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Original Research Article

Artocarpus heterophyllus Seed Oil Mitigates Oxidative Stress and Lipid Profile in Alloxan-Induced Diabetic albino rats

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ABSTRACT

Plant-based medicines have garnered attention in natural product research for years due to their potential for managing diabetic problems. In this study, rats with alloxan-induced diabetes were used to examine the effects of mineral-enriched *Artocarpus heterophyllus* seed oil (AhSO) on lipid profiles and redox signalling. Following chemical analysis on AhSO, 36 albino rats were divided into six groups (A-F of n=6). Group A: The typical controls received food and water. Groups B–F: One intraperitoneal injection of 100 mg/kg body weight of alloxan was used to induce diabetes. Group B, the negative control, was not given any treatment. Group C (treated with 1000 mg/kg body weight of metformin). For 28 days, groups D–F received daily dosages of AhSO at 2.5 mL/kg, 5.0 mL/kg, and 7.5 mL/kg. According to the results, the mineral compositions of AhSO were 80.34 (Ca), 79.78 (K), 62.90 (Mg), 52.87 (Na), 3.01 (Fe), 1.33 (Zn), 0.58 (P), 0.34 (Cu), and 0.13 (Mn) in decreasing order of concentration in mg/100 g. Furthermore, glutathione peroxidase (GPx), superoxide dismutase (SOD), very low-density lipoprotein (VLDL-C), catalase (CAT) activity, low-density lipoprotein (LDL-C), malondialdehyde (MDA), LDL-C (LDL-C), triglycerides, and total cholesterol were significantly ($p < 0.05$) lowered in treated than in untreated diabetic rats. This study proposed that AhSO may have mitigated lipid profiles and redox signaling in diabetic rats due to its enhanced mineral composition. Thus, we suggest that AhsO may be explored as a potential nutraceutical to treat diabetic conditions.

Keywords: AhSO, Mineral composition, Diabetes, Oxidative stress, Lipid profile

Introduction

According to estimates, 382 million people worldwide had varying degrees of diabetes in 2013, and by 2035, that figure will have doubled. Controversy has always surrounded the results of treatment[1]. Despite the success of oral hyperglycemic inhibitors in managing diabetes, there are still numerous issues with the synthetic pharmaceuticals currently on the market, prompting researchers to search for more effective treatments continuously. While native medicine systems have acknowledged their therapeutic characteristics, contemporary pharmaceuticals have not yet commercialised herbal remedies with antidiabetic activity[1,2]. Usually, Type 2 diabetes develops in individuals who have obesity linked to dyslipidaemia and hypertension[3].

Therefore, the goal of the treatment is to encourage the management of biochemical effects in obese individuals, such as reducing insulin resistance and increasing insulin secretion. The medication may also regulate the function of glucagon, enabling the liver to release glucose from its cells into the bloodstream for energy production, according to Lehninger *et al*[4].

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Numerous methods can induce diabetes in animal studies. Etuk [5] has demonstrated that the diabetogenic action of alloxan mediates oxygen radical species. Ahmed *et al*. [6] reported that alloxan quickly penetrates the pancreas to reach its target. Reactive oxygen species accelerate the breakdown of cells and cause significant fluctuations in the amount of calcium in the cytosol.

Herbal remedies are now the mainstay of all accessible therapies, particularly in rural regions, due to their low cost, few side effects, and availability. Underdeveloped nations, where the expense of conventional pharmaceuticals burdens the populace, currently exploit traditional (herbal) medicine to treat diabetes. Despite the demonstrated presence of chemicals such as alkaloids, glycosides, flavonoids, and terpenoids in most plants, along with other anti-diabetic compounds, there is a lack of biological evidence regarding the basic mechanisms of action in treating diabetes[7]. Numerous native African medicinal herbs are consistently convenient in the handling of diabetes. The availability and absence of adverse effects of medicinal plants are two of their main advantages. According to ethnobotanical knowledge, eight hundred (800) plants may have antidiabetic potential [8,9].

According to Olopete *et al.* [10], *Artocarpus heterophyllus* is a repository of numerous high-value chemicals that may have advantageous physiological effects. Traditional and folk medicines recognise the therapeutic qualities of several plant components. Research has demonstrated that the seeds contain abundant essential minerals, such as magnesium, that help maintain bones, aid in calcium absorption, and guard against bone-related illnesses like osteoporosis[11]. Research has never documented the phytotherapeutic potential of seed oil extract in reducing diabetes in animal models. Using phytotherapy, such as herbal

remedies, offers the advantages of being inexpensive, easily accessible, and having fewer adverse effects. We need to conduct more research to discover innovative natural therapies for diabetes, especially given the increasing number of reported cases with higher morbidity and death rates. Investigating *Artocarpus heterophyllus*, which has several medicinal potentials, would suffice. Given this, the study aimed to observe how AhSO affected the lipid profile and redox equilibrium in Alloxan-modelled diabetic Wistar albino rats.

Materials and Methods

The equipment and instruments employed in this investigation are of high analytical quality and included the Soxhlet apparatus (Bradford, England), calibrated precision pipettes (GR202, Japan), a rotary evaporator (Model 349/2, Germany, Model DK-420), a refrigerator (Haier Thermocol, England), a centrifuge (Gallenkamp, Germany), an electric weighing balance (Model Scoutt pro, Ohaus Corporation, USA), a spectrophotometer (SPM21-2000, Bio-trust Diagnostics, USA), a Landers/Qlink blender (Model No. OBI-151 40), desiccators (USA), a biochemical analyser Carl-Novel G. The test reagents were from commercial kits and items from Biosystem Reagents and Equipment, Spain, and Randox Laboratory Ltd., UK. Sigma Aldrich (St. Louis, Mo., USA) provided the analytical-grade chemicals, including n-hexane. The monohydrate alloxan was supplied by Oxford Lab. P India, Pine Chem l.l.

Plant material
Dried *Artocarpus heterophyllus* seeds (1000 g) were bought from local fruit vendors in Mgbo, Ohaukwu L.G.A., Ebonyi state, Nigeria, in April 2022. The plant material was identified as per the Forestry Herbarium Ibadan (FHI 113557) reported in Olopete *et al.*[10]

Extraction of Artocarpus heterophyllus Seed Oil
The seeds were cracked free of their seed shell, sun-dried them, and milled them into a fine powder. The *Artocarpus heterophyllus* seed oil was extracted using n-hexane in a Soxhlet apparatus from the dried powdered seeds, following the modified Nasri *et al*. procedure [12].

Determination of mineral constituents of Artocarpus heterophyllus seed oil (AhSO)
This study determined the mineral compositions of AhSO, which include K (potassium), Na (sodium), P (phosphorus), Ca (calcium), Mg (magnesium), Fe (iron), Sn (selenium), Mn (manganese), Zn (zinc), and Cu (copper), using the AOAC-established procedure from Poitevin (2012)[13].

Animals
Matured albino rats were acquired from the University of Nigeria's (Nsukka, Enugu, Nigeria) Animal Unit of the Faculty of Veterinary Medicine. The Ethical Committee on Animal Research, whose permission number is EBSU/BCH/ET/22/18, provided rats' handling guidelines. With the Committee's approval, the experiment was conducted in the Biochemistry Department's Animal House at Ebonyi State University in Abakaliki, Ebonyi State, Nigeria. The rats were acclimatised for a week to adjust to their new environment.

Animal grouping
Of the 36 male Wistar albino rats (105 ± 10 g), six groups (A to F) with six rats were randomly selected. Group A received only water and rat food as the standard control. A one-time intraperitoneal shot of 100 mg/kg body weight of alloxan monohydrate was used to induce diabetes in groups B to F. The rats in Group B received no treatment. Metformin (1000 mg/kg body weight) was administered to the rats in Group C. Rats in Groups D to F received daily dosages of *Artocarpus heterophyllus* seed oil (AhSO) based on their body weight for 28 days, 2.5 mL/kg, 5.0 mL/kg, and 7.5 mL/kg, respectively.

Tissue sample collection
After twenty-eight days of experimentation, the rats were sacrificed while under a trifling anaesthetic. The blood samples were collected via a cardiac puncture into EDTA bottles and chilled in ice chips before submitting for biochemical analysis.

Biochemical Analysis
Determination of oxidative stress indices
Flohe and Otting's approach[13] was used to quantify the activity of SOD. According to Aebi,[14] CAT activity was measured by tracking the breakdown of H_2O_2 at 240 nm. MDA and GSH levels were quantified using the Ohkawa *et al*. and Benke *et al*. techniques, [15,16] respectively.

Determination of lipid profile
Standard procedures were used to examine the lipid profile. Serum cholesterol was calculated using the Roeschlau *et al*. technique [17]. Serum triglycerides (TAG) were measured using Bucolo *et al*.'s technique[18]. A Randox kit was used for the determination of HDL-C concentration according to the method of Corso *et al*[19]. The biosystem commercial kit approach was utilised to assess the levels of HDL. The method worked on the basis that the sample's LDL and VLDL precipitated with magnesium ions and phosphotungstate. High-density lipoproteins present in the supernatant (HDL) were determined spectrophotometrically.

Statistical Analysis
Data were analysed using SPSS (version 19). For biochemical markers, one-way ANOVA and Duncan's Multiple Range Test (DMRT) were used to examine the data and compare the group averages. A value was considered statistically significant when it was $p < 0.05$.

Results and Discussion

The mineral profile of *Artocarpus heterophyllus* seed oil is shown in Figure 1, which illustrates the sequence in which the mineral content was determined as follows: 80.34 (Ca) > 79.78 (K) > 62.90 (Mg) > 52.87 (Na) > 3.01 (Fe) > 1.33 (Zn) > 0.58 (P) > 0.34 (Cu) > 0.13 (Mn). These are important minerals associated with possible therapeutic benefits found in plants and plant-derived products. This study revealed that calcium had the highest value, while copper and manganese had the lowest quantity. All bodily tissues and fluids include minerals, which are inorganic substances. Despite their lack of energy production, minerals play a crucial role in numerous bodily processes. The metabolism of carbohydrates, the development of bones and teeth, enzyme activity, and the maintenance of the body's acid-alkaline balance all depend on calcium, phosphorus, and magnesium. For the creation of blood, iron is a necessary nutrient. These minerals have a substantial impact on the treatment of several ailments. The mineral concentrations were 220.19±0.19 mg/100 g of calcium, 41.87±0.99 mg/100 g of phosphorus, 43.66±0.06 mg/100 g of magnesium, 326.32±0.18 mg/100 g of potassium, 16.75±0.13 mg/100 g of sodium, according to review reports[20]. Zinc is a necessary component of over 100 enzymes involved in energy metabolism, while manganese is a cofactor in many enzymes.[21] The results of this study were consistent with Sylvia and Pushpa[22]'s work, which revealed the mineral content of jackfruit seed flour. As observed, the amount of Ca in 100 grams of jackfruit seed flour was 234.24 ± 0.02 mg. The contents of magnesium and phosphorus were 162.51 ± 0.02 mg/100 g and 105.93 ± 0.03 mg/100 g, respectively. The amount of iron in 100 grams of jackfruit seed flour was 12.55 ± 0.03 mg. There were 4.25 ± 0.03 mg/100 g of copper, 2.03 ± 0.02 mg/100 g of zinc, and 2.02 ± 0.03 mg/100 g of manganese, respectively. Abedin *et al.*[23]observed similar amounts of zinc (1.50 mg/100 g), copper (3.16 mg/100 g), magnesium (150.70 mg/100 g), and phosphorus (139.00 mg/100 g) in jackfruit seeds. According to Ocloo *et al*.,[24] jackfruit seed flour has high levels of magnesium (338.0 mg/100 g), copper (1.04 mg/100 g), and calcium (308.7 mg/100 g). In 100 grams of jackfruit seed flour, Ngwere and Mongi[25] found 13.07 mg of Fe and 1.45 mg of Cu. The contents of jackfruit seed flour in terms of calcium, iron, magnesium, manganese, and copper were 166.10, 295.10, 1.30, 2.50, and 4.20 mg/100 g, respectively[2]. The observed discrepancy may be due to the jackfruit

variety, the plant's location, and the analytical techniques used for quantification[27]. The higher nutritional value of jackfruit seed flour comes from its excellent mineral content. On average, the fruit weighs 10 kilograms. According to Rahman *et al*.,[28,] the fruit's perianth section consists of yellowish bulbs that are rich in carbohydrates and carotenoids, as well as meat and fibrous tissue. Both Wei *et al.* and Li *et al.* regard it as an abundant source of dietary fiber, minerals, carboxylic acids, and vitamins like thiamine and ascorbic acid[29, 30].

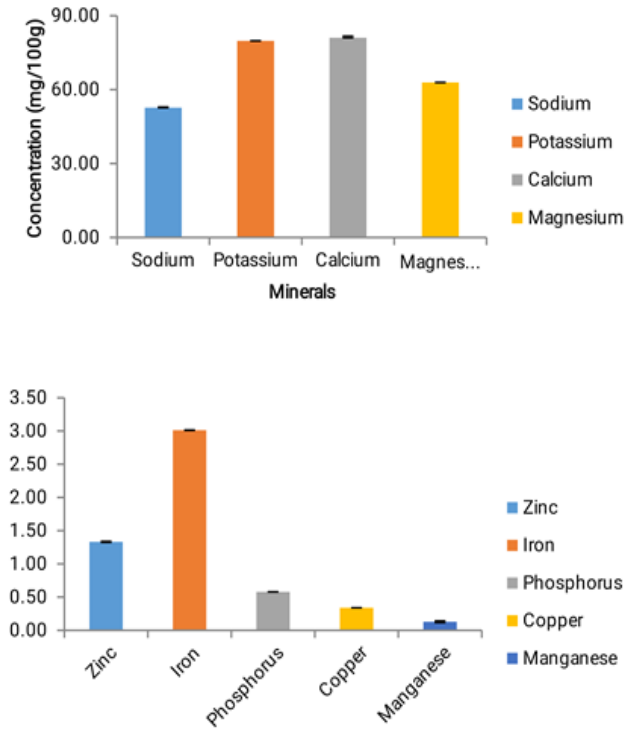

Figure 1: Mineral composition of *Artocarpus heterophyllus* seed oil. Data are shown as Mean ± SD.

On the evaluation of the oxidative effects of AhSO on Alloxan induced diabetic rats, the findings show that administering 100 mg/kg body weight of alloxan significantly increased the level of MDA (Figure 6) and significantly decreased the GSH level, as well as the activities of CAT, GPx, and SOD (Figures 2-6). Still, the effects were reversed by first using common medicines and different amounts of seed oil from *Artocarpus heterophyllus*. These findings demonstrate that *Artocarpus heterophyllus* seed oil (AhSO) can help mitigate diabetic conditions in rats exposed to alloxan. In metabolism, antioxidant enzymes often work by making free radicals less energetic or by donating some of their electrons to them so they may function more normally[31]. SOD is a metalloenzyme that initially catalyses the system's harvesting of oxygen-free radicals and is considered the first line of defense because it prevents biological molecules from oxidising [32]. The tetrameric enzyme GPx, consisting of four 22 kDa monomers, also contains a selenocysteine moiety in its active site subspecies, which facilitates the reduction of organic hydroperoxides and hydrogen peroxide to water [33, 34]. The tetrameric enzyme CAT catalyses the removal of hydrogen peroxides (H_2O_2) by converting them into oxygen and water. Peroxisomes in mammalian cells contain the majority of antioxidant enzymes[5]. These free radical scavenger enzymes, SOD, CAT, and GPx, may prevent oxidative stress by scavenging the very harmful free radicals. Furthermore, studies on diabetes have shown a connection between oxidative stress and blood glucose levels[36,37]. Reactive oxygen species may be created when blood glucose concentrations are higher because glucose binds to haemoglobin[38]. Similarly, researchers have linked the generation of reactive oxygen species to elevated blood glucose concentrations [39]. This is an established clinical condition that was not examined in this work, but it may cause glucose to bind to haemoglobin, a process known as glycation[40.] This investigation employs inhibitors of haemoglobin glycation, such as jackfruit extracts. According to the study's findings, jackfruit extracts can prevent haemoglobin from glycating. As the concentration of jackfruit extract increased, so did the concentration of haemoglobin glycation, a phenomenon that the extracts could potentially control. We also discovered from this investigation that the IC_{50} of jackfruit extracts is 56.43% [26]. The non-enzymatic process of reducing sugars and free amino groups in proteins is known as glycosylation. Tamanna and Mahmood [41] refer to this process as the Maillard reaction. The aetiology of glycogenation directly links to age- and diabetes-related problems such as neuropathy, angiopathy, and nephropathy [42, 43.] This process, which is a frequent posttranslational modification of proteins, can compromise the roles of proteins in living things[44].

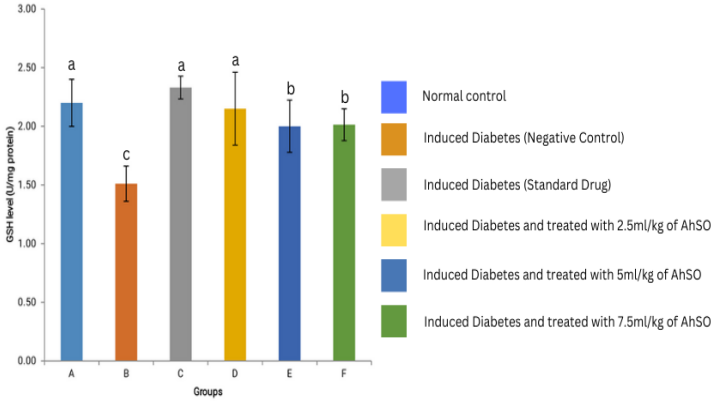

Figure 2: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of Reduced Glutathione in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at $p<0.05$ and $n=6$.

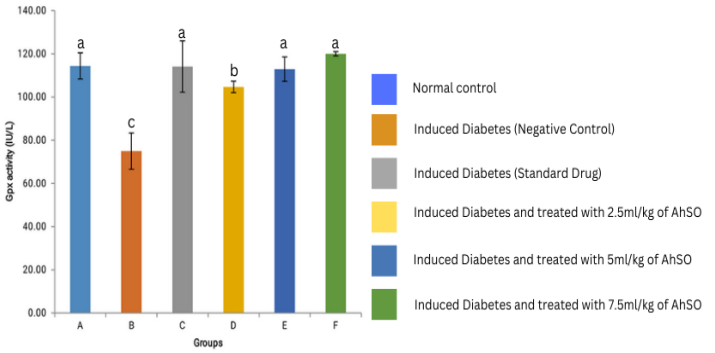

Figure 3: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Activity of Glutathione Peroxidase in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at $p<0.05$ and $n=6$.

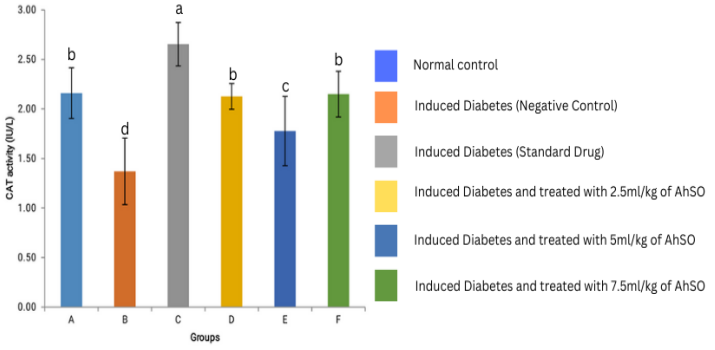

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Figure 4: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Activity of Catalase in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at p<0.05 and *n*=6.

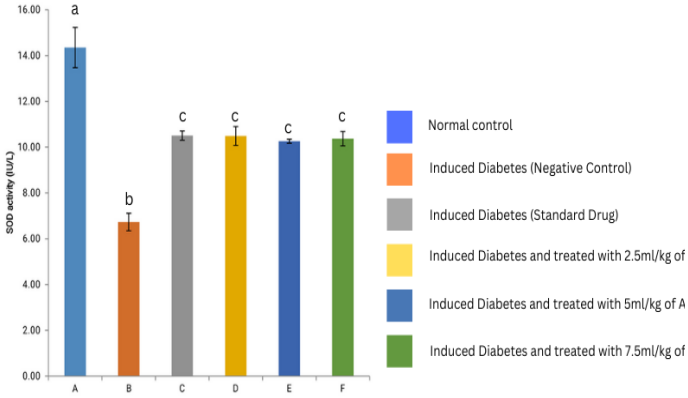

Figure 5: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Activity of superoxide dismutase in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at *p*<0.05 and *n*=6.

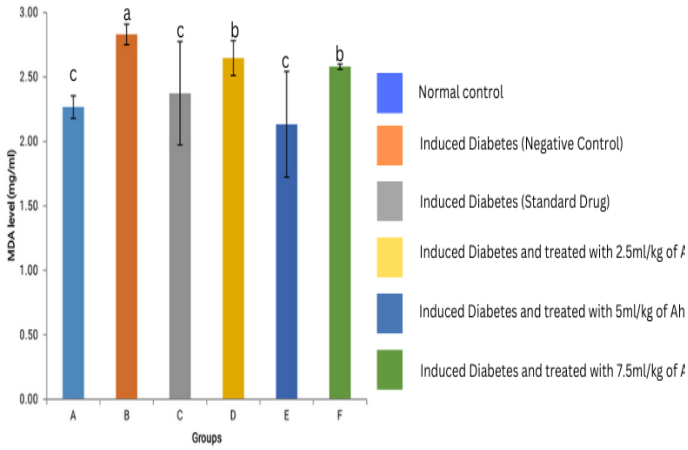

Figure 6: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of Malondialdehyde in Alloxan-induced Diabetic Rats. Bars with similar alphabet are not statistically significant at *p*<0.05 and *n*=6

The lipid outline provides important details regarding complications from diabetes. The effect of *Artocarpus heterophyllus* seed oil (AhSO) on the lipid profile in alloxan-induced diabetic rats showed interesting new results in this study (Figures 7–11). As can be seen, the lipid profile was remarkably ($p < 0.05$) altered by the administration of 100 mg/kg body weight of alloxan. This resulted in elevated levels of VLDL, triglycerides (TAG), LDL, and total cholesterol (CHOL), along with a significant decrease in high-density lipoprotein cholesterol (HDL-C). Interestingly, administering different doses of AhSO to diabetic rats markedly reversed this abnormal tendency in the lipid profile. After administering several doses of AhSO, there was a significant ($p < 0.05$) decrease in the levels of CHOL, VLDL, TAG, and LDL. This essentially brought these parameters back to a level that was equivalent to that of the normal control group. The ameliorative outcome underscores the potential medicinal effectiveness of *Artocarpus heterophyllus* seed oil in mitigating dyslipidaemia, a condition associated with alloxan-induced diabetes. Even though HDL-C levels didn't fully return to normal levels compared to the control group, the lipid profile mostly went back to normal after AhSO treatment. This supports the idea that *Artocarpus heterophyllus* seed oil is effective at reducing lipid problems, which is supported by other research [44, 45, 46]. This partial restoration shows that AhSO is effective at lowering the harmful effects on most lipid parameters, however with insignificant impact on HDL-C modulation. Therefore, this study has further highlighted a gap in understanding the exact biochemical pathways and mechanisms by which AhSO influences HDL-C levels, which calls for further investigations.

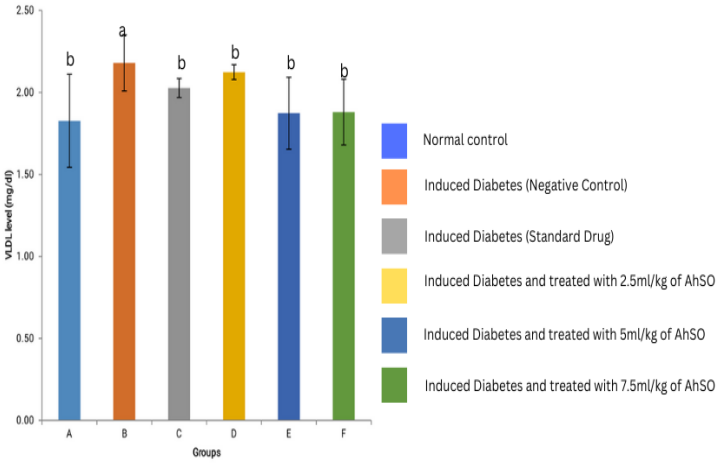

Figure 7: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of Very Low-Density Lipoprotein in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at *p*<0.05 and *n*=6.

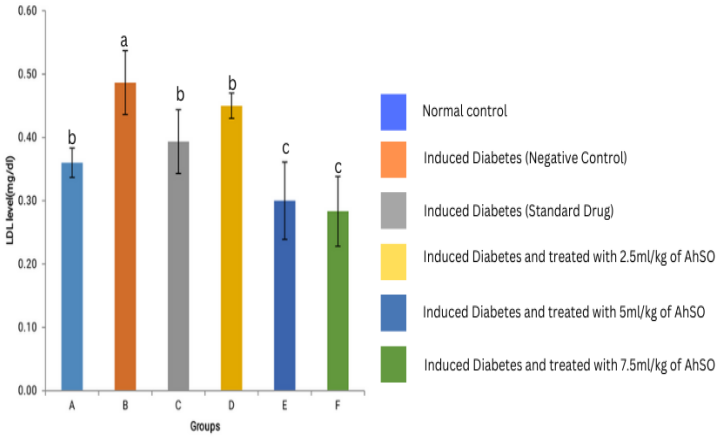

Figure 8: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of Low-Density Lipoprotein in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at *p*<0.05 and *n*=6.

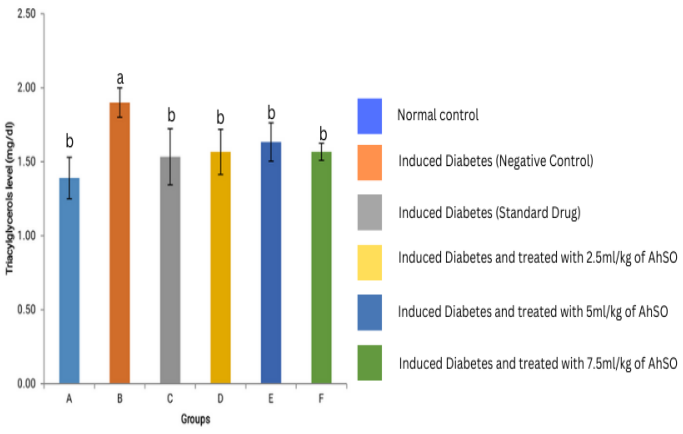

Figure 9: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of Triacylglyceride in Alloxan-induced Diabetic Rats. Bars with a similar alphabet are not statistically significant at $p<0.05$ and $n=6$.

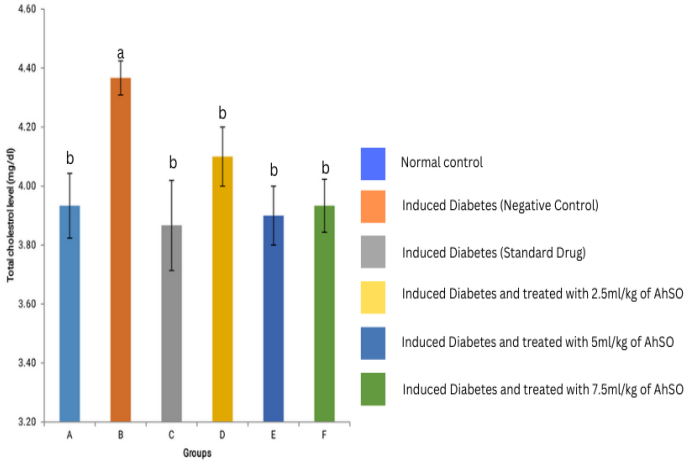

Figure 10: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of Cholesterol in Alloxan-induced Diabetic Rats. Bars with similar alphabets are not statistically significant at $p<0.05$ and $n=6$.

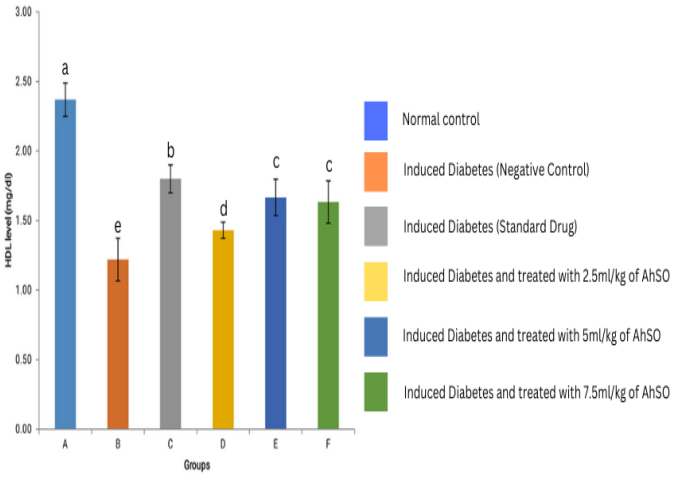

Figure 11: Effect of *Artocarpus heterophyllus* Seed Oil (AhSO) on the Level of High-Density Lipoprotein in Alloxan-induced Diabetic Wistar Albino Rats. Bars with similar alphabets are not statistically significant at $p<0.05$ and $n=6$.

Conclusion

Important minerals found in *Artocarpus heterophyllus* seed oil offer significant health advantages, aligning with previous research on the chemical profile of various plant extracts. Our findings showed that treatment of diabetic-induced rats with AhSO at several doses has antioxidant and antilipidaemic effects. This study has further consolidated the therapeutic effect of *Artocarpus heterophyllus*. However, there is a need for additional research on *Artocarpus heterophyllus* seed oil to explore its in managing the global diabetes epidemic.

Conflict of interest

The authors declare that there are no relevant financial or non-financial interests to disclose in this study.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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