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Evaluation of Hepatoprotective Activities of Bryophyllum pinnatum Leaf Extract in Paracetamol Induced Toxicity in Wistar rats

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Abstract

Paracetamol-induced hepatotoxicity poses a significant health risk. Bryophyllum pinnatum (commonly known as "Never Die") has traditional medicinal applications, including potential hepatoprotective effects. This study evaluated the protective effects of B. pinnatum leaf extract on paracetamol-induced liver toxicity in Wistar rats. Five groups were examined: a normal control, a paracetamol-only group (2 g/kg), two treatment groups receiving paracetamol with 200 mg/kg or 400 mg/kg B. pinnatum extract, and a standard control treated with 200 mg/kg vitamin E. After two weeks, blood samples were analysed for liver enzymes and antioxidant biomarkers. Paracetamol significantly elevated AST, ALT, ALP, LDH, and creatinine levels ($p<0.05$), indicating liver damage. Rats treated with 400 mg/kg B. pinnatum extract showed marked reductions in AST (94.48±3.38 U/L), ALT (79.74±4.12 U/L), and LDH (15.36±0.64 U/L), comparable to vitamin E treatment. Antioxidant markers were also altered: SOD, catalase, and GSH levels decreased in the paracetamol group, while MDA increased significantly. Treatment with 400 mg/kg B. pinnatum improved these parameters—SOD (5.90±0.17 U/mg protein), catalase (4.49±0.24), GSH (5.75±0.44), and MDA (2.85±0.18)—indicating restored oxidative balance. These effects mirrored those observed in the vitamin E-treated group. The study concludes that B. pinnatum extract, particularly at higher doses, offers significant hepatoprotective and antioxidant effects against paracetamol-induced liver damage. This supports its potential use in managing drug-induced hepatic injury.

Keywords: *Bryophyllum pinnatum*, paracetamol, hepatoprotective, antioxidant, liver enzymes, oxidative stress.

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1. Introduction

Paracetamol, a commonly employed painkiller and antipyretic, is a widespread cause of acute liver damage worldwide (1, 2). A variety of lesions are formed when this medicine interacts with vital liver components, such as proteins, lipids, RNA, and DNA. This is because the enzyme cytochrome P4502E1 is responsible for making the poisonous metabolite N-acetyl-p-benzoquinoneimine, or NAPQI. According to Chiew *et al*. (1), this chemical has the ability to disrupt calcium homeostasis and cause a dose-dependent reduction in intracellular glutathione levels. The role of oxygen free radicals (OFR) in a

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wide variety of diseases has received a lot of research interest in the last several decades. Notwithstanding the existence of strong antioxidant defence systems designed to counteract OFR and reduce possible oxidative damage, the buildup of OFR-induced harm to DNA and other biological molecules transpires throughout an organism's lifespan (3). Active oxygen molecules, such as superoxide and hydroxyl radicals, are well-documented as pivotal in the inflammatory response induced by paracetamol (4).

The liver, as the primary organ for biochemical processes in the human body, regulates metabolic balance and facilitates the transformation, detoxification, and excretion of various endogenous and exogenous substances, including drugs and environmental toxins (5). Thus, damage to the liver caused by hepatotoxic substances has significant consequences (6). A multitude of xenobiotics, including paracetamol, have been recognised as possible hepatotoxic agents (1). Consequently, liver damage caused by hepatotoxic substances is very consequential. A significant quantity of xenobiotic, including paracetamol, has been identified as a possible hepatotoxic agent (1). Liver damage results in decreased levels of the antioxidant glutathione (GSH) (7). This subsequently induces cellular necrosis and elevates the concentrations of biochemical markers in the serum, including creatine kinase, lactate dehydrogenase, amino transaminase, alanine transaminase, and alkaline phosphatase (8, 9).

B. pinnatum (Lam.) Crassulaceae is commonly referred to as the African never die leaf plant or air plant. Alcoholic and aqueous extracts of the leaves are extensively utilised as mono- or polyherbal remedies for several medical applications by indigenous communities, including anti-diabetic, anticancer, and antibacterial treatments (2). B. pinnatum contains a diverse array of phytochemicals that enhance its medicinal properties. Essential components comprise flavonoids, alkaloids, tannins, phenolic compounds, glycosides, and organic acids. Flavonoids, including quercetin and kaempferol, are recognised for their antioxidant properties, providing defence against oxidative stress and inflammation (10). Tannins facilitate wound healing and possess antibacterial qualities, whereas alkaloids confer analgesic and anti-inflammatory advantages to the plant. The cardiotonic effects are attributed to glycosides, but the antioxidant capacity is augmented by phenolic compounds. The antibacterial characteristics of organic acids like citric acid and malic acid augment the plant's therapeutic profile. *B. pinnatum* is a versatile medicinal herb that possesses compounds that aid in reducing inflammation, promoting wound healing, and treating ulcers (11).

According to Afzal *et al*. (11), *B. pinnatum* has a long history of medicinal use in treating a variety of conditions, such as diabetes, liver and kidney diseases, obesity, dyslipidaemia, cough, wounds, ulcers, infections, and anaemia (12). Herbs can cause a number of health problems, yet some people who use alternative and complementary medicine mistakenly think they have few, if any, negative effects compared to many mainstream drugs. This assumption may lead to the reckless use of herbs. Because of this misconception, *B. pinnatum* is being used more and more in traditional medicine. Inappropriate dosing of some medicinal plants and herbal treatments might endanger important bodily functions, such as the kidneys and liver. Ghasi *et al*. (13) suggested that the alkaloids and saponins in *B. pinnatum* leaves can be toxic to organs if consumed in large doses. This study aims to investigate the potential protective effects of an ethanol extract from *B. pinnatum* leaves against paracetamol-induced liver injury in Wistar rats.

2. Material and Methods

2.1. Collection and Preparation of Plant Extract

Fresh leaves of *B. pinnatum* were harvested in a home garden from Kpansia, Yenagoa Local Government, Bayelsa State. The plant sample was positively identified by Prof. Inetiminebi Arrow Ogidi of the Niger Delta University's Department of Plant Breeding in Bayelsa State, Nigeria. The plant sample was left under shade at room temperature for two weeks to dry. The next step was to finely powder them. Then, soak 500 g of the powder in 2 litres of ethanol and let it rest for 48 hours

while stirring occasionally. The extract was passed through a filter of Whattman size 110 mm, and the resulting filtrate was evaporated at 400 °C in a rotary evaporator. Distilled water was used to reconstitute the powdered residue as directed.

2.2. Experimental Animals

The College of Health Sciences, Department of Pharmacology at the University of Port Harcourt in Rivers State, obtained twenty-five (25) male albino rats from the University's animal house. Their weight ranged from 150 to 200 g. The rats were housed in standard rat cages at the College of Health Sciences, Faculty of Basic Medical Sciences, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria. Prior to the commencement of the trial, the animals were allotted 14 days to acclimatise to their new environment, which comprised a 12-hour light/dark cycle, fresh air, and unrestricted access to commercial grower's mash (Delta Feeds).

2.3. Experimental Design

The animals were randomly assigned to five (5) groups, each consisting of five (5) rats, and were pre-treated accordingly in a standard plastic rat cage.

Group I: Normal control group received distilled water for a duration of 14 days.

Group II: Positive control: Paracetamol (2 g/kg) administered with distilled water for a duration of 14 days.

Group III: Treatment group 1: Paracetamol (2 g/kg) combined with extract (200 mg/kg body weight for 14 days).

Group IV: Treatment group 2: Paracetamol (2 g/kg) extract (400 mg/kg body weight for 14 days).

Group V: Standard Control: Paracetamol (2 g/kg) Administration of Vitamin E at a dosage of 200 mg/kg body weight for a duration of 14 days.

2.4. Administration of Augmentin

Animals in groups 2, 3, 4, and 5 were administered 2 g of paracetamol per kilogram of body weight orally after acclimatisation to their environment to induce toxicity. The experimental design was implemented after a 24-hour period. Animals were subjected to chloroform anaesthesia and euthanised at the end of the fourteenth day.

2.5. Collection of Samples

Following a cardiac puncture, blood was extracted into standard arteries and allowed to stand for 30 minutes to facilitate coagulation. The blood samples were centrifuged at 2000 RPM for 10 minutes. A biochemical analysis was conducted on the serum-containing supernatant. The homogenate utilised in the antioxidant assays was prepared from samples of the liver, kidneys, and heart.

2.6. Biochemical Analysis

To assess liver function, we employed the method outlined in (6) to measure serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The same method was also employed to measure alkaline phosphatases (ALP). The protocols outlined in (6, 14) were used to measure the levels of blood creatinine (CREA) and lactate dehydrogenase (LDH). The antioxidant effects of vitamin E and paracetamol-induced oxidative stress in rats, specifically SOD, catalase, GSH, and MDA, were quantified using the methodologies outlined in (15-17).

2.7. Statistical Analysis of Data

The data was expressed using the Mean Percentage Error. The statistical analysis instrument for the social sciences (SPSS 17.0) was employed to determine whether there were significant differences among the groups using one-way analysis of variance (ANOVA).

3. Results

3.1. Effects of Different Treatments on Liver

Enzyme Levels in Experimental Animal Model

Table 1. represents the results of an experimental study conducted on different treatment groups in an animal model. The findings indicate that the liver enzyme levels in the normal control group were initially within the normal range, whereas the positive control group, which received paracetamol and distilled water, exhibited significantly elevated enzyme levels. In comparison to the control group, Treatment Group 1, which received paracetamol in conjunction with 200 mg/kg extract, exhibited significantly increased liver enzyme levels. The treatment group administered paracetamol and 400 mg/kg extract exhibited decreased enzyme levels in comparison to the positive control group. Following the administration of 200 mg/kg of vitamin E and paracetamol, enzyme levels in the placebo group were observed to be lower than those in the positive control group. Statistical analysis indicates that means within the same column and sharing superscripts do not exhibit significant differences (Figures 1 and 2). The findings of the study indicate that the extract and vitamin E may exert a protective effect on liver enzymes in the animal model.

3.2. Antioxidant Effects of Extract and Vitamin E in Paracetamol-Induced Oxidative Stress in Rats

The normal control group demonstrated statistically significant increases in superoxide dismutase (SOD), catalase, and glutathione (GSH) levels, alongside a decrease in malondialdehyde (MDA) levels, when compared to the paracetamol-treated positive control group. The second treatment group, administered 400 mg/kg of extract, exhibited the most favourable results, characterised by intermediate levels of SOD, Catalase, and GSH, alongside the lowest MDA levels. Consistent with the Normal Control group, the Standard Control group administered 200 mg/kg of vitamin E exhibited increased levels of SOD, GSH and catalase.

4. Discussion

The liver is the primary target of all poisonings. This is due to the fact that numerous studies have demonstrated the critical function of the liver in the biotransformation and elimination of toxic substances (7, 18). The results in Table 1 showed that paracetamol administration significantly increased AST levels (135.48±5.11 U/L) compared to the normal control (81.13±3.27 U/L). This aligns with the study by Mahmoud *et al*. (19), which reported elevated AST levels in paracetamol-induced hepatotoxicity. The *B. pinnatum* extract at 400 mg/kg (94.48± 3.38 U/L) and vitamin E (87.23±4.40 U/L) showed significant reduc-

Table 1. Effects of Different Treatments on Liver Enzyme Levels in Experimental Animal Model.

Experemental Group	AST (U/L)	ALP (U/L)	ALT (U/L)	CREATININE (U/L)	LDH (U/L)
Normal control	81.13±3.27^{c}	90.29±4.96^{c}	53.72±3.85^{c}	0.70±0.04^{a}	14.46±0.69^{b}
Positive control with 2g/kg paracetamol and distilled water	135.48±5.11^{d}	139.23±4.58^{d}	127.36±4.98^{d}	2.05±0.22^{a}	40.35±3.02
Treatment Group 1 induced with 2g/kg paracetamol and 200mg/kg extract	118.95±4.69^{d}	120.75±2.81^{d}	100.94±6.88^{d}	1.47±0.14^{a}	26.48±3.73^{c}
Treatment group 2 induced with 2g/kg paracetamol and 400mg/kg extract	94.48± 3.38^{c}	114.03±9.89^{d}	79.74±4.12^{c}	1.20±0.41^{a}	15.36±0.64^{b}
Standard control induced with 2g/kg paracetamol and 200mg/kg vitamin E	87.23± 4.40^{c}	110.16±9.89^{d}	75.07±4.13^{c}	1.00±0.66^{a}	14.82±0.97^{b}

Data are expressed as the mean ±SD (n=5). Means within the same column carrying the same superscripts are not significantly ($p<0.05$) different.

tion in AST levels, indicating hepatoprotective effects. This corresponds to the research by Afzal *et al*. (20), which demonstrated the hepatoprotective potential of plant extracts in reducing AST levels in paracetamol toxicity.

Paracetamol administration increased ALP levels (139.23±4.58 U/L) compared to the normal control (90.29±4.96 U/L). Both doses of *B. pinnatum* extract and vitamin E showed a reduction in ALP levels, with the 400 mg/kg dose (114.03±9.89 U/L) being more effective (Table 1 and Figures 1 and 2). This is in accordance with the research by Shabbir *et al*. (21), which reported similar ALP-lowering effects of plant extracts in paracetamol-induced liver damage. ALT levels were significantly elevated in the paracetamol group (127.36±4.98 U/L) compared to the normal control (53.72±3.85 U/L). The 400 mg/kg extract dose (79.74±4.12 U/L) and vitamin E (75.07±4.13 U/L) showed remarkable reductions in ALT levels. This is in agreement with the study by Olayinka *et al*. (22), which demonstrated the efficacy of plant extracts in normalising ALT levels in hepatotoxicity models.

While creatinine levels increased with paracetamol administration (2.05±0.22 U/L), the extract treatments and vitamin E showed a dose-dependent reduction. This aligns with the findings of Adeyemi *et al*. (23), who reported improved kidney function markers with plant extract treatments in drug-induced toxicity. Paracetamol significantly increased LDH levels (40.35±3.02 U/L) compared to the normal control (14.46±0.69 U/L). The 400 mg/kg extract dose (15.36±0.64 U/L) and vitamin E (14.82±0.97 U/L) effectively reduced LDH to near-normal levels. This corresponds to the research by Sabiu *et al*. (24), which showed similar LDH-lowering effects of plant extracts in hepatotoxicity models.

Nevertheless, when compared to the normal control group, the antioxidant effects of the extract and vitamin E in rats subjected to paracetamol-induced oxidative stress resulted in a considerable decrease in SOD levels (2.71±0.16 U/mg protein). The SOD levels were raised by both the extract dose and vitamin E, although the 400 mg/kg dose (5.90±0.17 U/mg protein) demonstrated supe-

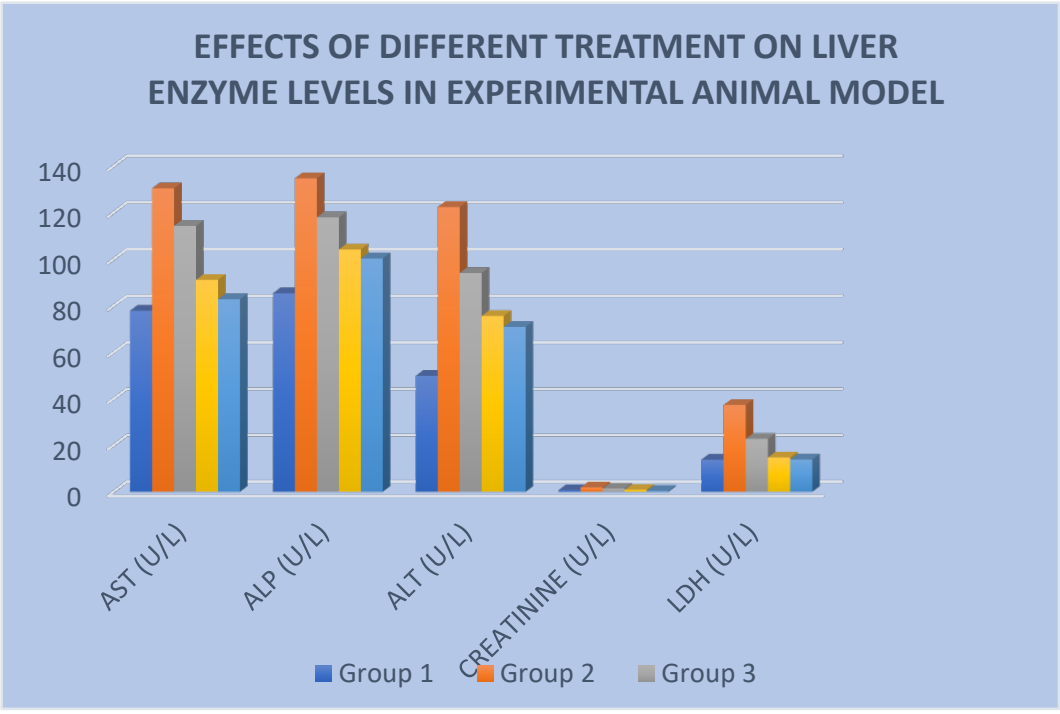

Figure 1. Comparative Effects of Treatments on Serum Liver Enzyme Activities in Paracetamol-Induced Hepatotoxicity Model in Rats.

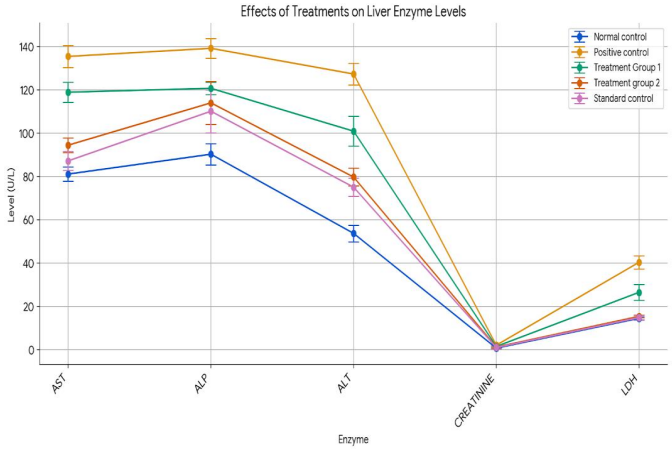

Figure 2. Error Bar Plot Depicting the Effects of Various Treatments on Serum Liver Enzyme Levels in Paracetamol-Induced Hepatotoxic Rats.

rior outcomes. This is in line with the findings of the study conducted by Njoku *et al*. (25), which indicated that drug-induced oxidative stress might be ameliorated with the use of plant extract therapies by increasing SOD activity. The normal control group had catalase activity of 6.45±0.44 U/mg protein, while the paracetamol group had a considerably lower level of 2.54±0.28 U/mg protein. The 400 mg/kg extract dose (4.49±0.24 U/mg protein) and vitamin E (6.00±0.64 U/mg protein) showed significant improvement in catalase activity. This aligns with the research by Oyedeji *et al.* (26), which demonstrated the antioxidant potential of plant extracts in restoring catalase activity in hepatotoxicity models.

Compared to the normal control group, GSH levels were lower after paracetamol treatment (2.77±0.12 U/mg protein). The GSH levels were elevated by both the extract dose and vitamin E, although the 400 mg/kg dose (5.75±0.44 U/mg protein) demonstrated superior outcomes. This is in line with what Okokon *et al*. (27) found, where they also found that plant extracts improved GSH levels in oxidative stress caused by drugs. The paracetamol group showed a considerably higher amount of MDA, a marker of lipid peroxidation (5.01±0.14 U/mg protein), in comparison to the normal control group (2.78±0.20 U/mg protein) (Table 2 and Figures 3 and 4). The 400 mg/kg extract dose (2.85±0.18 U/mg

Table 2. Antioxidant Effects of Extract and Vitamin E in Paracetamol-Induced Oxidative Stress in Rats.

EXPERIMENTAL GROUP	SOD (U/mg protein)	Catalase (U/mg protein)	GSH (U/mg protein)	MDA (U/mg protein)
Normal Control	7.67 ± 0.38^{d}	6.45 ± 0.44^{d}	7.04 ± 0.81^{d}	2.78 ± 0.20^{a}
Positive control with 2g/kg paracetamol and distilled water	2.71 ± 0.16^{a}	2.54 ± 0.28^{a}	2.77 ± 0.12^{a}	5.01 ± 0.14^{c}
Treatment Group 1 induced with 2g/kg paracetamol and 200mg/kg extract	5.72 ± 0.22^{c}	3.78 ± 0.15^{b}	4.76 ± 0.25^{c}	3.50 ± 0.15^{b}
Treatment group 2 induced with 2g/kg paracetamol and 400mg/kg extract	5.90 ± 0.17^{c}	4.49 ± 0.24^{c}	5.75 ± 0.44^{c}	2.85 ± 0.18^{a}
Standard control induced with 2g/kg paracetamol and 200mg/kg vitamin E	6.20 ± 0.34^{d}	6.00 ± 0.64^{d}	6.28 ± 0.41^{d}	2.86 ± 0.20^{a}

Data are expressed as the mean ± SD (n=5). Means within the same column carrying same superscript are not significantly ($p<0,05$) different.

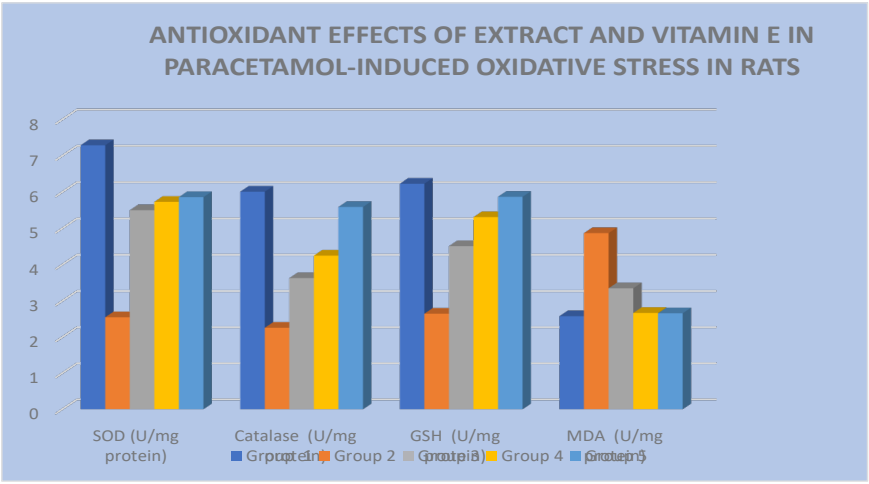

Figure 3. Comparative Antioxidant Effects of *B. pinnatum* Extract and Vitamin E on Oxidative Stress Markers in Paracetamol-Treated Rats.

protein) and vitamin E (2.86±0.20 U/mg protein) effectively reduced MDA levels to near-normal values. This is in accordance with the research by Ajiboye *et al*. (28), which showed similar MDA-lowering effects of plant extracts in hepatotoxicity models.

5. Conclusion

This study demonstrates that *B. pinnatum* extract significantly reduces paracetamol toxicity in Wistar rats by acting as an antioxidant and hepatoprotective agent. Particularly at the high dose of 400 mg/kg, the extract significantly reduced the overdose-induced increase in creatinine and liver enzymes (LDH, AST, ALP, ALT). An increase in GSH, SOD, and catalase activity further improved the antioxidant capabilities of B. pinnatum extract. Lipid peroxidation was reduced as shown by reduced levels of MDA. Like the well-known antioxidant vitamin E, the hepatoprotective and antioxidant effects of 400 mg/kg were striking. The results suggest that *B. pinnatum* extract could be a good natural choice for avoiding or dealing with drug-induced liver damage, particularly when paracetamol is involved.

This study's results indicate that additional research is necessary to thoroughly clarify the hepatoprotective and antioxidant processes of *B. pinnatum* extract. Subsequent research should concentrate on isolating and

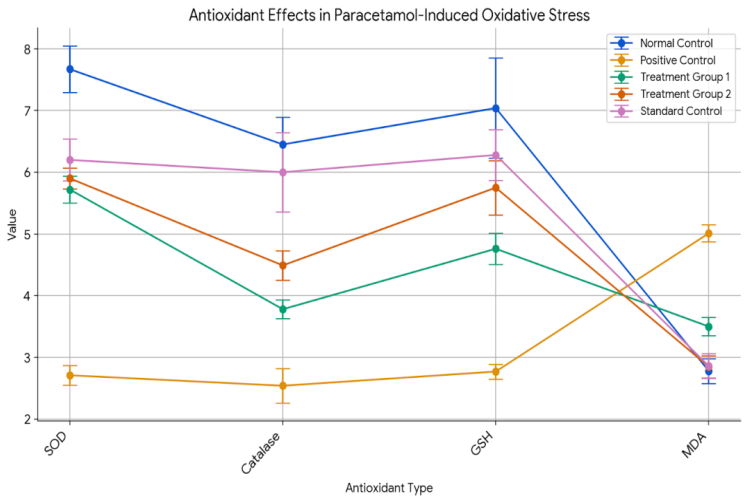

Figure 4. Error Bar Plot Illustrating the Antioxidant Effects of *B. pinnatum* Extract and Vitamin E on Oxidative Stress Biomarkers in Paracetamol-Induced Hepatotoxic Rats.

identifying the specific bioactive chemicals that contribute to these advantageous effects. Furthermore, it is advisable to conduct long-term safety research and clinical trials to evaluate the extract's efficacy and safety in humans. Investigating the potential synergistic benefits of *B. pinnatum* extract in conjunction with current hepatoprotective medications might be beneficial. Furthermore, investigation into the creation of standardised formulations of *B. pinnatum* extract for prospective medicinal applications should be prioritised. Ultimately, investigating the extract's protective properties against various hepatotoxic substances and in diverse liver injury models could expand its prospective applications in liver health management.

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Authors contributions

Concept – O.I.O., H.A.O.; Design – O.I.O, B.E.P.; Supervision – O.I.O., B.E.P.; Resources – B.E.P., O.I.O., H.A.O.; Materials – H.A.O.; Data Collection and/or Processing – O.I.O.; Analysis and/or Interpretation – D.A.., O.I.O.; Literature Search – B.EP.; Writing – O.I.O., H.A.O.., B.E.P.; Critical Reviews – O.I.O, H.A.O.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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