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ORIGINAL RESEARCH

**Petiveria alliacea** EXTRACT HAS A PROTECTIVE IMPACT ON OXIDATIVE STRESS BIOMARKERS IN MALE RATS WITH LIPOPOLYSACCHARIDE-INDUCED ENDOTOXICITY**Olabisi O. Ogunrinola, Olusegun O. Fajana, Rahmon I. Kanmodi, Oluwaseyi A. Ogunrinola, Aderemi Adeyemi, Oluwatosin B. Adu, Olugbenga S. Oladimeji, Babajide O. Elemo***Department of Biochemistry, Faculty of Science, Lagos State University, Nigeria***Abstract:****Introduction:** An imbalance between free radicals and antioxidants causes oxidative stress, which has detrimental consequences for a variety of health issues. *Petiveria alliacea* (*P. alliacea*) is a medicinal plant having a variety of bioactive chemicals that have a variety of therapeutic uses.**Aims:** The objective of this study was to investigate the protective effect of *P. alliacea* leaf aqueous extract on oxidative stress biomarkers in male rats with lipopolysaccharide (LPS) induced-endotoxicity.**Materials and Methods:** Twenty-five (25) male albino rats were divided into five ($n = 5$) groups at random. Group 1 was used as a control, Group 2 was given *P. alliacea* aqueous extract (1000 mg/kg body weight), Group 3 was given LPS, a single intraperitoneal dose (4 ml/kg body weight), and was observed for 4 hours before being sacrificed, Group 4 was given LPS (observed for 4 hours) and treated with *P. alliacea* for 7 days, Group 5 was given *P. alliacea* extract for 7 days, then Spectrophotometric analysis was used to evaluate the activities of oxidative stress biomarkers (catalase (CAT) and superoxide dismutase (SOD) in plasma, erythrocytes, brain, liver, kidney, and heart.**Results:** As seen in this work, oxidative stress is a characteristic of LPS-induced endotoxicity. Following LPS injection, *P. alliacea* leaf aqueous extract significantly ($p > 0.05$) increased CAT and SOD activities compared to control and LPS group respectively in the plasma, erythrocytes, brain, liver, kidney and heart compartments.**Conclusion:** The aqueous extract of *P. alliacea* leaf reduced the effect of LPS-induced endotoxins in the body by mopping up free radicals, according to the findings.**Keywords:** *Petiveria alliacea*, Lipopolysaccharide, Oxidative stress markers, Antioxidants**Correspondence***Olabisi O. Ogunrinola, Drug Discovery Lab., Department of Biochemistry, Faculty of Science, Lagos State University, Nigeria.
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1. INTRODUCTION

The majority of inflammatory and metabolic disease states are linked to oxidative stress [1, 2]. Excessive generation of reactive oxygen species, such as superoxide, hydrogen peroxide, and hydroxyl radicals, occurs when the homeostatic balance between the creation of reactive oxidizing/oxygen species and their elimination by endogenous antioxidant scavenging substances is disrupted. Inadequate anti-oxidative defenses, such as superoxide dismutase (SOD), catalase (CAT), vitamins C and E, reduced glutathione (GSH), glutathione S-transferase (GST), and glutathione peroxidase (GPx), which act as free radical scavengers in conditions associated with oxidative stress, pose major challenges to public health by causing oxidative damage [1, 3, 4]. Increased rates of free radical production and chronic inflammation are examples of the clustering of causes of oxidative stress [1]. Lipopolysaccharides (LPS) are harmful inflammatory stimulants secreted by Gram-negative bacteria's outer membrane. LPS interacts with various naturally occurring cellular and humoral components in the host, causing macrophages to create inflammatory cytokines and release a spectrum of reactive oxygen and nitrogen species, resulting in complex organ dysfunction [5-8].

The focus is on using medicinal plants to lower the development of inflammation and oxidative stress mediators in order to treat the difficulties that emerge from organ failure. As a result, plants with antioxidant capabilities may be effective in averting problems. One of these medicinal plants, *Petiveria alliacea* (*P. alliacea*), is used to cure a number of ailments such as diabetes, arthritis, toothaches, skin infections, and so on. (Fig.1) [9, 10]. It works as an immunomodulator, analgesic, antibacterial, anti-helminthic, anticonvulsant, and anticancer agent [11, 12]. The current study looked at the preventive effect of *P. alliacea* aqueous leaf extract on oxidative stress indicators (CAT and SOD) in plasma, erythrocytes, brain, liver, heart, and kidney in male rat LPS induce endotoxicity.



Fig. 1: Snapshot of *Petiveria alliacea* plant

2. MATERIAL AND METHODS

2.1 COLLECTION OF PLANT MATERIAL, AUTHENTICATION AND EXTRACTION

PROCEDURE: Fresh *P. alliacea* leaves were collected from Agbara, Ado-Odo Ota Local Government Area, Ogun State, Nigeria. The plant was identified and authenticated by a Botanist in the Department of Botany, Faculty of Science, Lagos State University, Ojo, Nigeria and a voucher specimen was deposited in the Herbarium. The leaves were cleaned and soaked in four litres (4L) of water for 48 hours. The extract was collected and stored for further use.

2.2 MEDIAN LETHALITY DOSE (LD₅₀): The median lethality dose (LD₅₀) of the aqueous leaf extract of *P. alliacea* was determined by oral route using the modified method of Lorke [13] and Adu *et al.* [14].

2.3 LIPOPOLYSACCHARIDE (LPS) PREPARATION:

LPS (Sigma-Aldrich Chemical Company, St Louis, MO, USA), was prepared in solution by diluting with dextrose (2:1 w/v).

2.4 EXPERIMENTAL ANIMALS AND STUDY

DESIGN: Twenty-five (25) male adult albino rats weighing around $150 \pm 1.8\text{g}$ were acclimatized for fourteen (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 standard diet (Lagos State Ministry of Agriculture, Ojo, Lagos, Nigeria) and drinking water. They were grouped casually into five (5) (n=5) namely: Group 1 – the control rats were given water only; Group 2- were administered with 1000 mg/kg body weight of *P. alliacea* leaf aqueous extract for seven (7) days; Group 3- were given a single intraperitoneal dose of LPS (4 ml/kg body weight) to induce endotoxicity and observed closely for 4 hours before they were sacrificed; Group 4- were given a single intraperitoneal dose of LPS (4 ml/kg body weight) to induce endotoxicity, observed closely for 4 hours then administered with *P. alliacea* (1000 mg/kg body weight) leaf aqueous extract for 7 days and Group 5- were administered with 1000 mg/kg body weight of *P. alliacea* leaf aqueous extract for seven (7) days, then, given a single intraperitoneal dose of LPS (4 ml/kg body weight) to induce endotoxicity, observed for 4 hours then administered with *P. alliacea* (1000 mg/kg body weight) leaf aqueous extract for seven (7) days. The animals were given 1000 mg/kg body weight of aqueous *P. alliacea* leaf extract based on the measured LD₅₀ value.

At the end of the administration, the animals were starved overnight, sacrificed under light ketamine anaesthesia. The blood was collected by cardiac puncture into heparinized tubes and the organs (brain, liver, kidney and heart) were excised. The blood, brain, liver, kidney and heart were processed as previously described by Ogunrinola *et al.* [15, 16]. 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 [17].

2.5 BIOCHEMICAL ANALYSIS: Reagent chemicals used are of analytical grade from Sigma-Aldrich Inc, St. Louis, USA. The superoxide dismutase (SOD) activity was determined by an indirect method of inhibiting auto-oxidation of epinephrine to its adrenochrome spectrophotometrically at 480 nm according to the method of Misra and Fridovich [18] as modified by Ogunrinola *et al.* [19]. Catalase (CAT) activity was estimated by the method of Aebi [20] as modified by Adu *et al.* [14].

2.6 STATISTICAL ANALYSIS: The statistical analyses were performed with SPSS (IBM) version 20.0 statistical software (IBM Corp., Armonk, NY, USA). Results are expressed as mean \pm S.E.M of four replicates. One-way analysis of variance (ANOVA) was carried out to test for the level of homogeneity at $p < 0.05$ among the groups.

3. RESULTS AND DISCUSSION

The *P. alliaceae* aqueous leaf extract's acute toxicity was investigated in rats via oral administration. At dose levels of 50 mg/kg, 100 mg/kg, 500 mg/kg, 1000 mg/kg, and 1100 mg/kg body weight, no animal death was observed, showing that the median fatal dose LD₅₀ of *P. alliaceae* aqueous leaf extract was not poisonous. In this study we assessed the effect of *P. alliaceae* aqueous leaf extract on oxidative stress biomarkers - CAT and SOD in animals with endotoxicity induced by LPS in the plasma, erythrocytes, brain, liver, heart and kidney of the control and treatment groups respectively. CAT and SOD established a mutually supportive team of defense against reactive oxygen species [1]. Oxidative stress biomarkers are important in the evaluation of the disease status and of the health-enhancing effects of antioxidants [21]. SOD, an endogenous antioxidant enzyme, is the most powerful antioxidant in the cell, being the first detoxification enzyme against reactive oxygen species (ROS), protecting body cells from excessive oxygen radicals, free radicals, and other harmful agents that promote aging or cell death [19, 22]. The antioxidant enzyme CAT, which is located in peroxisomes, is found in practically all biological tissues that use oxygen. It catalyzes the breakdown or reduction of hydrogen peroxide (H₂O₂) to water and molecular oxygen, completing the detoxification process started by SOD [22, 23]. Oxidative stress which sometimes occur as a consequence of inflammation is the hallmark of LPS induced-endotoxicity [24] as observed in this study. Data from the study depicted a significant ($p < 0.05$) reduction of oxidative stress markers CAT activities in plasma (Fig. 2), erythrocytes (Fig. 3), brain (Fig. 4), liver (Fig. 5), heart (Fig. 6) and kidney (Fig. 7) and SOD (Table 1) activities in all compartments compared with the control. This is in accordance with many

authors [6,24–26]. The reduction of the biomarkers may be affected by the alteration in oxidative and anti-oxidant balance in the body following LPS administration, which stimulates immune response leading to the activation of cascade of immune activities that may results in tissue damage, multiple organ failure and even death [6,26]. Also, it may be due to rapid consumption and exhaustion of storage in anti-oxidant fighting the free radical generated [1]. The erythrocyte damage that occur due to oxidative stress is assumed to be the result of two mechanism: (1) the oxidation of hemoglobin, followed by the conversion of methionine hemoglobin (methHb) to hemichromes; and (2) the free radicals outbreak on membrane components, including the polyunsaturated fatty acid side chains of the reduced thiol groups, membrane lipids, and other susceptible amino acid chains of membrane proteins [25,27].

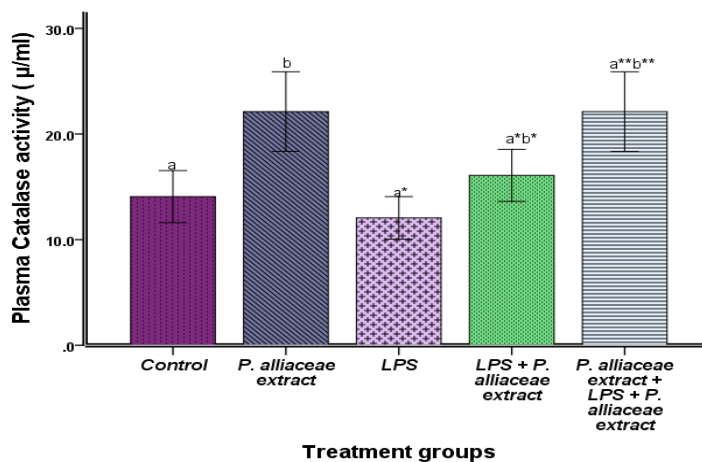


Fig. 2: Effect of *P. alliaceae* aqueous leaf extract on plasma catalase (CAT) activity. The level of CAT activity was measured after 7 and 14 days of experiment: Control; *P. alliaceae*; LPS; LPS + *P. alliaceae* and *P. alliaceae* extract + LPS + *P. alliaceae* extract groups. Each bar represents the mean \pm S.E.M (Standard Error of Mean), $n=5$ for each group. The bars with different alphabets are significantly different at $p < 0.05$ among groups: a* - compared to control group, a*b* - compared to *P. alliaceae* group and control, a**b** - compared to the control and *P. alliaceae* groups respectively.

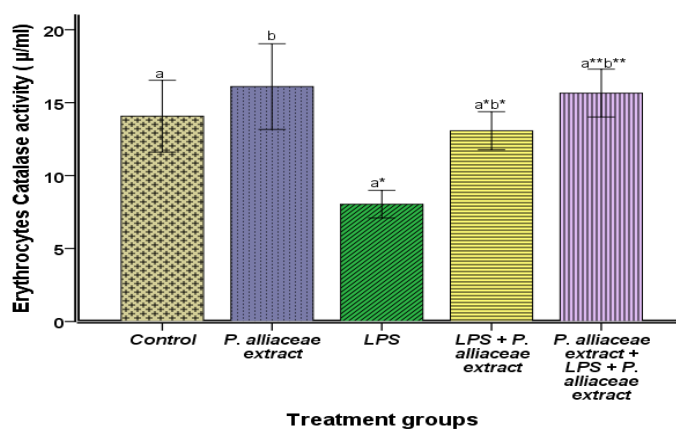


Fig. 3: Effect of *P. alliaceae* aqueous leaf extract on erythrocytes catalase (CAT) activity. The level of CAT

activity was measured after 7 and 14 days of experiment: Control; *P. alliaceae*; LPS; LPS + *P. alliaceae* and *P. alliaceae* extract + LPS + *P. alliaceae* extract groups. Each bar represents the mean ± S.E.M (Standard Error of Mean), n=5 for each group. The bars with different alphabets are significantly different at p < 0.05 among groups: a* - compared to control group, a*b* - compared to *P. alliaceae* group and control, a**b** - compared to the control and *P. alliaceae* groups respectively.

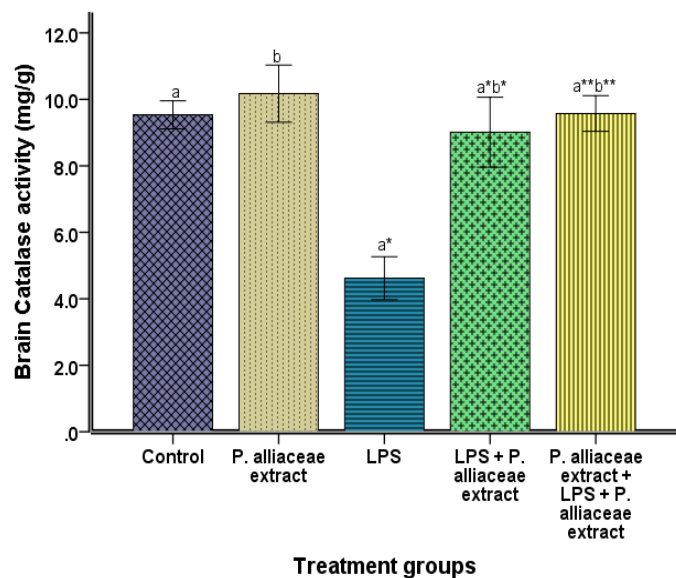


Fig. 4: Effect of *P. alliaceae* aqueous leaf extract on brain catalase (CAT) activity. The level of CAT activity was measured after 7 and 14 days of experiment: Control; *P. alliaceae*; LPS; LPS + *P. alliaceae* and *P. alliaceae* extract + LPS + *P. alliaceae* extract groups. Each bar represents the mean ± S.E.M (Standard Error of Mean), n=5 for each group. The bars with different alphabets are significantly different at p < 0.05 among groups: a* - compared to control group, a*b* - compared to *P. alliaceae* group and control, a**b** - compared to the control and *P. alliaceae* groups respectively.

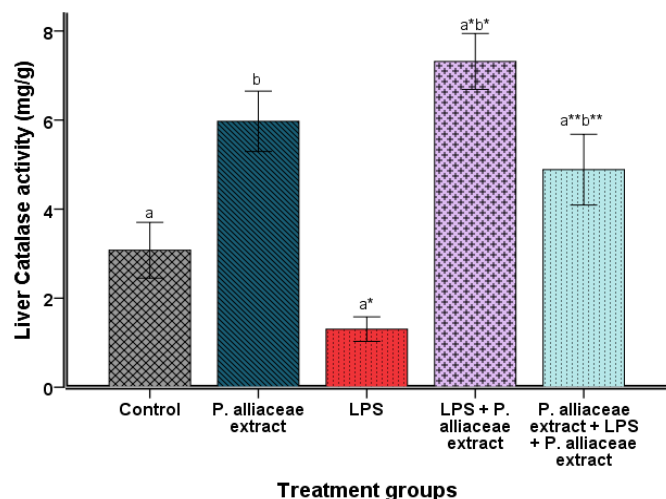


Fig. 5: Effect of *P. alliaceae* aqueous leaf extract on liver catalase (CAT) activity. The level of CAT activity was measured after 7 and 14 days of experiment:

Control; *P. alliaceae*; LPS; LPS + *P. alliaceae* and *P. alliaceae* extract + LPS + *P. alliaceae* extract groups. Each bar represents the mean ± S.E.M (Standard Error of Mean), n=5 for each group. The bars with different alphabets are significantly different at p < 0.05 among groups: a* - compared to control group, a*b* - compared to *P. alliaceae* group and control, a**b** - compared to the control and *P. alliaceae* groups respectively.

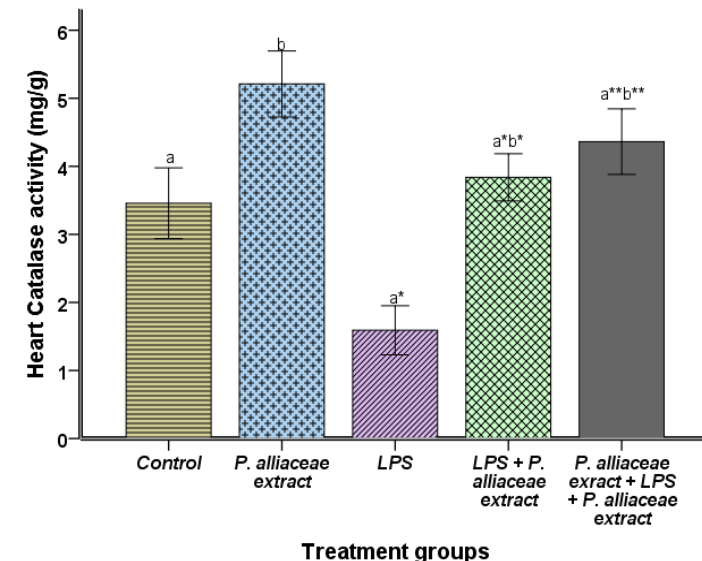


Fig. 6: Effect of *P. alliaceae* aqueous leaf extract on heart catalase (CAT) activity. The level of CAT activity was measured after 7 and 14 days of experiment: Control; *P. alliaceae*; LPS; LPS + *P. alliaceae* and *P. alliaceae* extract + LPS + *P. alliaceae* extract groups. Each bar represents the mean ± S.E.M (Standard Error of Mean), n=5 for each group. The bars with different alphabets are significantly different at p < 0.05 among groups: a* - compared to control group, a*b* - compared to *P. alliaceae* group and control, a**b** - compared to the control and *P. alliaceae* groups respectively.

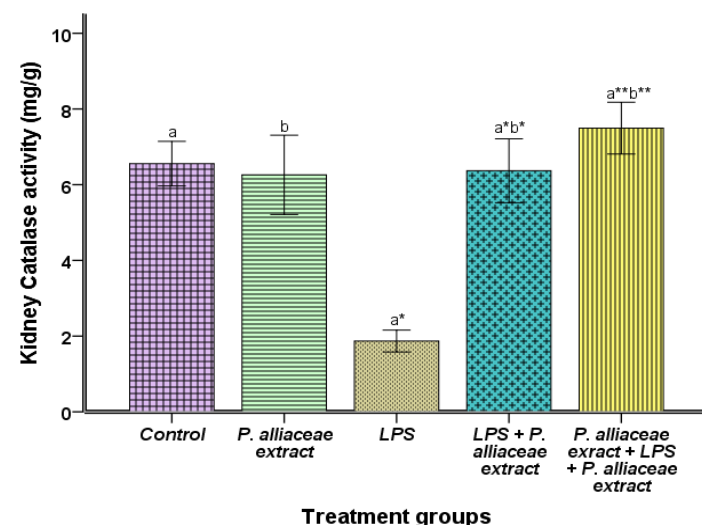


Fig. 7: Effect of *P. alliaceae* aqueous leaf extract on kidney catalase (CAT) activity. The level of CAT activity was measured after 7 and 14 days of experiment: Control; *P. alliaceae*; LPS; LPS + *P.*

alliaceae and *P. alliaceae* extract + LPS + *P. alliaceae* extract groups. Each bar represents the mean ± S.E.M (Standard Error of Mean), n=5 for each group. The bars with different alphabets are significantly different at p < 0.05 among groups: a* - compared to control group, a*b* - compared to *P. alliaceae* group and control, a**b** - compared to the control and *P. alliaceae* groups respectively.

The activities of both CAT and SOD were inhibited by LPS treatment in all the compartments, which may be as a result of superoxide anion (O²⁻) reported to be implicated as one of the toxic mediators responsible for most toxicities observed in LPS-induced cellular injury [25]. The SOD enzyme is a metalloprotein that is involved in the protection of cells by spontaneously dismutating O²⁻ secreted during activation of Kupffer cells to hydrogen peroxide (H₂O₂). Hence, it is important for living organism to remove H₂O₂ to avoid cellular damage [25]. The produced H₂O₂ is usually decomposed to water and oxygen by the CAT, a hemoprotein in the peroxisomes [6,24,28]. The significantly decreased activities of plasma, erythrocytes, brain, hepatic, heart and kidney CAT and SOD by LPS in this study may be an adaptive physiological response of CAT to the overproduction of H₂O₂ resulting from SOD activity [6, 22]. Medicinal plants are of great importance to the health of individuals and the handover of indigenous knowledge of the plants activities and properties from generation to generation has significantly contributed to the development of different traditional systems of medicine [10,29-31]. In herbal medicine, *P. alliaceae* with high levels of bio-active compounds such as polyphenols and flavonoids, is used for the treatment of various ailments in different parts of the world [10]. These compounds can minimize oxidative stress by mopping free radicals and thereby reduce the risk associated with stress related diseases like heart disease and stroke [11]. There was significant (p<0.05) increase in CAT activities in the plasma (Figure 2), erythrocytes (Figure 3), brain (Figure 4), liver (Figure 5), heart (Figure 6), kidney (Figure 7) and SOD activities in the plasma, erythrocytes, brain, liver, heart, kidney (Table 1) of animals administered with *P. alliaceae* aqueous leaf extract only, before and after LPS injection compared to the control. The presence of flavonoids, triterpenes, steroids, thiosulfinates as well as sulfur containing compounds such as polysulfides, sulfoxides and sulfides, are responsible for *P. alliaceae* medicinal properties [12,13, 31-33]. Results further showed that administration of *P. alliaceae* aqueous leaf extract for 7 days prior and after the LPS injection in animals, reversed the changes observed in the activities of SOD and CAT activities. Our findings are consistent with those of Vasanthkumar *et al.* [27] and Hou *et al.* [26], as well as Ajuwon *et al.*, [6]. The modulation of these antioxidant enzymes activities by the administration of *P. alliaceae* aqueous leaf extract could be ascribed to the direct reduction of reactive oxygen and nitrogen species (RONS) generated by LPS, due to its numerous bio-active compounds such as flavonoids compounds that

are free radical scavengers [34]. It is crucial to note that while this research was done on male rats, the results may or may not apply to female rats. Some animal research found a sex-related differential in oxidative stress and cellular antioxidant enzyme activity, which could be organ specific [6. 35,36].

Table 1: Plasma, erythrocytes, brain, liver, heart, and kidney superoxide dismutase (SOD) activities of *Petiveria alliaceae* aqueous leaf extract to male rats with lipopolysaccharide induced-endotoxicity

Treatment dose	Superoxide dismutase activities					
	Plasma (µ/ml)	Erythrocytes (µ/ml)	Brain (mg/g)	Liver (mg/g)	Heart (mg/g)	Kidney (mg/g)
Control	0.11±0.02 ^a	0.026±0.03 ^a	0.08±0.01 ^a	0.46±0.07 ^a	0.13±0.01 ^a	0.24±0.04 ^a
<i>P. alliaceae</i> extract	0.27±0.07 ^b	0.035±0.02 ^b	0.14±0.02 ^b	0.57±0.04 ^b	0.21±0.02 ^b	0.13±0.01 ^b
LPS	0.08±0.01 ^{a*}	0.03±0.01 ^{a*}	0.06±0.01 ^{a*}	0.04±0.01 ^{a*}	0.03±0.01 ^{a*}	0.03±0.01 ^{a*}
LPS + <i>P. alliaceae</i> extract	0.14±0.03 ^{a*b*}	0.44±0.01 ^{a*b*}	0.11±0.01 ^{a*b*}	0.09±0.02 ^{a*b*}	0.16±0.02 ^{a*b*}	0.25±0.04 ^{a*b*}
<i>P. alliaceae</i> extract + LPS + <i>P. alliaceae</i> extract	0.37±0.06 ^{a**b**}	0.035±0.01 ^{a**b**}	0.12±0.02 ^{a**b**}	0.48±0.04 ^{a**b**}	0.17±0.01 ^{a**b**}	0.42±0.03 ^{a**b**}

4. CONCLUSION

Based on the findings, it is reasonable to conclude that LD₅₀ shows of *P. alliacea* aqueous leaf extract is nontoxic and prevents LPS-mediated oxidative stress by increasing CAT and SOD activities. Also, LPS-mediated cellular damage is also prevented by pretreatment with *P. alliacea* aqueous leaf extract. This could be owing to its antioxidant defense system's direct free radical scavenging activity.

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COMPETING INTERESTS

There are no competing interests declared by the authors regarding the publication of this paper.

AUTHORS' CONTRIBUTIONS

'OOO' designed the study with 'OOF', and RIK managed the analyses of the study, wrote the protocol and the manuscript. 'OAO' and 'AA' managed the literature searches and performed the analyses of the study, performed the statistical analysis. 'OBA', 'OSO' and 'BOE' give guidance on the protocol. All authors read and approved the final manuscript."

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