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Research Article

Hepatoprotective Effects of Vernonia amygdalina Leaves and Persea americana Seed Extracts in a Lipopolysaccharide-Induced Preeclamptic Rat Model

Funmilola C. OLADELE[1*], Augustine I. AIRAODION[2], Bukola OJO[3], Omolola O. AJAYI[4]
[1]Department of Medical Biochemistry, College of Medicine, Ekiti State University, Ado-Ekiti, Nigeria.
[2]Department of Biochemistry, Lead City University, Ibadan, Oyo State, Nigeria.
[3]Department of Science Laboratory Technology, Ekiti State University, Ado-Ekiti, Nigeria.
[4]Department of Obstetrics and Gynaecology, Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria.

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***Corresponding author:** Funmilola C. Oladele. 1Department of Medical Biochemistry, College of Medicine, Ekiti State University, Ado-Ekiti, Nigeria.

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Abstract:

Background: Preeclampsia is a pregnancy-specific hypertensive disorder associated with liver dysfunction. This study evaluated the hepatoprotective potentials of *Vernonia amygdalina* (bitter leaf) and *Persea americana* (avocado) extracts in a lipopolysaccharide (LPS)-induced preeclamptic rat model.

Materials and Methods: Fifty-four pregnant female albino rats were grouped into nine groups (A–I). Preeclampsia was induced with lipopolysaccharide (0.1 mL, intraperitoneally) at gestational days 13–15. Groups D–I received either 100 mg/kg or 200 mg/kg of ethanolic extracts of *V. amygdalina* leaves, *P. americana* leaves, or *P. americana* seeds. Group C received Aldoxi (0.036 mg/kg), while Group A served as a control, and Group B received lipopolysaccharide (LPS) only. Extracts were administered orally for seven days. Blood samples were collected at gestational days 20–21 for biochemical analysis of hepatic indices.

Results: LPS significantly impaired liver function, as indicated by increased ALT, AST, ALP, and bilirubin levels, and decreased total protein and albumin. Treatment with plant extracts, especially at 200 mg/kg doses, significantly restored liver function parameters toward normal, comparable to the standard drug group. Notably, *P. americana* seed extract (200 mg/kg) showed comparable efficacy to *V. amygdalina* and *P. americana* leaf extracts.

Conclusion: Ethanolic extracts of *V. amygdalina* leaves and *P. americana* seed and leaf possess hepatoprotective effects in LPS-induced preeclamptic rats. Their bioactive compounds may contribute to ameliorating hepatic dysfunction associated with preeclampsia.

Keywords: Hepatoprotection, *Vernonia amygdalina*, *Persea americana*, preeclampsia, lipopolysaccharide, liver enzymes

Introduction:

Preeclampsia remains a major obstetric complication and a significant contributor to maternal and perinatal morbidity and mortality worldwide, particularly in low- and middle-income countries. It is a multifactorial hypertensive disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation [1]. Despite extensive research, its pathogenesis remains incompletely understood. However, increasing evidence supports the role of systemic inflammation, oxidative stress, endothelial dysfunction, and placental ischemia in the progression of preeclampsia [2][3].

Lipopolysaccharide (LPS), a bacterial endotoxin, has been widely used in animal models to mimic the inflammatory aspects of preeclampsia by activating toll-like receptor 4 (TLR4)-mediated pathways, leading to hepatic and vascular inflammation [4].

The liver plays a critical role in systemic metabolism and detoxification, and hepatic dysfunction in preeclampsia is associated with elevated liver enzymes, oxidative stress, and in severe cases, HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count) [5][6]. These hepatic complications contribute significantly to maternal morbidity and necessitate the exploration of hepatoprotective agents that can ameliorate liver injury associated with preeclampsia.

In recent years, there has been growing interest in the use of plant-based therapies for the management of preeclampsia and its complications, owing to their antioxidant, anti-inflammatory, and hepatoprotective properties [7]. Two promising medicinal plants in this regard are *Vernonia amygdalina* and *Persea americana*, which are widely used in African traditional medicine.

Vernonia amygdalina, commonly known as bitter leaf, is a perennial shrub of the Asteraceae family known for its wide range of pharmacological effects, including antioxidant, anti-inflammatory, hepatoprotective, antihyperlipidemic, and antihypertensive activities [8][9][10]. The leaves of *V. amygdalina* contain bioactive compounds such as flavonoids, saponins, alkaloids, and terpenoids that are effective in scavenging free radicals and modulating inflammatory cytokines, which are pivotal in the pathology of preeclampsia [11].

Persea americana (avocado), particularly its seed, is an underutilised part of the plant but is increasingly gaining recognition for its high antioxidant content and pharmacological activities. Studies have demonstrated the seed extract's hepatoprotective, anti-inflammatory, and antihypertensive effects attributed to its rich phytochemical composition, including phenolics, flavonoids, and triterpenoids [12][13]. Its antioxidative effects make it a potential candidate for mitigating oxidative stress and hepatocellular damage associated with preeclampsia.

Several studies have explored the protective effects of natural products in LPS-induced organ damage models. For instance, plant-derived antioxidants have shown efficacy in modulating oxidative damage and restoring liver enzyme activities in animal models of preeclampsia and systemic inflammation [14][15]. However, few studies have examined the synergistic hepatoprotective effects of combining *V. amygdalina* and *P. americana* seed extracts in the context of LPS-induced preeclampsia.

Given the increasing burden of preeclampsia and its associated hepatic complications, coupled with the limitations of current therapeutic approaches, there is a compelling need to investigate safer and more effective alternatives. This study, therefore, seeks to evaluate the hepatoprotective potentials of *Vernonia amygdalina* leaves and *Persea americana* seed extracts in a lipopolysaccharide-induced preeclamptic rat model. By elucidating the mechanistic pathways through which these plant extracts exert protective effects, the study aims to contribute to the development of novel adjunct therapies for managing preeclampsia-associated hepatic dysfunction.

Materials And Methods

Collection and preparation of samples

Bitter leaves (*Vernonia amygdalina*) and Avocado leaves and seed (*Persea americana*) were sourced locally in Ikere-Ekiti, Ekiti State, Nigeria. They were identified and authenticated at the Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Ibadan, Oyo-State, Nigeria and assigned the voucher specimen numbers 2022010 and 2022009 for *V. amygdalina* and *P. americana* respectively. The leaves of the bitter leaf and avocado leaf were detached from the stem. They were rinsed thoroughly with clean water and they were spread on a sack and placed under room temperature for drying. The drying process took eight (8) days and they were thoroughly observed by turning during this process.

The avocado fruits were cut and opened to remove the avocado seed and grated into smaller pieces for an easy drying process. The grated avocado seed was spread on a sack and was placed at room temperature for drying. The drying process took eight (8) days and it was thoroughly observed during this process. The samples were weighed using a weighing balance after. It has dried before it was turned into a powder form. The samples (bitter leaf, avocado leaf etc) were blended using a blending machine and weighed in the laboratory using weighing balance.

Extraction of Samples

The weighed samples were soaked with 95% ethanol for 72 hours in different labelled containers with periodic stirring. After 72 hours, each sample was filtered using the Whatman filter paper and dried. They were preserved at 4 ^{o}C in the refrigerator for further analysis.

Experimental Design

Fifty-four female albino rats were obtained from the animal house Faculty of Basic Medical Sciences, College of Medicine, Ekiti State University, Ado Ekiti. They were housed in a plastic cage with steel wire lids, and two male albino rats were introduced into each cage for copulation.

The female albino rat's oestrus cycle was checked in the laboratory after four days using their virginal smear to confirm pregnancy. Few rats were confirmed pregnant on the fourth day and on the sixth day, the entire fifty-four rats were confirmed pregnant, and the male rats were removed from each cage. The pregnant albino rat was then grouped in another cage (Group A to Group I) with six in each cage. The rats were transported to the Cardio Renal Unit Laboratory, Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, College of Medicine, University of Ibadan, Oyo State, Nigeria.

Animal Treatment

Lipopolysaccharide (LPS) was used for the induction of preeclampsia at gestational ages 13 and 14 days of pregnancy. Administration of 0.1 mL of LPS through the intraperitoneal route for 3 consecutive days. Treatment was done concurrently with induction but lasted for 7 days. The treatment was as follows:

Group A: Normal control (Feed and water only)
Group B: LPS only
Group C: LPS + 0.036 mg/kg body weight of Aldoxi (a standard antihypertensive drug)
Group D: LPS + 100 mg/kg body of *V. amygdalina* leaf extract
Group E: LPS + 200 mg/kg body of *V. amygdalina* leaf extract
Group F: LPS + 100 mg/kg body of *P. americana* leaf extract
Group G: LPS + 200 mg/kg body of *P. americana* leaf extract

Group H: LPS + 100 mg/kg body of *P. americana* seed extract
Group I: LPS + 200 mg/kg body of *P. americana* seed extract

At the end of the 7-day treatment period, the animals were sacrificed at gestational ages of 20 and 21 days. Blood samples were obtained by cardiac puncture and dispensed into labelled lithium heparin bottles. The blood samples were centrifuged at 4000 rpm for 5 minutes to obtain plasma, which was then stored in sterile plastic bottles and refrigerated at -20°C until analysis.

Biochemical Analysis

Hepatic indices were assessed following the procedures outlined by Airaodion et al. [16].

Data Analysis

One-way ANOVA was used to analyze the data, and the Tukey post hoc mean comparison test was employed to see whether there were any statistically significant differences between the variables. The analyzed data were expressed as the mean and standard deviation of the mean for six replicates. Statistical significance was defined as a P-value of 0.05 or below ($P \leq 0.05$). GraphPad Prism was used for all statistical analyses (version 8.0).

Results

The concentration of total protein (Figure 1) was highest in the normal control group A (92.32 ± 5.48 mg/dl) and lowest in the LPS-only group B (62.48 ± 3.55 mg/dl). Treatment with Aldoxi (Group C) and plant extracts (Groups E, G, I) helped restore protein levels closer to control values. Treatment with Aldoxi and plant extracts helped restore protein levels closer to control values. Albumin (Figure 2) followed a similar pattern, with Group A having the highest value (61.32 ± 3.14 mg/dl) and Group B the lowest (40.71 ± 3.49 mg/dl). Groups C, E, G, and I showed improved albumin levels.

AST levels (Figure 3) were elevated in Group B (36.46 ± 1.61 IU/L), while Group A recorded the lowest (27.44 ± 4.92 IU/L). Treatment groups, especially C, E, G, and I, showed reduced AST values. ALT (Figure 4) was also increased in Group B (35.79 ± 4.15 IU/L) but reduced in Group C (26.06 ± 2.75 IU/L) and others like E, G, and I, approaching the control level (24.91 ± 1.79 IU/L). ALP (Figure 5) was highest in Group B (96.79 ± 5.75 IU/L) and lowest in Group A (60.78 ± 4.29 IU/L). Groups C, E, G, and I had ALP values (ranging 67.34–69.03 IU/L) closer to normal. Total and conjugated bilirubin (Figures 6 and 7) increased in Group B (0.30 ± 0.02 mg/dl), while Group A maintained the lowest value (0.16 ± 0.02 mg/dl). This elevation was moderately reduced in treated groups, with Groups C, E, G, and I exhibiting near-normal values (0.18–0.19 mg/dl).

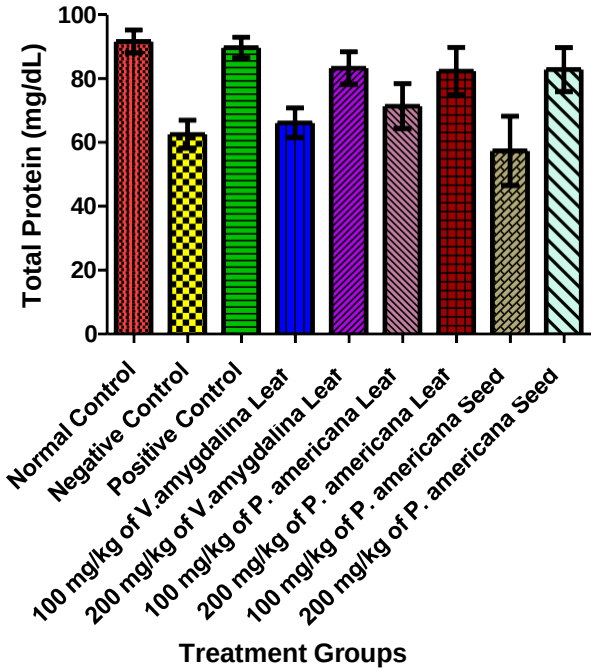

Figure 1: Effect of *Persea americana* and *Vernonia amygdalina* on the Total Protein level of Lipopolysaccharides-exposed Pregnant Rats

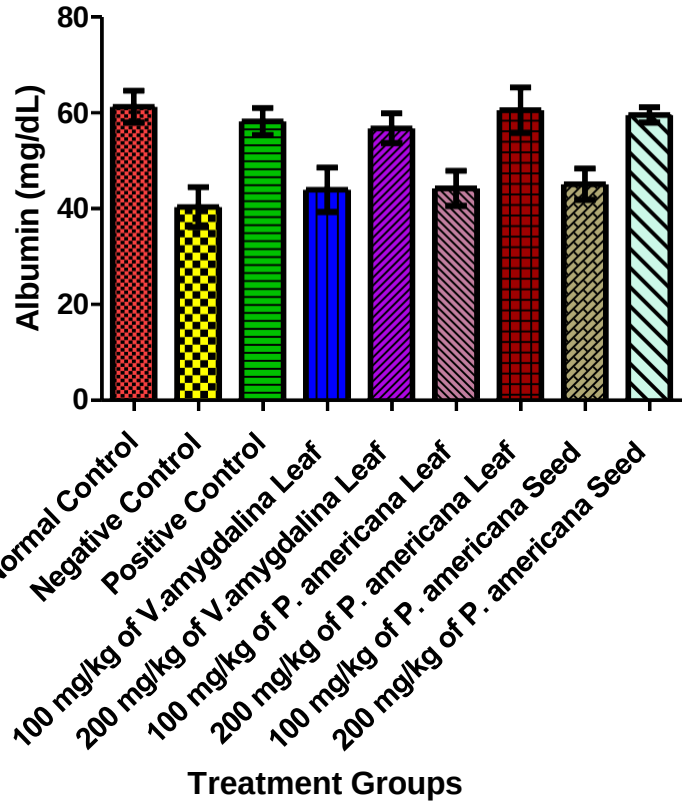

Figure 2: Effect of *Persea americana* and *Vernonia amygdalina* on the Albumin level of lipopolysaccharides-exposed Pregnant Rats

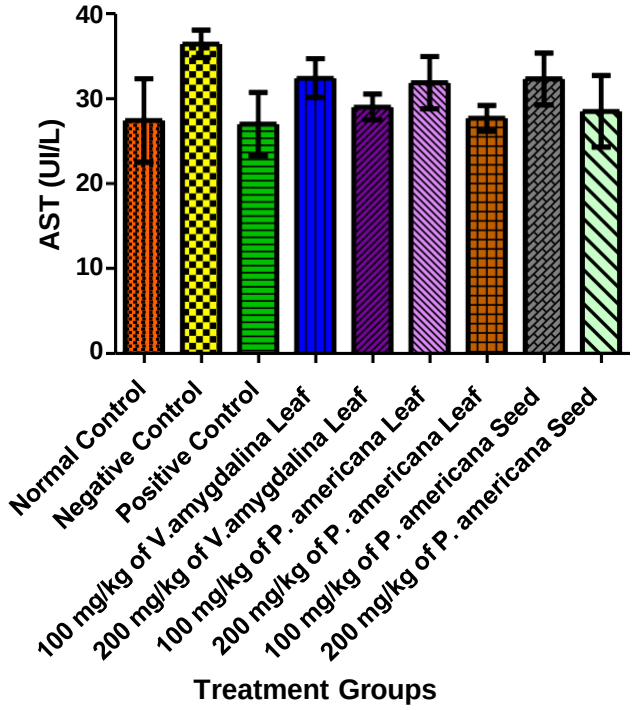

Figure 3: Effect of *Persea americana* and *Vernonia amygdalina* on the Aspartate Aminotransferase level of lipopolysaccharides-exposed Pregnant Rats

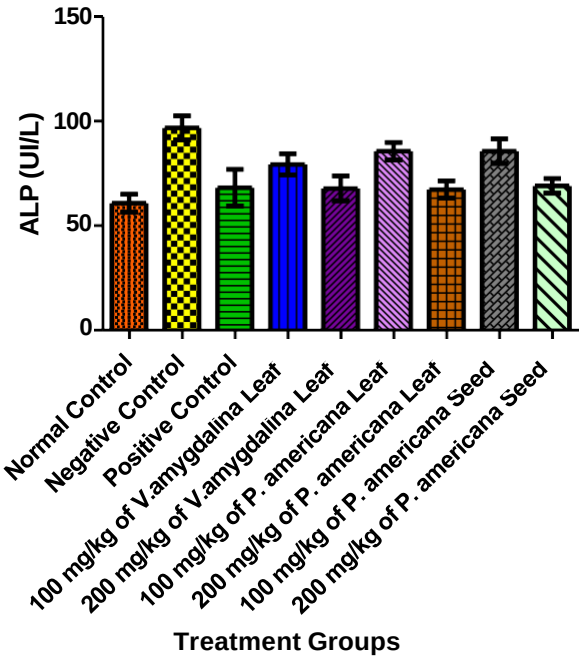

Figure 5: Effect of *Persea americana* and *Vernonia amygdalina* on the Alkaline Phosphatase level of lipopolysaccharides-exposed Pregnant Rats

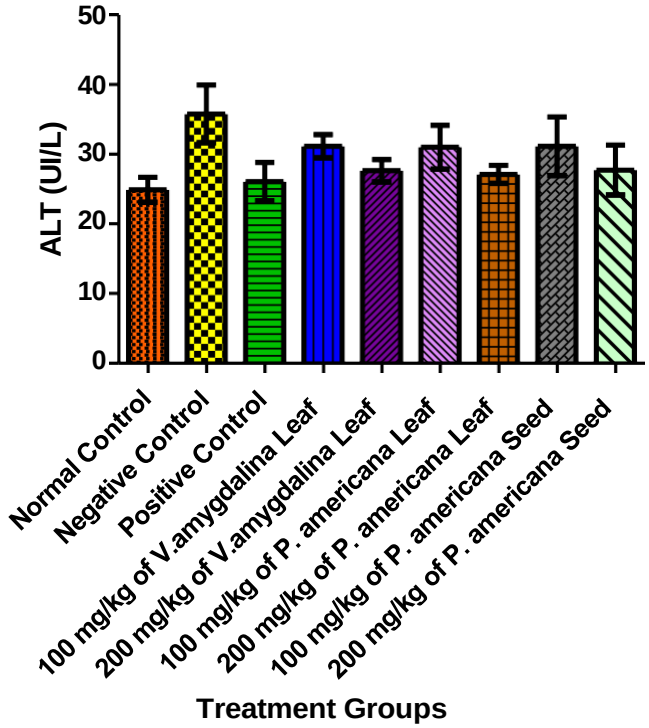

Figure 4: Effect of *Persea americana* and *Vernonia amygdalina* on the Alanine Aminotransferase level of lipopolysaccharides-exposed Pregnant Rats

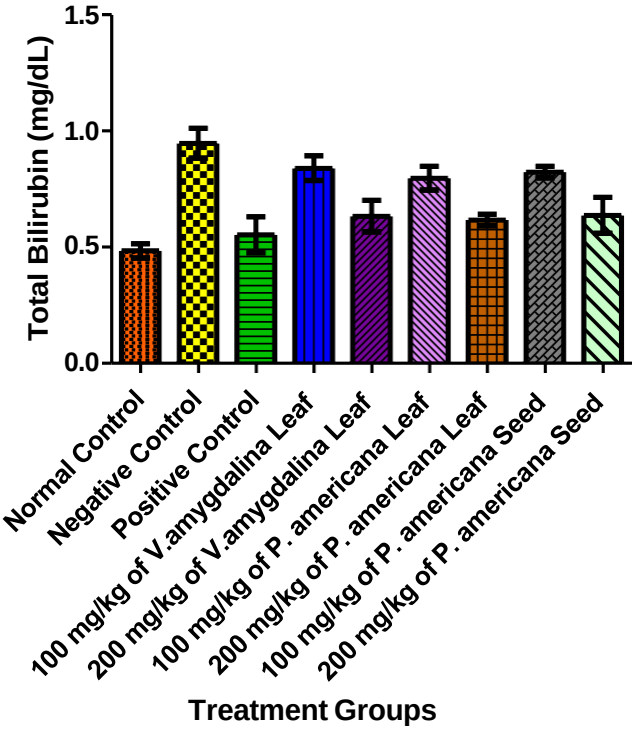

Figure 6: Effect of *Persea americana* and *Vernonia amygdalina* on the Total Bilirubin level of lipopolysaccharides-exposed Pregnant Rats

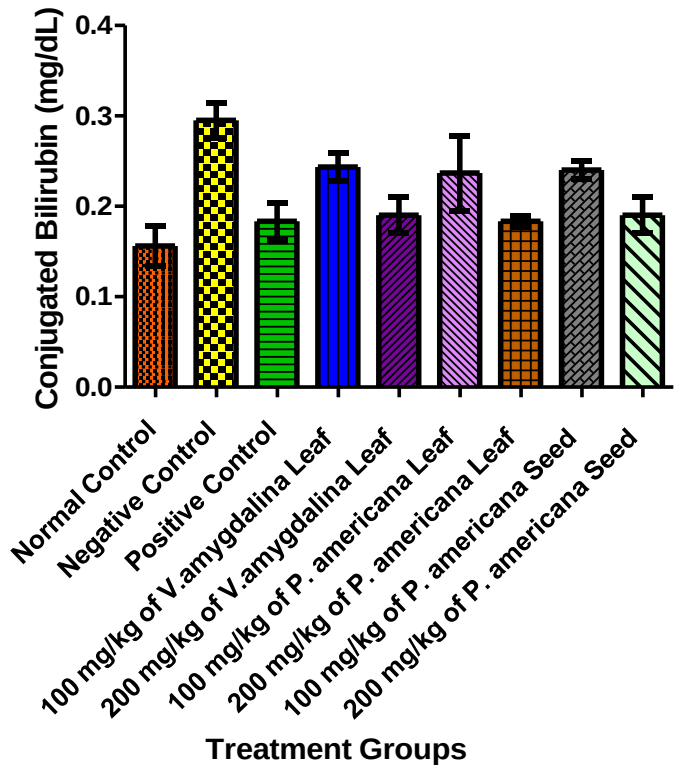

Figure 7: Effect of *Persea americana* and *Vernonia amygdalina* on the Conjugated Bilirubin level of lipopolysaccharides-exposed Pregnant Rats

Discussion

The present study evaluated the hepatoprotective effects of *Vernonia amygdalina* (VA) leaf and *Persea americana* (PA) seed and leaf extracts on hepatic biomarkers in a lipopolysaccharide (LPS)-induced preeclamptic rat model. The induction of preeclampsia with LPS resulted in significant hepatic dysfunction, as evidenced by elevated levels of hepatic enzymes (AST, ALT, and ALP), increased conjugated bilirubin, and decreased total protein and albumin levels in LPS only group, compared to the normal control. These changes align with previous reports that associate LPS-induced inflammation with hepatic injury and compromised liver function [17][18].

LPS induces oxidative stress and inflammatory cascades, triggering hepatocellular damage and disrupting normal liver functions [19]. The significant increase in AST, ALT, and ALP in the LPS-treated group is indicative of hepatocellular damage, cholestasis, or both. Concurrently, the reduction in albumin and total protein levels may be attributed to impaired protein synthesis by damaged hepatocytes.

Interestingly, the groups co-treated with VA and PA extracts showed notable improvement in hepatic function parameters, suggesting protective effects against LPS-induced hepatic damage. Specifically, rats treated with higher doses (200 mg/kg) of VA leaf, PA leaf, and PA seed showed near-normal levels of liver enzymes and protein indices, comparable to those of the Aldoxi-treated group.

The total protein levels were significantly restored in the high-dose VA (83.30 ± 5.09 mg/dl), PA leaf (82.38 ± 7.38 mg/dl), and PA seed (82.85 ± 6.88 mg/dl) groups, compared to the LPS-only group (62.48 ± 3.55 mg/dl), and approached the normal control value (92.32 ± 5.48 mg/dl). This restoration is consistent with previous findings that *V. amygdalina* enhances protein synthesis through its antioxidant constituents, including flavonoids and saponins, which protect hepatocytes from oxidative stress [20][9].

Similarly, the ALT and AST levels in the high-dose groups decreased significantly compared to the LPS group. In Group E, ALT and AST were 27.63 ± 1.60 IU/L and 29.03 ± 1.51 IU/L, respectively, while Group G showed ALT and AST of 27.11 ± 1.30 IU/L and 27.70 ± 1.51 IU/L, values comparable to those in the Aldoxi-treated rats. These reductions in liver enzymes further corroborate the hepatoprotective effect of the extracts and suggest membrane stabilization and reduced hepatocyte leakage [16][21].

Notably, the PA seed extract demonstrated a hepatoprotective profile almost equivalent to that of the leaves, an observation not extensively reported in the literature. However, recent studies have begun to explore the pharmacological potential of *P. americana* seeds, highlighting their antioxidant and anti-inflammatory properties [12][22]. The seed extract's efficacy in normalizing liver parameters such as AST (28.53 ± 4.23 IU/L) and ALP (69.03 ± 3.52 IU/L) underscores its potential as a therapeutic candidate for hepatic dysfunction.

Furthermore, the reduction in conjugated bilirubin levels across all extract-treated groups, particularly Groups E, G, and I, suggests improved liver detoxification and bile excretion. The elevated bilirubin in the LPS group (0.30 ± 0.02 mg/dl) reflects hepatic insufficiency or biliary obstruction, both of which were mitigated following extract administration, likely due to the anti-inflammatory properties of phytochemicals in the extracts [23].

These findings align with those of Nwangwa et al. [24] and Babalola et al. [25], who reported significant hepatoprotective effects of *V. amygdalina* and *P. americana* in models of chemically induced liver injury. The mechanism is believed to involve scavenging of reactive oxygen species, inhibition of lipid peroxidation, and preservation of hepatocyte integrity.

In comparing the standard drug (Aldoxi) and the extracts, the standard drug performed comparably to the high-dose extract groups, suggesting that VA and PA possess therapeutic effects potentially equivalent to synthetic antihypertensive and hepatoprotective agents, though further clinical validation is required.

Conclusion

The findings of this study demonstrate that *V. amygdalina* leaf and *P. americana* seed and leaf extracts exert substantial hepatoprotective effects in an LPS-induced preeclamptic rat model. These protective effects are dose-dependent and are likely mediated by antioxidant, anti-inflammatory, and membrane-stabilizing properties of the phytochemicals present in the extracts. These findings not only validate the traditional use of these plants in ethnomedicine but also suggest potential integrative applications in managing pregnancy-associated hepatic complications, such as those observed in preeclampsia.

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