Global Scientific JOURNALS

GSJ: Volume 13, Issue 10, October 2025, Online: ISSN 2320-9186

www.globalscientificjournal.com

EVALUATION OF ANTI-DIABETIC PROPERTIES OF METHANOLIC EXTRACT OF AVOCADO PEAR SEED

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ABSTRACT

Proximate and anti-nutritional constituent of avocado seed were determined, 100g of the sample was extracted with 1000ml of both water and methanol using the maceration method. The extracts were evaporated to dryness using a rotary evaporator and stored at 4^{o}C until use. The effect of different doses(200mg/kg.b.wt,300mg/kg b.wt.) of both water and methanolic extracts of P.americana seed on alloxan induced diabetic albino rats was compared with those of reference drug, insulin. The glucose level and weight of the rats were measured weekly for 21 days .The liver function test and the histopathologies of the liver and kidney were investigated .Results showed that methanolic extracts exhibited significant anti diabetic effects on the experimental rats .However the methanolic extracts showed a better anti diabetic effect than the water extract .The extracts showed no significant effect on the liver function parameters (bilirubin, conjugate bilirubin ,AST,ALP and ALT) compared with the normal control but rather reversed the histo-pathological damage that occurred in alloxan induced diabetic rats. Conclusively ,the present study provides a pharmacological basis for the traditional use of P.americana seed for the management of diabetes mellitus, P. americana seed contains substantial amount of nutrients that could warrant its utilization in animal feed or food ,however further studies are required to identify the active ingredients responsible for the anti diabetic properties of the seed.

1.0 INTRODUCTION

Medicinal plants have suddenly become attractive for the treatment of major disease affecting human (Sofowora 2008), because of the continuous need for less expensive means of treatment. Diabetes mellitus is a metabolic disease caused by a deficiency in the secretion or action of insulin (Nelson and co. 2005). This disorder is characterized by major symptom such polyuria, glycosuria and hyper-glycemia (glucoserate on an empty stomach higher than 1.2g/l in plasma blood and confirmed in at least two occasions), (N, guessan et al., 2009). P.americana fruit ,commonly known as avocado is an edible fruit from central America which is easily adaptable in tropical region(Leite et al 2009).The fruit is used for human consumption and also used in Mexico as medicinal plant (Dreher and Davenport 2013).The avocado seed, has been reported to be a source of bioactive compounds (Ramos et al 2004) it represents about 13-18% of the fruit, it is a by-product of the fruit which is discarded during the processing of the fruit, it has diverse application in ethno-medicine ranging from treatment of diarrhoea, dysentery, toothache, intestinal parasite to the area of skin treatment and beautification. (Pamplora and Roger, 1999), it has also has been used traditionally for the

treatment of Diabetes mellitus and other ailment without any scientific explanation.

1.1Background of the study

Medicinal plants are used extensively in Nigeria for the traditional treatment of all forms of disease usually in different forms such as decoction in which un specified amount are consumed usually without regards to toxicological effect .The seed of P. americana has been reported to contain phytosterol ,triterpenes ,fatty acids and two new glycosides of abscisic acid ,Several biological activities of the seed has been reported including antioxidant ,antihypertensive, larvicidal, fungicidal, hypo-lipidemic and recently amoebicidal and giardicidal activities (Rodriguez –Carpena et al) . Additionally several studies have focused on the evaluation of acute toxicity of the fruit and leaves, the seeds are rich in tannin and carotenoids. Tocopherols from the fruit were shown to inhibit the in vitro growth of prostate cancer cell lines (Lu etal, 2005) and persin from avocado leaves was shown to have antifungal properties and to be toxic to silkworms. The effect of P.americana extract was evaluated on in vitro rat lymphocyte proliferation (Gomez –Flores et al., 2008). Reporting on the antimicrobial and phytochemical screening of the seed extract of Persea Americana (avocado pear) carried out by Ilozue et al. (2014), concluded that the seed showed anti-microbial property. P. americana leaves have also been reported to possess anti-inflammatory and analgesic activities (Adeyemi et al., 2002). Alhassan and colleagues evaluated the hypoglycemic activity of P.americana aqueous seed extract on alloxan induced diabetic rats and concluded that the anti diabetic effects of the extract might be due to certain mineral elements and phytochemical and that an increase in weight could be due to proper nutrient utilisation that is most likely induced by the avocado seed extract (Alhassan et al., 2012).

However the work by Okonta et al ., 2007) suggests that P. Americana can lower blood glucose level in cases of mild hyperglycemia but not severe hyperglycemia.(Edem et al ., 2009) studied the effect of aqeous alligator pear seed extract on normal and alloxan induced diabetic rats ,and their results suggested a restorative effect of the extract on pancreatic islet cells.

The aforementioned studies provided insight into the restorative and antioxidant activities of P.americana, however the tissue protective potential of P.americana necessitated a look into the hispathological activity of the plant extract in the pancreas, liver and kidney .Therefore this study was conceived and designed based on the obvious gaps in what has been done or known about the plant.

1.2 AIM AND OBJECTIVE

1.2.1. AIM

The aim of this work is to evaluate the anti diabetic properties of seed extract of Persea Americana in alloxan induced diabetic rats.

1.2.2 OBJECTIVE

To evaluate the anti diabetic properties of seed extract of P.americana in diabetic rats.

To ascertain the effect of seed extract of P.americana on liver function enzymes

To investigate the histo- pathological effect of P. Americana on liver activities of diabetic rats.

2.0 MATERIAL AND METHOD

2.1 SAMPLE COLLECTION

Samples of ripe avocado pear (P.americana) was purchased in Nasarawa market ,the succulent fleshy part of the fruit was removed to obtain the seed .The seed was minced and dried to a constant weight in an oven at 50^{o}C .,It was then

ground to powder using a mill and stored in a container. 100g of the sample was extracted with 1000ml of methanol using the maceration method.100g of dried, ground sample was soaked in methanol (1L methanol in 20% water) for 5days separately. The soaked sample was stirred every 18 hrs using sterilized glass rod. The final extract was passed through Whatmann filter paper No 1, the filtrate obtained was concentrated under vacuum using a rotary evaporator at 40 ^{o}C and stored at 4 ^{o}C until when needed for analysis.

2.2 ANIMALS

Twenty five (25) healthy male rats of body weight ranging between 160- 220 g were used for the experiment .The rats were housed in metal cages group of five in a photoperiod cycle of 12h; 12 (light and dark), at room temperature (28 ^{o}C) and fed with standard laboratory diet and tap water for a period of one week for acclimatization.

2.3 Grouping of Animals

The animals were grouped into five as shown below:

Group 1- Normal control rats (negative control)

Group 11- Diabetic control rats (positive control)

Group 111- Diabetic rats treated with insulin (1 unit of u40 /50 gkg b.wt/day).

Group IV- Diabetic rats treated with 200mg /kg b.wt methanol extract

Group V- Diabetic rats treated with 300mg /kg b. wt methanol extract

Induction of Diabetes

Diabetes mellitus was induced by intra-peritonal (IP) injection of 150mg /kg body weight of alloxan monohydrate solution after determining baseline glucose levels of rats. (Yanerday and Colae, 1998).

The blood glucose level of the animals were determined using a glucometer (Tyson Bio Evolve glucometer) and subsequently on a weekly basis for 21 days of administration of the extracts .Body weights of the rats before diabetic induction was recorded.

2.4 Administration of Extract

The prescribed doses of plant extract was orally administered to the rats daily for 21 days of experiment ,After diabetic induction and at 7 days interval throughout the extract administration, body weights of the rats were measured.

2.5 Blood Sample collection

Collection of blood sample was done using the perioerbiytal method. The rats were scuffed with thumb and the forefinger of the non-dominant hand and the skin around the eye was pulled taut, Slight thumb pressure was used to puncture the tissue and enter the plexus sinus. Blood collection was done from plexus, capillary tube was removed gently and wiped with sterile cotton. The blood was centrifuged at 3000rpm for 10 minutes, serum was harvested from the blood and used for the assay.

2.6 Liver function Test

2.6.1. Total Bilirubin test

0.05 ml of Sodium nitrite reagent per 1ml of total bilirubin reagent was prepared, four test tubes labelled blank, Standard, control and

samples were provided. Each test tube required a blank tube,0.1ml of total bilirubin reagent was dispensed into the blank tubes ,one milllimeter of the working reagent was dispensed into the labelled except blank tubes 0.1ml of the standard ,control and sample was added to each respective tube after one minute 3.0ml of methanol reagent was added to all the tubes ,mix by inversion and allowed to stand for five minutes at room temperature .The absorbance of all the tubes was read at 550nm ,using the reagent blank (Kochmar and Moss ,1976)

2.6.2 Conjugated bilirubin Test

Four test tubes labelled blank standard ,control and samples were provided, 1ml of total bilirubin reagent (Sulfanilic acid and Hcl) was added into labelled test tubes.50 ul (1 drop) of Sodium nitrite reagent was added into a sample test tube only .The solution was mixed and allowed to stand for 1-2 minutes .50ul of the sample was added to both the sample blank and the sample test tubes .The test tubes are allowed to stand for 5 minutes .The absorbance of all the samples were read at 550nm using the reagent blank.

2.6.3 Alanine aminotransferase Test

Four test tubes labelled blank ,calibrator ,control and sample was provided,0.5ml of ALT substrate was dispended into each of the test tubes and placed in a 37 ^{o}C heating bath for 3-5 minutes .0.1ml of the sample was added to each labelled tube at various time interval .The solution was mixed and immediately returned to the heating bath for exactly 30 minutes .0.5 ml of ALT a colour reagent was added to each tube maintaining the timed interval sequence .It was then mixed and returned to the heating bath for 10 minutes, 2.01 of ALT colour developer was added and returned to the heating bath for another 5 minutes .The absorbance was read at 550nm using the blank to zero .

2.6.4 Aspartate Aminotransferase (AST) Test

0.5ml of AST was added to test tubes labelled control ,calibrator and sample .These were warmed in 37^{o}C heating bath for at least 4 minutes .At various intervals 0.1ml of samples were added into the respective tubes ,mixed and returned to the heating bath for exactly 10 minutes .After 10 minutes ,in the same timed sequence ,0.5ml, of AST colour reagent was added ,mixed and immediately returned to the heating bah for another 10 minutes .After 10 minutes ,2.0ml 0f 0.1N HCl was added and mixed by inversion .The absorbance was read at 530nm.using distilled water as blank .

2.6.5 Alkaline Phosphate test (Alp)

Into labelled test tubes, 0.5ml of alkaline phosphate was dispensed and kept at 37 ^{o}C for 3 minutes. At intervals 0.5ml of standard, control and sample was added and mixed gently. Using Deionised water, the mixtures were incubated at 37^{o}C for 10 minutes, 2.5ml of Alkaline Phosphate colour developer was added sequentially at interval and mixed well. The absorbance was read at 590 nm.

2.6.6 Histological study

Group	Initial weight	Day 1	Day 7	Day 14
I	155.43±11.30^{a}	171.23±16.68*(↑10.2)	198.98±28.02^{b}(↑16.2)	214.48±30.15*(↑7.9)
II	208.58±21.63^{b}	195.63±19.01*(↓6.2)	180.43±11.45^{ab}(↓7.8)	177.33±19.10*(↓1.7)
III	166.18±14.28^{a}	184.03±22.31*(↑10.7)	189.18±22.49^{ab}(↑2.8)	205.30±19.69*(↑8.5)
IV	171.73±5.60^{a}	178.33±45.37*(↑3.8)	200.90±20.90^{b}(↑12.7)	210.83±28.94*(↑5.0)
V	152.65±13.80^{a}	149.85±19.42*(↓1.8)	149.90±19.09^{a}(↑0.03)	155.50±20.37*(↑3.7)

Group	Total Bilirubin (mg/dl)	Conjugate Bilirubin (mg/dl)	Aspartate Bilirubin (IU/L)	Alanine Transaminase (IU/L)	Alkaline Phosphate (IU/L)
I	0.7±0.03[a]	0.31±0.19[a]	33.75±5.50[a]	32.85±17.33[a]	30.50±3.32[a]
II	2.93±0.7[bc]	1.38±0.21[bc]	57.00±16.91[c]	101.00±24.90[b]	167.25±24.24[d]
III	0.68±0.24[a]	0.28±0.10[a]	33.50±11.68[a]	58.00±24.43[a]	27.50±3.32[a]
IV	3.75±0.26[c]	2.23±0.51[d]	44.25±3.30[ab]	46.25±13.40[a]	52.25±11.70[bc]
V	5.78±0.8[d]	4.65±0.06[e]	31.75±1.71[a]	34.50±4.43[a]	37.25±1.71[ab]
Normal range	0.2–1.0	0.05–0.5	10–40	5–35	9–35

The animal were sacrificed by euthanasia, the organs were harvested and fixed in 40% formaldehyde solution and sent to histopathology laboratory for sample processing.

3.0 RESULTS

Table 3.1: Effect of Extracts on blood glucose level of Normal and diabetic Rats.

Body weight

Group	Day 0	Day 1	Day 7	Day 14	Day 21
I	4.47±0.52[a]	5.35±0.42[a]	5.35±0.88[a]	4.31±0.55[a]	5.71±1.31[a]
II	3.78±0.34[a]	16.93±2.8[b]	17.49±6.52[b]	24.11±6.37[e]	24.13±7.36[c]
III	3.94±0.69[a]	9.69±2.75[a]	8.92±2.36[a] (↓8.0)	10.55±1.28[bc](↑8.9)	8.27±2.36[a] (↓14.7)
IV	4.27±0.00[a]	21.60±10.18[b]	7.45±0.87[a](↓65.5)	6.13±1.14[ab](↓71.6)	6.34±0.59[a](↓70.7)
V	3.94±0.53[a]	24.27±5.31[b]	13.90±1.51[b](↓42.7)	16.44±1.39[d] (↓32.3)	9.99±1.73[a](↓58.8)

Mean ± S.D Means with different superscript in the same column are significantly different ($p<0.05$). Figures in parenthesis indicates percentage decrease ↓ or increase ↑ in blood glucose level when compared to normal blood glucose levels.

KEYS: I=Normal Control Rats;

II=Diabetic Control (Untreated);

III=Diabetic Insulin treated;

IV=Diabetic200mg/kg.b.wt.methanol extract treated;

V=Diabetic300mg/kg.b.wt.methanol extract treated.

RESULTS OF BODY WEIGHT ANALYSIS

Table 3.2: Effects of Extracts on Mean Body Weight (g) of Normal and Diabetic Rats

Mean ± S.D* Not significant, Means with the same superscript in the same column are not significantly different (p<0.05). Figures in the parenthesis indicate percentage decrease ↓or increase ↑in body weights.

KEYS: I=Normal Control Rats;

II=Diabetic Control (Untreated);

III=Diabetic Insulin treated;

IV=Diabetic200mg/kg.b.wt.methanol extract treated;

V=Diabetic300mg/kg.b.wt.methanol extract treated.

LIVER FUNCTION TEST RESULTS

Tables 3.3: Effect of Extraction Mean Liver Parameters of Normal and Diabetic Rats.

Values are mean ± standard deviation, n=4.Means with the superscript in the same column are not significantly different (p<0.05).

KEYS: I= Normal Control Rats;

II=Diabetic untreated group;

III=Diabetic Control (Untreated);

IV=Diabetic200mg/kg.b.wt.methanol extract untreated;

V=Diabetic300mg/kg.b.wt.methanol extract untreated.

4.0 DISCUSSION, CONCLUSION AND RECOMMENDATION

4.1 DISCUSSION

As shown in table 3, statistical analysis of the blood glucose shows that there is no significant difference (p>0.05) in the glucose levels in all the group. At day 1 there is no significant difference in the mean glucose levels between group 1 and group 11 (5.39mmol/L and 6.69mmol/L).However Group III (9.69mmol/L) is significantly higher above the normal glucose level 3.7mmol/L-5.6mmol/L) indicating manifestation of diabetes. There is no significant difference (p>0.05) between the other groups V, IV and II, with group V having the highest glucose level (28.47 + 4.92 mmol/L) and it follows the trend with group II having the lowest glucose level (16.93 +2.82mmol/L).However Groups IV, V and II are significantly different (p> 0.05) from the Group I and III showing that the extract treatment had not taken any significant effect at this time.

At day 7 as shown in Table 3.1, there is no significant difference (p>0.05) between Group I, III and IV, that is Group IV significantly lowered the blood glucose to a level comparable to that of the control Group I .In Group IV also there was a significant percentage decrease in blood glucose (65.5%) meaning that Group IV (200mg/kg b.wt methanol extract) treatment has the potential to modulate high blood glucose.

Glucose levels of groups IV and V are not significantly different (p.0.05) from the untreated diabetic Group II. Therefore at day 7 the best treatment is Group IV .At day 14 of the treatment ,there is no significant difference (p>0.05) between group IV and I ,also no significant difference in glucose level exist between group III,and IV .These doses could be effective as insulin in the control of blood sugar. There is no significant difference between Group III and IV which also suggest the treatment in Group IV could marginally lower blood glucose .No significant difference between Group IV and V, therefore both have

little effect in modulating the effect on high blood glucose .There is significant difference ($p<0.05$) between all the groups and Group II showing that all the treatment have effect in modulating the effect of high blood glucose.

At the end of 21 days treatment, there is no significant difference between Groups I, IV III, V, this suggest that treatment Groups IV and V (methanol extract treated with 200 and 300 mg/kg b.wt .respectively) may lower effectively and Group V (300mg/kgb.wt.) may marginally substitute for insulin in lowering high blood glucose back to normal control group level in the long run. No significant differences ($p>0.05$) exist between group IV and V respectively which indicates that they have similar effect ,with Group IV having a better glucose lowering effect .No significant difference ($p>0.05$) exist between Group II and all the other group showing that Group II is diabetic while others modulated the effect at varying degrees. Methanolic extract treated Group IV and V showed higher decrease in their glucose level than the untreated .Results from the present study showed that the group treated with methanol extract seed showed a better result than the water seed extract in terms of its anti diabetic effect. The extract were able to lower the blood glucose of the rats even better than insulin which is an established anti diabetic agent. In general Group IV (200mg/kg b.wt. methanol extract dose group showed the best performance in terms of modulation of high blood glucose.

The hypo-glycemic effect of avocado seed observed in the present study agrees with results of earlier studies. Ezejiofor et al ., (2013) reported a percentage reduction of blood glucose of diabetic rats treated with aqueous extract of avocado seed ranging from 45.8%(200mg/kg on day 7) to 58.9% (400mg/kg on day 21). Similarly Al -hassan et al (2012) reported a significant decrease in the blood glucose level of diabetic rats with water extract of avocado seed .Anti diabetic effect of avocado seed extract indicates the presence of hypoglycaemic agents in the P. americana seed.

Analysis of seed extract on liver enzymes in this study indicates that alloxan induced diabetes caused elevated liver enzyme levels in rats (Table 3.2) ,this observation is consistent with previous reports by Felig et al., (1970) ,and Iweala and Oludare ,(2011).Results of liver function test showed a significantly ($p<0.05$) increased liver enzyme level in the untreated diabetic rats as compared with the treated groups (insulin and extract treated groups).There is significant difference ($p<0.05$) in the total bilirubin levels between Groups I and II (0.7$\pm$0.03 mg/dl and 0.68 $\pm$0.24 mg /dl respectively).Bilirubin levels of Group I and III were significantly lowered than those of Groups II,IV and V, this may be due to insulin treatment.

The Bilirubin levels of Groups II,V and IV (2.93$\pm$0.26mg/dl,2.93$\pm$0.03 mg/dl and 5.78$\pm$0.8mg/dl) are not significantly different from each other ,while bilirubin levels of Group IV,II and V (3.75$\pm$0.6 mg/dl ,2.93 $\pm$0.03 mg /dl and 5.78$\pm$0.8 mg/dl) are not also significantly different from each other .Group V (5.78 $\pm$0.8 mg/dl) recorded a significant difference ($p < 0.05$) higher total bilirubin than the other group implying that methanol extract significantly elevate total bilirubin compared to the normal control and insulin treated.

Results of conjugate bilirubin shows there is no significant difference ($p.>0.05$) between Groups I and III, (Table 3.3) shows there is no significant difference ($p>0.05$) between Groups I and II (0.31 $\pm$0.19mg/dl and 0.28$\pm$0.10mg/dl respectively. Groups I and II have comparable conjugate bilirubin levels ($p>0.05$), Groups II and IV also have comparable conjugate bilirubin levels (0.31$\pm$0.19mg/dl and 1.73$\pm$0.36mg/dl)respectively,this means that both water extract compared with the

untreated diabetic group .However Group IV has a conjugate bilirubin (2.23±0.51 mg/dl) which is significantly higher than Group I to III (0.31±0.19mg/dl, 1.38±0.21mg/dl and0.28±0.10mg/dl)and significantly lower than Group V.

This further shows that methanolic extract also significantly elevate conjugate bilirubin concentration compared to both the insulin and water extract treated groups.

AST levels in Table3.3 indicates no significant difference between groups III and I respectively (33.50±11.68 IU /L and 33.75±5.50 IU/L),On comparison the normal Group (I) and Group V (300mg/kg .b.wt.methanol treated) have lower AST level than both the insulin and the other treated Groups (methanol extract treated groups),however this difference is not significant (p>0.05), there is no significant difference between (p>0.05)between Group IV and II (44.25±3.30 IU/L and 57.00±16.19IU/L).However on comparison with the normal AST levels (10IU/L-40IU/L),Groups I, III,IV and V all presented AST levels within the normal range ;Group II showed an increase in AST level which could imply that there could be a relationship between diabetes and AST levels. This is also an indication of liver injury associated with alloxan induced diabetes.

ALT levels (Table 3.3) reveals that there is no significant difference (p>0.05) between groups III,I,IV and V ,however group V has the lowest ALT levels ,therefore each treatment appears to modulate the activity of Alanine transmitase. Alanine transmitase level in Group II presented a higher value than those of other groups implying than high blood glucose may affect liver activity .Comparing with the normal ALT range (51IU/L-35IU/L),Group V (34.50IU/L±4.43IU/L) presented a value within the normal range while all the other groups have values above the normal range. Elevation in activities of ALT, AST and ALP are considered predictions of diabetes mellitus, furthermore elevation in levels of these gluconeogenic enzymes, whose gene transcription is suppressed by insulin could indicate impairment in insulin signalling rather than purely liver cell injury (O'Brien and Granner, 1991).

The ALP levels (Table 3.3) showed that there is no significance difference (p>0.05) between Group III, I and V (27.50 ± 3.32IU/L, 30.50±3.32IU/L and 37.25±1.71IU/L)with group II (insulin treated group) having the lowest enzyme level. There is no significant difference between Groups V and IV, comparing with the normal ALP range (9IU/L-35IU/L), Groups III, I and V (27.50±3.32IU/L, 30.50±3.32IU/L and 37.25±1.71IU/L)all presented values within the normal. Group IV (52.25±11.70IU/L)presented values that were mildly higher than the normal range .All the treatment modulated the liver enzymes in varying proportions ,Group V appears to have the best result showing liver function parameters. The methanolic extract treated group (IV and V) were observed to significantly (p>0.05) elevates the total bilirubin and conjugate bilirubin concentration. Thus, the increased activities of ALT, AST and ALP in serum of diabetic rats may primarily be due to leakage of these enzymes from liver cytosol into the blood stream as a consequence of hepatotoxic effect of alloxan. (El-Demordash et al 2005).

However, the relatively higher values of the groups treated with the extracts suggest that there may be presence of certain toxic compounds in the extract.

4.2 CONCLUSION

This study shows that abnormal symptoms observed with diabetes mellitus could be reversed and treated with methanolic extract of avocado seed in alloxan induced diabetic rats. The methanolic extract of avocado seed extract is effective compares with standard drug

(insulin), therefore the extract possess good anti hyper-glycemic agent which helps to balance glucose level and repair liver functions in the body, thereby helping to manage diabetic condition.

4.3 RECCOMENDATION

There will be need to carry out further investigation in other higher primates in order to validate the traditional use of avocado extract in the management of diabetes ,phytochemical analysis of the avocado seed extract should also be carried out to identify the specific compounds responsible for the observed anti diabetic and anti hyper lipidemic activities .

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