric acid (TBA) and malondialdehyde (MDA): an end product of lipid peroxidation. Briefly, 0.4 ml of the sample was mixed with 1.6 ml of Tris–KCl buffer and 0.5 ml of trichloroacetic acid (TCA, 30%). This was followed by the addition of 0.5 ml of TBA (0.75%). The reaction mixture was heated in a water bath for 45 min at 80 °C, cooled in ice and centrifuged at $3000 \times g$ for 5 min. Absorbance of the resulting supernatant was determined at 532 nm against a reference blank of distilled water. Lipid peroxidation in units/mg protein was computed with a molar extinction coefficient of $1.56 \times 10^5\ m^{-1}\ cm^{-1}$.

2.7. Reduced glutathione (GSH) assay

The method of Jollow et al. [38] was used in estimating the concentration of reduced glutathione (GSH). Liver homogenates were deproteinized by the addition of 0.15 M sulphosalicyclic acid (1:1, v/v). The protein precipitate was centrifuged at $4000 \times g$ for 5 min. Thereafter, 0.5 ml of the supernatant was added to 4.5 ml of DTNB (0.001 M). At 412 nm, absorbance of the mixture was read against a blank consisting of 0.5 ml of de-proteinizing agent diluted with water (1:1) and 4.5 ml of DTNB. The concentration of reduced glu-

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