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Research Article
Cholesterol and Triglycerides Concentrations of Lipopolysaccharide-Induced Inflammatory Male Rat in Response to *Petiveria alliacea* L. Leaf Extract

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Abstract

Background and Objectives: Medicinal plants persevere to facilitate developments in novel therapeutic pathways involved in the treatment of various diseases. This study investigated the cholesterol and triglycerides concentrations of lipopolysaccharide-induced inflammatory male rats in response to *P. alliacea* leaf extract. **Materials and Methods:** Twenty adult male Albino rats weighing 150±1.8 g were grouped randomly into four (n = 5) namely; control (Group 1): Feed and water only, Group 2: *P. alliacea* leaf aqueous extract only for 7 days, Group 3: Injected with lipopolysaccharide and Group 4: Injected with lipopolysaccharide, treated with *P. alliacea* leaf aqueous extract for 7 days. After the administration, the rats were sacrificed and blood was collected, brain and liver were excised homogenized and stored at 4°C for determination of cholesterol and triglycerides concentrations using the spectrophotometry method. **Results:** The administration of *P. alliacea* resulted in the up-regulation of plasma, erythrocytes cholesterol and liver triglycerides concentrations as well as down-regulation of plasma triglycerides, brain cholesterol and liver cholesterol concentrations. It was observed that lipopolysaccharide significantly ($p<0.05$) decreased the cholesterol concentration of the liver, plasma, erythrocytes along with brain cholesterol and triglycerides concentrations but significantly ($p<0.05$) increased the liver triglycerides concentration compared to the control and *P. alliacea* group respectively. However, administration of *P. alliacea* leaf aqueous extract to lipopolysaccharide-induced rat, reverse the up/down-regulation of cholesterol and triglycerides concentrations. **Conclusion:** *P. alliacea* leaf aqueous extract override the impact of lipopolysaccharide.

Key words: *Petiveria alliacea*, cholesterol, triglycerides, inflammatory, leaf, lipopolysaccharide, Up/down-regulation

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Lipids molecules play key roles in the metabolism of living organisms. Dyslipidemia is a major risk factor for atherosclerosis and inflammation[1]. Inflammation is primarily a physiologic defence mechanism that shields the body system against infections, stress, toxins, allergens or other deleterious stimuli. However, insistent inflammation may act as a diagnostic factor for many chronic weakening musculoskeletal, metabolic disorders and multiple organ dysfunction[1,2]. The LPS has been implicated in the interruption of normal cellular intermediary metabolism and systemic inflammatory response syndrome, which might result in multiple organ dysfunction. Man is known to have exploited medicinal plants as drugs to treat ailments since ancient times, using the crude extracts form known to contain important bioactive compounds which could possess therapeutic benefit against inflammatory-related diseases with minimal side effects than synthetic drugs[3-5].

Lipids molecules (cholesterol, triglycerides, phospholipids and fatty acids) play key roles in metabolic pathways[6,7] and disorders in the homeostasis of these lipids resulted in dyslipidemia[1,8] which has effects on health conditions, therefore great attention is necessary on the abnormal levels of lipids and its associated factors[8,9]. The medicinal plant, *Petiveria alliacea* (*P. alliacea*) (Phytolaccaceae) is a herbaceous plant found in Africa and Tropical America. It is utilized as a diuretic, sedative, analgesic and abortive agent as well as in the treatment of rheumatism, diabetes, headaches and allergies. It is also known to possess anti-leukemic, antitumor, anti-helminths and anticonvulsant activities[10,11]. These ailments/diseases are known to be associated with dyslipidemia which is a risk factor for inflammation but the mechanism of action of *P. alliacea* leaf aqueous extract in the treatment of this risk factor remains enigmatic. Therefore, this study was designed to evaluate the effect of *P. alliacea* leaf aqueous extract on cholesterol and triglycerides concentrations of LPS-induced inflammatory male rats.

MATERIALS AND METHODS

Collection of plant material, authentication and extraction procedure: The fresh leaves of *P. alliacea* were collected from its natural environment in Agbara, Ado-Odo Ota Local Government Area, Ogun State, Nigeria, in March, 2021 and a voucher specimen was deposited in the Herbarium of Department of Botany, Faculty of Science, Lagos State University, Ojo, Nigeria. The study was carried out at the Department of Biochemistry, Drug Discovery Lab, Faculty of Science, Lagos State University, Ojo from April to July, 2021. The leaves (1 kg) were cleaned under running water and soaked in 4 L of water in a stainless container for 48 hrs. The extract was collected through filtration and stored in the refrigerator for further use.

Acute toxicity studies: The acute toxicity (LD_{50}) of aqueous leaf extract of *P. alliacea* was determined by oral route using the modified method of Erhirhie[12] and Adu *et al.*[13].

Preparation of lipopolysaccharide (LPS): The LPS (Sigma Aldrich Chemical Company, St Louis, MO, USA), due to its high level of the toxin was prepared in solution by diluting with dextrose (2:1 w/v) and the solution was administered at 4 mL kg^{-1} b.wt.

Experimental animals and study design: Twenty male adult albino rats weighing approximately 150±1.8 g were accommodated in neat metabolic cages of dimensions 33.0×20.5×19.0 cm placed in well-aired standard housing. The rats were acclimatized for 14 days under natural hours of day/night conditions in the animal house of the Department of Biochemistry, Faculty of Science, Lagos State University, Ojo, Lagos State. All the animals were fed with a standard diet (Lagos State Ministry of Agriculture, Ojo, Lagos, Nigeria) and drinking water They were grouped randomly into four (n = 5) namely; Group 1: Control rats were given water and animal feed only, Group 2: Administered with 1000 mg kg^{-1} b.wt. of *P. alliacea* leaf aqueous extract for 7 days, Group 3: Induced-inflammation by single intraperitoneal dose (4 mL kg^{-1} b.wt.) of LPS and observed closely for 4 hrs before they were sacrificed and Group 4: Induced-inflammation by single intraperitoneal dose (4 mL kg^{-1} b.wt.) of LPS, observed closely for 4 hrs when administered with *P. alliacea* leaf aqueous extract for 7 days.

At the end of the administration, the animals were starved overnight, sacrificed under ketamine anaesthesia and blood was collected by cardiac puncture into heparinized tubes and organs (brain and liver) were excised. The blood, brain and liver were processed as previously described by Ogunrinola *et al.*[8,14] All experiments were performed in acquiescence with the approval of the *ad hoc* Animal Ethical Committee of the Department of Biochemistry, Lagos State University, Ojo, Lagos-Nigeria and Ethical guiding principles of laboratory animal care[15].

Biochemical analysis: The total plasma cholesterol and triglycerides concentrations were determined using commercially available kits according to the manufacturer's instructions and performed according to our earlier researches[8,16]. Lipids were extracted from the erythrocytes, brain and liver according to the modified method of Axelsson and Gentili[17]. Then, the cholesterol and triglycerides determination was performed by the methods earlier described by Ogunrinola *et al.*[8,14] and Rotimi *et al.*[18], respectively.

Statistical analysis: The statistical analyses were performed using IBM SPSS version 20.0 Statistical Software (IBM Corp., Armonk, NY, USA). Results are expressed as Mean±SEM of 4 replicates. One-way analysis of variance (ANOVA) was carried out to test for the level of homogeneity at $p<0.05$ among the groups.

RESULTS

As depicted in Fig. 1a, there was a significant ($p<0.05$) increase in plasma cholesterol concentration with the oral administration of *P. alliacea* only. Similarly, treatment of *P. alliacea* of inflammatory-induced rat increased plasma cholesterol concentration. However, induction of inflammation with LPS caused a significant reduction in the plasma and triglycerides concentrations. In Fig. 1b, the administration of *P. alliacea* only and LPS to the animals significantly ($p<0.05$) reduced the plasma triglycerides concentration but the treatment of LPS induced rats with *P. alliacea* resulted in increased plasma triglycerides concentration.

The administration of *P. alliacea* in groups 2 and 4 resulted in a significant ($p<0.05$) increase of erythrocytes cholesterol compared to the control as depicted in Fig. 2a, but administration of LPS caused significant ($p<0.05$) reduction. On the other hand, in Fig. 2b, while the administration of *P. alliacea* has little or no effect on the erythrocyte triglyceride concentration, the administration of *P. alliacea* shows significant ($p<0.05$) reduction compared to control. The administration of *P. alliacea* to the LPS-induced inflammatory rats caused a significant ($p<0.05$) increase in erythrocytes triglycerides concentration.

Figure 3a and b shows that administration of *P. alliacea* and LPS only resulted in a significant ($p<0.05$) decrease of the brain cholesterol (Fig. 3a) and triglycerides (Fig. 3b) concentrations, respectively compared to the control. It was observed that administration of *P. alliacea* to the LPS-induced animals leads to a significant ($p<0.05$) increase in brain cholesterol (Fig. 3a) and triglycerides (Fig. 3b) concentrations, respectively.

There was a significant ($p<0.05$) decrease in liver cholesterol concentration with the administration of *P. alliacea* and LPS to animals respectively while the administration of *P. alliacea* to the LPS-induced rats resulted in increased concentration of liver cholesterol (Fig. 4a). However, the administration of *P. alliacea* and LPS independently caused a significant ($p<0.05$) increase in liver triglycerides concentration compared to control (Fig. 4b) whereas, the administration of *P. alliacea* to LPS-induced animal down-regulated the liver triglycerides concentration.

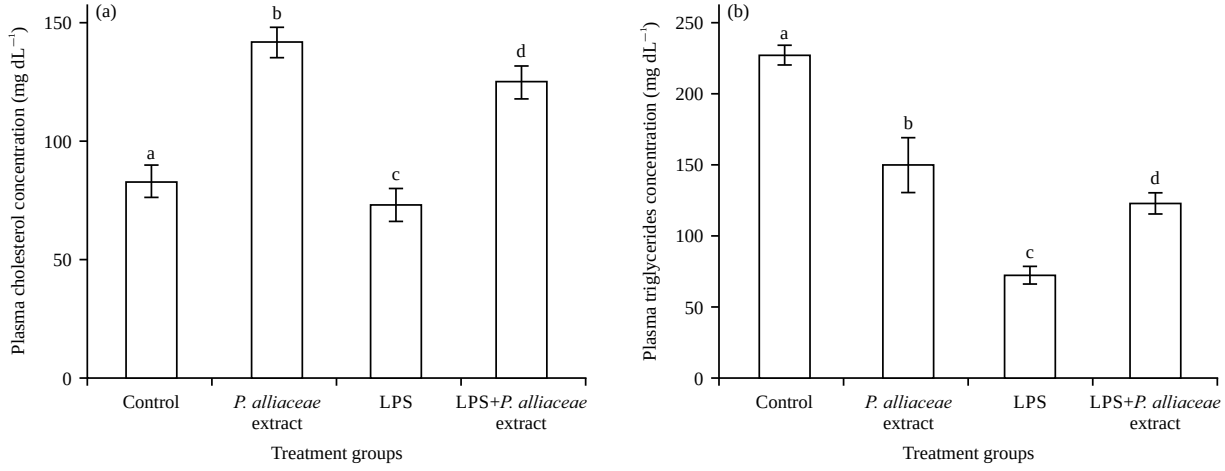

Fig. 1(a-b): Effect of *P. alliaceae* aqueous extract on (a) Plasma cholesterol and (b) Triglycerides concentrations of Lipopolysaccharides (LPS) induced-inflammatory male rat

Each bars represent the Mean±SEM (n = 5), Bars with different alphabets are significantly different at $p<0.05$

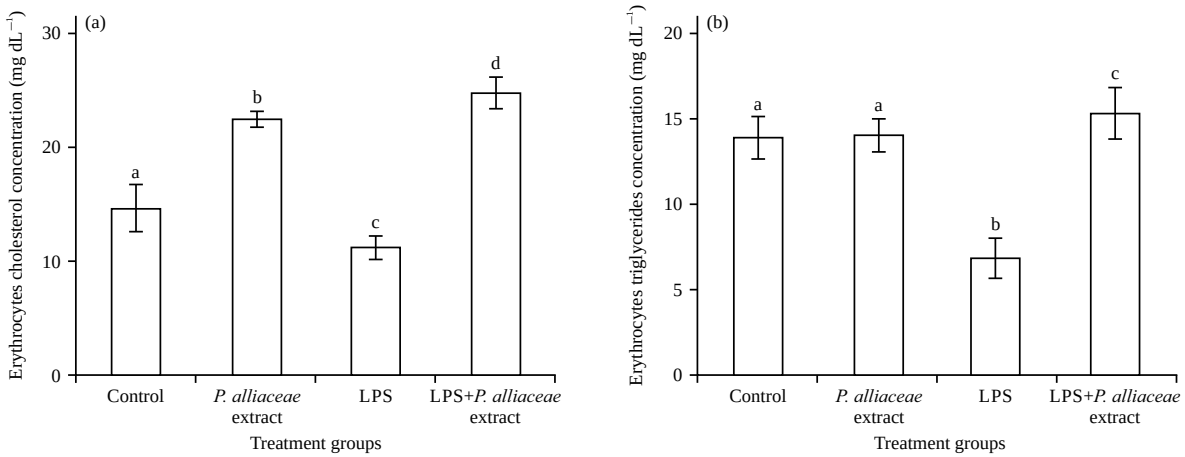

Fig. 2(a-b): Effect of *P. alliaceae* aqueous extract on (a) Erythrocytes cholesterol and (b) Triglycerides concentrations of lipopolysaccharides (LPS) induced-inflammatory male rat

Each bars represent the Mean±SEM (n = 5), Bars with different alphabets are significantly different at p<0.05

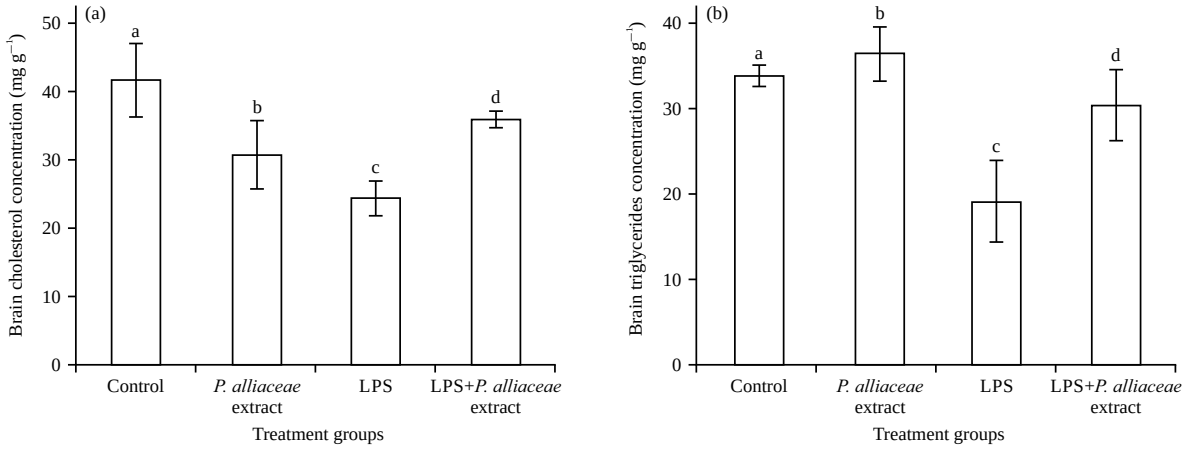

Fig. 3(a-b): Effect of *P. alliaceae* aqueous extract on (a) Brain cholesterol and (b) Triglycerides concentrations of lipopolysaccharides (LPS) induced-inflammatory male rat

Each bars represent the Mean±SEM (n = 5), Bars with different alphabets are significantly different at p<0.05

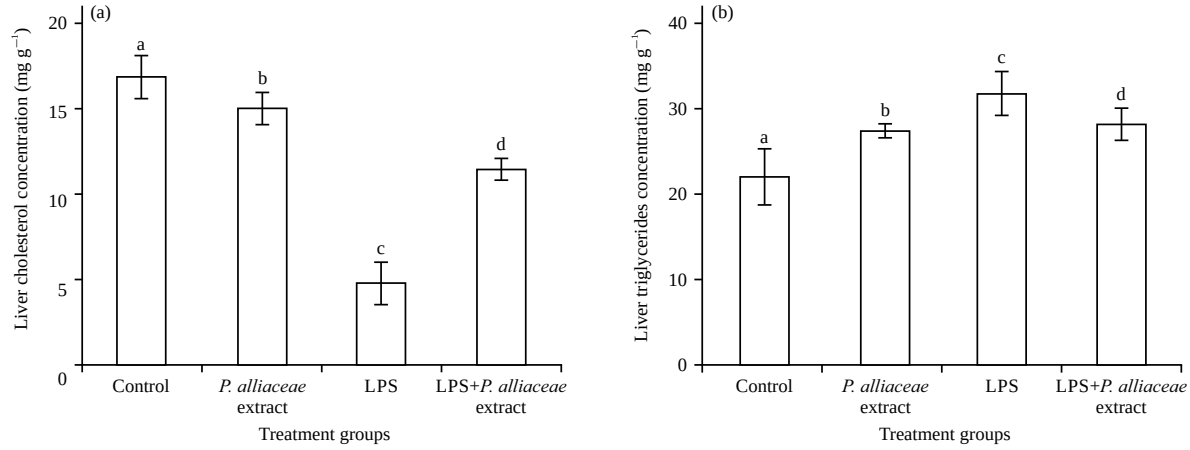

Fig. 4(a-b): Effect of *P. alliaceae* aqueous extract on (a) Liver cholesterol and (b) Triglycerides concentrations of lipopolysaccharides (LPS) induced-inflammatory male rat

Each bars represent the Mean±SEM (n = 5), Bars with different alphabets are significantly different at p<0.05

DISCUSSION

Dysregulation of lipids metabolism, which are macromolecules required for maintaining several homeostatic, physiologic and cellular processes, can contribute to the pathogenesis of different diseases such as cardiovascular disease, diabetes and inflammation[1]. Lipopolysaccharide (LPS) is the major component of the outer membrane of Gram-negative bacteria known to be a key pathogenic stimulator for metabolic dysfunctions. It stimulates the innate immune system, which mediates a local or systemic inflammatory response and can also stimulate non-immune cells and initiate the inflammatory process, which is usually detrimental. Inflammation induces various alterations in lipid metabolism that increase the risk of atherosclerosis in which both cell-mediated and humoral immune responses participate[19,20]. Atherosclerosis is a progressive disease considered as a form of chronic inflammation, resulting from the interaction between modified lipoproteins, mainly oxidized low-density lipoprotein, monocytes or macrophages and T lymphocytes with the components of the arterial wall[21]. There are several therapeutic strategies to modulate lipid metabolism and prevent metabolic disease, such as inflammation, thus, this study was carried out to elucidate the response of daily oral administration of aqueous extract of *P. alliacea* on cholesterol and triglycerides concentration in LPS-induced inflammatory male rats.

The LPS directly cause dysfunction of lipid metabolism, thereby causing hepatotoxicity, renal failure and lipid peroxidation via the induction of free radicals[20,22,23]. This study agrees with these metabolic disorders and organ failure caused by LPS. The data show a significant reduction in the cholesterol and triglycerides concentrations of plasma, erythrocytes, brain and liver in LPS administered rats compared to the control. This is following the research of Ostos *et al.*[21] and Lehr *et al.*[24]. This reduction might be caused by liver toxicity from the injection of LPS as observed in increased liver triglycerides concentration. The observed decrease in cholesterol concentration is strongly associated with mortality suggesting a relationship between inflammatory conditions and altered cholesterol homeostasis, which altered fluidity and function of the membrane. The host metabolism response to inflammation is mediated by cytokines and growth factors, which is capable of influencing lipid metabolism[8,25]. As revealed in this study, the increase in liver triglycerides might be as a result of increased liver fatty acid mobilization and delivery to the liver, which is coupled with increased hepatic lipogenesis and decreased secretion of very-low-density lipoprotein[16,26,27].

P. alliacea has been used in traditional medicine for several purposes such as anti-rheumatic, analgesic, anti-microbial, anti-malarial, anti-cancer and to treat respiratory conditions etc[11] Phytochemical constituents of *P. alliacea* are characterized by the presence of flavonoids, triterpenes, steroids, thiosulfinates as well as sulfur-containing compounds such as polysulfides, sulfoxides and sulfides, which are responsible for its medicinal properties[10,11]. The flavonoid intake required to provide effective and pharmacological properties can be affected by its abundant, amount ingested as well as the inter-individual variability[1]. The administration of aqueous extract of *P. alliacea* as observed, promoted the up-regulation of plasma, erythrocyte and liver cholesterol concentrations, down-regulation of plasma, liver triglycerides and brain cholesterol and triglycerides concentrations but had no significant impact on erythrocyte triglycerides. The observed down-regulation of brain cholesterol concentration and significantly unchanged erythrocytes triglycerides concentration is following the reports of Thomson *et al.*[28] in the use of garlic extract, which is due to the presence of active constituents in the plant. However, the active constituents present in the aqueous extract of *P. alliacea* was found to reverse the effects caused by LPS on the cholesterol and triglycerides concentrations in the different organ compartments of the animals. The mechanism of the reversal might be that the plant was able to control the cholesterol homeostasis by stabilizing the fluidity and function of the membrane. Also, this may be as a result of decreased liver fatty acid mobilization and delivery to the liver, which is coupled with decreased hepatic lipogenesis and increased secretion of very-low-density lipoprotein as evident in the decreased liver triglycerides by increasing the activity of hepatic lipases[29]. This also suggests that the presence of flavonoids can enhance the clearance of LPS-induced inflammation which takes place in the Kupffer and parenchyma cells of the liver, where it is catabolized[30].

The LPS-induction in the rat model revealed hepatic dysfunction and dysregulation of lipid metabolism through up/and down-regulation of cholesterol and triglycerides concentrations. The implication of this is that there will be endotoxic shock leading to hormonal stress since cholesterol is the obligatory intermediate in the biosynthesis of corticosteroids. The administration of *P. alliacea* aqueous extract was able to reverse the dysfunction and dysregulation of cholesterol and triglycerides concentrations and thus, can be recommended as a supplement for lipid metabolism dysfunction, but there is a need for other membrane and liver function studies. Overall, the changes observed in this study may be associated to be the underlying mechanism whereby induced-inflammation signals liver damage and *P. alliacea* aqueous extract can overturn the damage.

SIGNIFICANT STATEMENT

This present study provides a significant understanding of changes sustained in the lipid metabolism by LPS that induced inflammation and the ability to reverse the changes through oral administration of *P. alliacea* aqueous leaf extract in a rat model. The mechanism of action of these changes may be due to the observed dysregulation of plasma, erythrocytes, brain and liver cholesterol and triglycerides concentrations by LPS that is known to be associated with the risk of cardiovascular diseases. The bioactive components in aqueous leaf extract of *P. alliacea* target the reversal of the dysregulation in the different compartments.

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