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The outcome of *Annona Muricata* Leaf Extract on Glucose, Malondialdehyde levels and Total Antioxidant Status in Alloxan-Induced hyperglycaemia in Wistar Rats

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ABSTRACT

Background: *This contemporary study was conducted to investigate the potential effects of Annona muricata aqueous leaf extract on serum glucose levels, malondialdehyde (MDA) concentration, and total antioxidant status (TAS) in alloxan-induced diabetic Wistar rats. Annona muricata, a member of the Annonaceae family, is a fruit tree widely distributed in tropical and subtropical regions and is known for its diverse traditional uses. Commonly referred to as soursop, graviola, or guanabana, previous studies have demonstrated its pharmacological activities, including anticancer, anticonvulsant, anti-arthritic, hepatoprotective, and antidiabetic properties.*

Methods: *Twenty (20) male Wistar rats divided into four groups; consisting of five rats each as follows: group 1= rat pellet + water + alloxan + chlorpopromide, group 2 = rat pellet + water + alloxan + extract, group 3= rat pellet + water + alloxan and group 4 = rat pellet + water, and rats in group 4 served as control. Hyperglycaemia was induced in Groups 1, 2 and 3 by intra-peritoneal injection of alloxan. Blood samples were collected at baseline and by the end of 3weeks of administration of aqueous leaf extract Annona muricata, another blood sample was collected. The samples were used for estimation of glucose, MDA and TAS by standard spectrophotometric methods.*

Results: *The administration of alloxan to the test groups; B, C and D, resulted in hyperglycaemia, increased MDA levels and decreased TAS. A notable decrease ($p<0.05$) was observed when the extract and chlorpopromide treated diabetic groups were compared with the untreated diabetic group. A significant decrease ($p<0.05$) in elevated MDA levels was observed when extract and chlorpopromide treated diabetic groups were compared with the corresponding diabetic control group. Increase in the mean TAS of chlorpopromide and extract treated groups when compared with the untreated diabetic group and treated diabetic group was observed.*

Conclusion: *A decrease in glucose level suggests that, leaf extract A. muricata has hypoglycaemic effects on alloxan induced hyperglycaemia in rats. A decreased MDA level suggests a reduction in free radical generation, an increase in TAS may reflects the ability of the antioxidative system to combat free radical related oxidative stress, which has been implicated in the pathology of various diseases.*

Keywords: *Diabetes mellitus, Annona muricata, Malondialdehyde, Total Antioxidant Status.*

1.0 Introduction

Diabetes milletus is a chronic metabolic disease envisioned by increased levels of blood glucose, which not controlled or managed over time leads to serious damage to the eyes, kidneys, nerves, blood vessels, and heart, in Nigeria, a national survey conducted by the Non – Communicable Disease Expert Committee (NCDEC) of the Federal Ministry of Health[1] recorded a prevalence of 2.2% lowest of which was 0.5% in Plateau state and highest 7% in Lagos Island. The increase in prevalence of diabetes progressively has been linked to modifiable factors (lifestyle changes, physical activities, consumption of alcohol, cigarette smoking, overweight and obesity) and non- modifiable factors [1].

Diabetes is generally classified into two main types: Type I and Type II. Type I diabetes is an autoimmune disorder characterized by the destruction of pancreatic β-cells, resulting in an absolute insulin deficiency [2]. It accounts for approximately 5–10% of all diabetes cases and is the most common subtype diagnosed in individuals under 20 years of age. Type II diabetes arises from a combination of peripheral insulin resistance and an inadequate insulin secretory response by pancreatic β-cells, leading to a "relative insulin deficiency" [2,28]. While traditionally considered "adult-onset," the prevalence of Type II diabetes among children and adolescents has been steadily increasing [3].

The primary clinical manifestation of diabetes, hyperglycemia, contributes to diabetic complications by altering vascular cellular metabolism, vascular matrix molecules, and circulatory lipoproteins [4]. Chronic hyperglycemia in diabetes mellitus leads to multiple biochemical disturbances, and oxidative stress is believed to play a significant role in both the symptoms and progression of the disease [5,37].

The increased generation of reactive oxygen species from diseases results to oxidative stress in cells and tissue in antioxidants defence potential[6,32], and several hypothesis have been proposed to explain the genesis of these radicals in diabetes milletus.

The Total antioxidant Status (TAS) can be described as a role of dietary, enzymatic and systemic antioxidants which is therefore an indicator of an individual free radical load [7,38]. TAS which consist of both enzymatic and non-enzymatic antioxidant assessment, is usually aimed at measuring the balance between free radicals activity and the antioxidants defence system. Low TAS is a significant indicator of oxidative stress, such oxidative stress occurs, when there is an imbalance between the oxidants and antioxidants status at the systemic level [8,29]. Insulin dependent diabetes mellitus (type I) is managed with exogenous insulin [9,31] and non-insulin dependent diabetes mellitus (type II) is managed with oral hypoglycaemic agents like sulfonylurea and biguanides [10]. Sulfonylurea acts as insulin stimulants and enhances the function of insulin at the receptor site [11]. Examples of commonly used drugs for the treatment of diabetes include metformin, glibenaclamide and chlorpopromide.

However, different cultures have used various parts of many plants for the treatment of diseases [12] and this includes the plant *Annona muricata* (*A. muricata*) which is commonly found in West Africa. All aspects of the plant, bark; leaves; roots; fruits and seeds, are used in natural medicine preparations in the tropics [13]. Previous study [14] showed that *A. muricata* contains flavonoids, and antioxidant activities due to the presence of quercetin in the leaves and other morphological parts of the plant and that these chemical components may exert an antidiabetic effects.

The main active chemical component of *Annona muricata* is acetogenin which has been demonstrated to exert a high potency against various types of cancer cells *in vitro* [15]. Other biochemical elements such as lactones; isoquinoline; alkaloids; tannins; coumarins; flavonoids; saponnins; stearic acid; myristic acid; ellagic acid; B, C vitamins; etc has been reported to be extracted from parts of Annona muricata, (root, bark, leave, fruit and seed) [14]. Therefore, this study was design to measure the possible effects of *Annona muricata* leaf extract on glucose concentration, malondialdehyde (MDA) and TAS in experimental animal.

2.0 Materials and Methods

2.1 Selection of animals

Twenty (20) healthy male Wistar albino rats, of average weight 150g, were obtained from the Animal house of Ladoke Akintola University of Technology, (LAUTECH) were used for the experiment. After a two weeks acclimatization period to ensure uniform nutritional status, the animals were assigned to 4 groups; consisting of 5 rats in each group as follows; Group 1= Rat pellet + water + alloxan + chlorpopromide; group 2 = Rat pellet + water + alloxan + extract; group 3= Rat pellet + water + alloxan; and group 4 = Rat pellet + water. Groups; B, C and D were induced with alloxan, two days after, test groups; C and D were treated with chlorpopromide and soursop extract respectively for 2 weeks. The wooden cages were cleaned daily as well as the feed and water trough. All animals were taken care-of in accordance with the principle of laboratory animals care of the National Society of Medical Research [27]. The experiments lasted for a period of 4 weeks.

2..2 Annona muricata leaf extraction

Fresh mature leaves of the *Annona muricata* tree were harvested from a farm in Egbedore Local Government area, Osun state Nigeria. The matured leaves were spread singly on the laboratory bench and were allowed to dry for a period of two weeks before granulation. The dried leaves were granulated with mortar and pestle and then blended into powder. Leaves extract was prepared by dissolving 10g of granulated leaves in 100mls of distilled water. The solution was then placed in a magnetic field for exactly 2hrs while being agitated continuously using a magnetic stirrer. The solution was sieved using a piece of white muslin cloth into a clean beaker. The content was poured into clean Petri dishes and placed in the oven at 45°C for 72 hrs. 1.2grams of the extract was recovered. The extract was diluted at 10% concentration w/v. 10mg of the extract was weighed and dissolved into 10mls of water. It was shaken and allowed to dissolve completely. The doses administered per kg body weight were calculated with the formula below,

$$\text{Administered volume} = \frac{\text{Intended dose} \times \text{Body weight} \times \text{Concentration}}{1000}$$

2.3 Induction of Diabetes in animals

After an overnight fast, hyperglycaemia was induced in rats in groups 1, 2 and 3. This was done by the single dose (150 mg/kg body weight) injection of freshly prepared solution of alloxan monohydrate dissolved in saline. Hyperglycemia was assessed by estimating the blood glucose concentration, 48 hours after injection of alloxan.

2.4 Blood sample collection and Biochemical Analysis

Two millilitres (2ml) of blood was obtained from the tail vein of each of the animals after an overnight fast and was used for the determination of fasting blood glucose (FBG) level. The rats with blood glucose level above 260mg/dl were selected for the experimental study.

Determination of glucose level was by the glucose oxidase/peroxidase (GOD/POD) method [16]. The method of Stocks and Dormandy describe by Vani et al, was used to determine the level of malondialdehyde and TAS [17] .

2.5 Statistical Analysis

Results were reported as Mean± standard deviation (SD). Mean values were statistically analyzed using Statistical Package for Social Sciences (SPSS). Statistical analysis was performed using ANOVA. Relationships between the means of variables were determined using Pearson's correlation coefficient. Results were regarded as significant at $p<0.05$.

3.0 Results

As presented in table 1; mean glucose concentration of the test group; (120.05±3.36) and control group; (114.20±7.76) was normal before the induction of alloxan. After the induction of alloxan, the mean glucose concentration of the other three groups; B C and D (423.80±28.89) became higher than that of the control group; (114.20±7.76) with a statistical significance of, *P<0.05. following 2-3 weeks administration of extract and known drug (chlorpopromide), the result, showed a significant

reduction in the level of elevated mean glucose level of the test groups from (423.80±28.89) to (129.00±5.46).

Table 1: Shows Glucose Levels Before Alloxan, After Alloxan and After Extract Administration

Groups	Baseline Before Alloxan	Hyperglycemic State	3 Weeks After Extract Administration	F-Value	P-Value
A (n=5)	114.20±7.76	---	---	8.821	P>0.05
B (n=5)	118.20±9.41	409.40±51.94	---	8.821	*P<0.05
C (n=5)	127.90±5.0	468.40±46.19	138.90±9.15	8.821	*P<0.05
D (n=5)	120.50±3.36	423.80±28.89	129.00±5.46	8.821	*P<0.05

As depicted in table 2; there is no significant difference in the mean MDA concentration of all the groups at baseline. After the induction of alloxan, there was a significant increase in the mean MDA value from (2.99±0.24) to (4.38±0.33) with a statistical significance of p<0.05. following 2-3 weeks, after treatment with extract, there was a decrease in the mean MDA concentration and the mean difference was not statistically significant.

Table 2: Mean (±SD) of MDA at Baseline, Hyperglycaemic State and 2 Weeks after Administration of Extract

Groups	Baseline Before Alloxan	Hyperglycemic State	3 Weeks After Extract Administration	F-Value	P-Value
A (n=5)	2.99±0.24	---	---	12.194	P>0.05
B (n=5)	2.99±0.24	4.38±0.33	---	12.194	*P<0.05
C (n=5)	2.99±0.24	4.38±0.33	3.35±0.15	12.194	P>0.05
D (n=5)	2.99±0.24	4.38±0.33	3.50±0.13	12.194	P>0.05

As presented in table 3; there was no significant difference in the mean TAS of all d groups at baseline. After the induction of alloxan, there was a decrease in the mean TAS concentration of the test groups C and D (2.55±0.16) when compared with the control group (2.98±0.18). 2-3 weeks after treatment with extract, there was an increase in the mean TAS of groups C and D and the mean difference was not statistically significant.

Table 3: Shows Mean (±SD) Of TAS at Baseline, Hyperglycaemic State and 3 Weeks after Administration of Extract

Groups	Hyperglycemic State	3 Weeks After Extract Administration	F-Value	P-Value
A (n=5)	---	---	1.758	P>0.05
B (n=5)	2.55±0.16	---	1.758	P>0.05
C (n=5)	2.55±0.16	3.01±0.17	1.758	P>0.05
D (n=5)	2.55±0.16	3.12±0.15	1.758	P>0.05

4.0 Discussion

Results we obtained from this study showed an increase in serum glucose, in alloxan treated Wister Rats when analogize with the corresponding control animals. Single daily dose of extract from *Annona muricata* leaf, greatly reduced glucose concentration in diabetic induced rats which caused a remarkable increase in serum insulin level. In a previous experiment [14,18], Ojewole and colleagues, reported that increased glucose level observed in streptozotocin induced diabetic rats was also reduced after treatment with *Annona muricata* leaf extract[19]. Another study also reported a remarkable difference between blood glucose concentrations of *Annona muricata* treated rats and untreated hyperglycaemic group of rats [15,31]. This current data therefore; shows, treatment of diabetic induced Wister rats with leaf extract of *Annona muricata,* caused a marked reduction in hyperglycaemia, which suggests an increased activity of serum insulin level, this is in consonance with study by Sawant and Dongre[15]. The decrease in glucose level of diabetic induced rats, after extract administration might be attributed to its ability (leaf extract) to enhance plasma membrane activity, through increment of hepatic GSH levels. This results to interference with progression of lipid peroxidation activites[15,20]. The results of this study, also showed a significant increase in the levels of Malondialdehyde (MDA) of alloxan treated rats when compared with the control group. Treatment of group D. rats with *Annona muricata* leaf extract resulted to a significant decrease in elevated Malondialdehyde level of the diabetic induced rats. In a previous study, [14,21] reported a decrease in Malondialdehyde level when alloxan induced diabetic rats were treated with leaf extract of *Annona murricata* .

The marked decrease in the MDA levels of diabetic induced rats treated with *Annona muricata* extract, may suggests that the leaf extract has some antioxidant properties, which probably save the tissues from the damaging consequences caused by lipid peroxidation [22,35].

The results of this current study shows a reduction in the total antioxidant activity (TAS) of alloxan treated Wister rats when compared with corresponding control groups. Treatment of the diabetic induced Wister rats with leaf extract of *Annona muricata,* boosted the antioxidant activity of the rats by increasing the total antioxidant activity (TAS). In a previous study by Adewole and colleagues [23], a significant increase in antioxidant activity was reported when streptozotocin induced diabetic rats were treated with Quercetin, which is one of the major compounds present in *Annona muricata* plant [18]. However, the results of this study showed only a slight increase in total antioxidant activity (TAS) level, which may be due to the variation in the duration of the experiment. This study lasted for a period of 4 weeks while the study by Adewole et al, lasted for 6 weeks [23]. The increase in total antioxidant status of *Annona muricata* extract treated diabetic rats also suggests that antioxidant activity shields the tissues against the damaging consequences of oxidation [24,29] .

Even-though, the specific mechanism of action on the different biochemical variables exacted by the leaf extract explained in this study, could not be confirmed due to limited funds, some earlier investigators [30,34] has depicted that compounds like tannins and other polyphenolic elements, for example (coumarins, flavonoids, triterpenoids, saponnins, quercetin) and plant secondary metabolites, possesses hypoglycemic, hypolipidemic, antioxidant, anti-inflammatory, with varied pharmacological and biochemical properties in numerous exploratory animal models[19,30,31]. *Annona muricata* is said to contain, ellagic acid; tannins; flavonoids; polyphenolic compounds; triterpenoids; β-sistosterol [25,26,29], it is therefore reasonable to hint that some constituents of *Annona muricata* (coumarins, flavonoids and triterpenoids) might be held accountable for the anti-diabetic and antioxidant properties of *Annona muricata,* which we observed with the plants leaf aqueous extract" in this study.

4.1 Conclusion

leaf extracts of *Annona muricata* has proven to possess a wide spectrum of biochemical activities, it is a desired tropical tree, in which a rich array of biochemical investigations has been conducted.

It's a desired fount for the staple food industry, in addition of being an indigenous medicinal plant. The effects of *Annona muricata* leaf extracts are completely amazing, further research is crucial to elucidate all the elements contributing to this amazing effect and the threshold of these effects. In conclusion, our study demonstrated that alloxan treatment maybe associated with oxidative stress and leaf extract of *Annona muricata* may possesses hypoglycaemic properties, in addition to antioxidant activities, it being able to inhibit and/or prevent oxidative stress and related advanced glycation end products (AGEs) caused by hyperglycemia.

Declarations

Ethical Approval: Ethical approval was sought and obtained from the Ethics Committee of Ladoke Akintola University of Technology (LAUTECH).

Data availability: The data generated in this study are available from the corresponding author upon reasonable request.

Funding: None.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Limitations: The limitations to our study include, Time and Funding.

Authors Contribution: OJM conceptualized and designed the study. OJM and AOA contributed to implementation of the project and revision of the manuscript. The authors were involved in the writing and revision of the manuscript. IC and OJA were involved in the sample analysis. OJM and NJC collected the samples.

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Consent to publications: The authors read, approved the final manuscript for publication and agree to be accountable for all aspects of the work.

Key

Group A (control group) = Rat pellet + water only =group 4
Group B (diabetes control) = Rat pellet + water + alloxan =group 3
Group C (test group) = Rat pellet + water + alloxan + chlorpopromide = group1
Group D (test group) = Rat pellet + water + alloxan + extract =group 2
Group C (test group) = Rat pellet + water + alloxan + chlorpopromide = group1
Group D (test group) = Rat pellet + water + alloxan + extract =group 2
Group B (diabetes control) = Rat pellet + water + alloxan =group 3
Group A (control group) = Rat pellet + water only =group 4
Group 1= Rat pellet + water + alloxan + chlorpopromide, group 2 = Rat pellet + water + alloxan + extract, group 3= Rat pellet + water + alloxan and group 4 = Rat pellet + water

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