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Research on garlic capsule and selenium-vitamin A, vitamin B, vitamin C applied in therapy of acute hepatocellular damage in a rat model

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ABSTRACT

Objectives: To evaluate the toxicity of lisinopril in liver of male rats and its reversal effect of garlic capsule (GAR) and selenium-vitamin A, vitamin B, vitamin C (SACE).
Methods: Thirty five adult male wistar rats were randomly assigned into 5 groups of 7 animals per group. Group I serves as the control, animals in Groups II, III, IV and V received 28 mg/kg body weight of lisinopril via oral route. Group III was co-treated with GAR at therapeutic dose of 250 mg/kg body weight per day. Group IV was co-treated with SACE at dose of 500 mg/kg body weight. Lastly, group V was co-treated with GAR and SACE at doses of 250 and 500 mg/kg body weight respectively, and the experiment last for 8 days.
Results: Administration of lisinopril caused systemic toxicity in liver as well as adverse histopathologic changes in the tested tissue. While GAR and SACE significantly ($P < 0.05$) reversed the toxic effects induced by lisinopril.
Conclusions: Collectively, the results suggest that therapeutic dose of lisinopril elicits toxicity in male rats through induction of oxidative damage and depletion of cellular adenosine triphosphate. The reversal effects of GAR and SACE during lisinopril treatment suggest that these antioxidants may find clinical application in cellular damage involving ROS and adenosine triphosphate.

1. Introduction

Lisinopril is one of the antihypertensive medications that belong to the angiotensin-converting enzyme (ACE) inhibitor group. The ACE inhibitors are considered first line drugs for the therapy of hypertension and are considered particularly helpful in preventing the renal complications of diabetes and high blood pressure[1]. ACE inhibitors are sometimes used even in patients with relatively normal blood pressure for treatment of heart failure and prevention of diabetic neuropathy[2,3]. Lisinopril works by inhibiting a chemical process involving high amount of salt and water in the body. It has been reported that less salt and water decrease the blood volume, thereby making blood arteries and veins flow smoother[4–6]. Lisinopril, paradigm of ACE inhibitors acts on the mechanism that narrows blood vessels, so that by blocking it, lisinopril causes blood vessels to relax, allowing more blood to flow in the body[7,8]. However, patients who suffer from hypertension can bring their blood pressure back to normal by recommending the drug. This is imperative because excessive pressure will damage the blood vessels and lead to cardiovascular diseases (*e.g.* heart attack). Lisinopril is a commonly prescribed ACE inhibitor and this type of medication is commonly used to decrease blood pressure by the renin-angiotensin-aldosteron system[9,10]. These inhibitors block the conversion of angiotensin I to angiotensin II, which ultimately leads to the reduction of blood pressure[11]. Other enzymes besides that which converts angiotensin I to II may also be inhibited. This may account for some of the side effects of the ACE inhibitors.

Lisinopril was approved for use by the Food and Drug Administration in the United States and is currently one of the most widely prescribed medications in clinical practice, with more than 60 million prescriptions filled yearly[12–14]. Despite its wide scale use, cases of clinically apparent acute liver injury and deaths attributed to lisinopril complications have been

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published[15,16]. Strikingly, lisinopril have been associated with instances of acute liver injury after 1–4 years of therapy, a distinctly unusual pattern of drug induced liver injury[17–19]. Other common side effects of lisinopril therapy include dizziness, fatigue, headache, cough, gastrointestinal upset and skin rash[20,21]. In addition, previous study had shown immuno-allergic manifestations (rash, fever, eosinophilia) in patients treated with lisinopril, in which; they develop no auto-anti-bodies[22]. Lisinopril might cause mild hepatitis[23,24] and it was also reported that lisinopril therapy showed sexual dysfunction in hypertensive male patients therapeutically administered[13,25].

Several xenobiotics enter the body through gastrointestinal tract and after absorption are transported by the hepatic portal vein to the liver; thus the liver is the first organ perfused by drugs that are absorbed in the gut. To date, research has largely concentrated on hepatic cells, since the liver plays a major role in the metabolism of xenobiotics and consequently the primary target of most toxic responses. More so, GAR and selenium ACE might be useful in treatment of liver damage. Thus, the aim of the present study was (a) to validate the evidence whether therapeutic dose of lisinopril induces hepatotoxicity in rats (b) to investigate the combination therapy of garlic capsule (GAR) and selenium-vitamin A, vitamin B, vitamin C (SACE) against lisinopril sub-acute induced hepatic damage (c) and possibly to validate the underlying biochemical mechanisms of lisinopril toxicity in liver as well as its prevention by GAR and/SACE.

2. Materials and methods

2.1. Chemicals and reagents

Lisinopril, GAR, SACE, epinephrine, glutathione (GSH), 5,5-dithio-bis-2-nitrobenzoic acid, hydrogen peroxide, tri-chloroacetic acid and thiobarbituric acid were purchased from Sigma (St Louis, MO, USA). All other reagents were of analytical grade and were obtained from the British Drug Houses (Poole, Dorset, UK).

2.2. Experimental protocol

Thirty five adult male wistar rats weighing approximately 200–220 g obtained from the Department of Biochemistry, University of Ilorin, Nigeria were randomly assigned into 5 groups of 7 animals per group. They were housed in a plastic suspended cage placed in a well ventilated rat house, provided rat pellets and water *ad libitum*, and subjected to a natural photoperiod of 12 h light and 12 h dark cycle. 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. Ethic regulations have been followed in accordance with National and institutional guidelines for the protection of animal welfare during experiments[26].

Rats in Group I served as control and were administered distilled water. Animals in Groups II, III, IV and V received 28 mg/kg body weight of lisinopril via oral route. Group III was co-treated with GAR at therapeutic dose of 250 mg/kg body weight per day. Group IV was co-treated with ACE at dose of 500 mg/kg body weight. Lastly, group V was co-treated with GAR and ACE at doses of 250 and 500 mg/kg body weight respectively, and the experiment last for a week. The animals were fasted overnight and sacrificed by decapitation 24 h after the last treatment, livers were removed and cleared of adhering tissues, washed in ice-cold 1.15% potassium chloride and dried with blotting paper.

2.3. Biochemical assay

The livers were homogenized in 50 mmol/L Tris–HCl buffer (pH 7.4) containing 1.15% KCl and the homogenate was centrifuged at 10000 r/min for 15 min at 4 °C. The supernatant was collected for the estimation of catalase activity using hydrogen peroxide (H_2O_2) as substrate according to the method of Clairborne[27]. Also, H_2O_2 level was estimated using the method described by Clairborne[27]. Superoxide dismutase (SOD) activity was determined by measuring the inhibition of autoxidation of epinephrine at pH 10.2 at (30 ± 1) °C according to Misra and Fridovich[28]. Protein concentration was determined by the method of Lowry *et al.*[29].

2.4. Reduced GSH assay

GSH was determined at 412 nm using the method described by Jollow *et al.*[30].

2.5. Lipid peroxidation assay

Lipid peroxidation was quantified as malondialdehyde (MDA) according to the method described by Ohkawa *et al.*[31] and expressed as μmol/mg tissue.

2.6. Lactate dehydrogenase (LDH) assay

The liver homogenate was assayed for LDH activity using commercially available kit (Randox Laboratories, UK). Assay was carried out according to the manufacturer's instructions[32].

2.7. Histopathological evaluation

The livers were fixed in 10% formalin. They were directly dehydrated in a graded serious of ethanol and embedded in paraffin. Thin sections, 5–6 μm, were cut by using a microtome, mounted on albumenized glass slides and stained with eosin and hematoxylen. Morphological examination of liver was done by using an ocular micrometer scale under light microscope.

2.8. Statistical analysis

The results of the replicates were pooled and expressed as mean ± SE. One-way ANOVA was used to analyze the results and Duncan multiple tests was used for the *post hoc*[33]. SPSS 17.0 for windows was used for the analysis and the least significance difference was accepted at $P < 0.05$.

3. Results

3.1. Hepatic biochemical indices

The effect of lisinopril, lisinopril plus GAR, lisinopril plus SACE, and lisinopril plus SACE plus GAR on hepatic biochemical indices were presented in Figures 1–3. Lisinopril