

2 **Effect of Aqueous Extract of Guava (*Psidium guajava*)**
3 **Leaf on Blood Glucose and Liver Enzymes in Alloxan**
4 **Induced Diabetic Rats**

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11 **ABSTRACT.**

12 **Aim:** The aim of this study is to determine the effect of aqueous extract of *Psidium guajava* leaf on blood
13 glucose level and liver enzymes of alloxan –induced diabetic rat.

14 **Study Design:** The animals were grouped into six of 6 rats each. Groups A, B, C and E were induced
15 diabetes by intraperitoneal injection of alloxan monohydrate with a dose of 100mg/kg body weight. The
16 extract was administered through gastric tube per kilogram body weight as follows: group A 200mg/kg,
17 group B 150mg/kg, group C 100mg/kg, group D none (normal control), group E none (untreated diabetic
18 control) and group F 150mg/kg (extract control).

19 **Methodology:** Blood samples were collected by cardiac puncture after fasting overnight and standard
20 methods were used for the extraction of spices, determination of fasting blood glucose and liver enzymes.

21 **Place and duration of study:** The study was carried out at Abia State University Uturu-Nigeria and the
22 entire experiments lasted between December 2011 and July 2012.

23 **Result:** The results showed a significant ($P<0.05$) decrease in the blood glucose level compared to
24 untreated diabetic control. There was no significant ($P<0.05$) difference observed in alkaline phosphatase
25 (ALP) and aspartate aminotransferase (AST) activity compared to all the controls (normal, untreated and
26 extract control) while alanine aminotransferase (ALT) activity decreased significantly ($P<0.05$) compared
27 to untreated diabetic control.

28 **Conclusion:** Therefore, this result revealed that aqueous extract of *Psidium guajava* leaf possess anti-
29 hyperglycemic properties with no side effect on selected liver enzymes compared to normal control and
30 since the leaf did not show interference with functional integrity of the liver tissues it has a better potential
31 for treatment of diabetes.

32 *Keywords: Psidium guajava, alkaline phosphatase, alanine aminotransferase, aspartate*
33 *aminotransferase, blood glucose*

34 **1. INTRODUCTION**

35 Diabetes mellitus, a syndrome of disordered metabolism is usually caused by a combination of hereditary
36 and environmental effects, resulting in abnormally high blood sugar levels (hyperglycaemia) [1]. In
37 diabetes mellitus, the **blood** glucose level becomes high due to defects in either insulin secretion or
38 insulin action in the body or both [2]. It has been estimated that World-wide prevalence of diabetes
39 mellitus in 2008 was more than 347 million with varying prevalence among different ethnic groups [3, 4]
40 and it is expected that in 2025 the number will rise to 500 million [5]. Cases of type 2 diabetes mellitus
41 have been increasing in contrast of type 1 diabetes mellitus; cure and prevention of type 2 diabetes
42 mellitus have become important concern in developed countries and in the same way, due to urbanization
43 and life style changes toward “Western style” diet, cure and prevention of type 2 diabetes mellitus
44 supposed to become a more serious problem in developing countries [6]. Diabetes mellitus is a chronic
45 disease that can be managed effectively through modified life styles such as monitoring ones weight, diet,
46 exercise to long term use of oral hypoglycemia drugs [7]. Treatment can also be achieved by the use of
47 synthetic drugs such as sulphonylureas [8].

48 Herbs and vegetables have contributed significantly in providing remedies for improvement of human
49 health in terms of prevention and/or treatment of diseases. Thousands of plant species grow wild in Africa
50 and have both nutritional and therapeutic purposes hence, traditional doctors and leaders are the
51 dispensers of such concoctions [9]. Guava (*Psidium guajava*) is a common shade tree or shrub in
52 dooryard gardens in the tropics which are classified in to *Myrtaceae* family. The tree is easily identified by
53 its distinctive thin, smooth, copper-coloured bark that flakes off, showing a greenish layer beneath [8].
54 There are so many reports on the phytochemical analyses of guava leaf which revealed the presence of
55 more than 20 isolated compounds such as alkaloids, anthocyanins, carotenoids, essential oils, fatty acids,
56 lecithins, phenols, saponins, tannins, triterpenes and vitamin C [10, 11, 12]. The decoctions made from the
57 leaf and /or bark of *P. guajava* have been reported to be used by many countries and tribes traditionally
58 for treatment of diarrhea, dysentery, sore throat, vomiting, stomach upsets, vertigo, haemorrhages,
59 intestinal worms, gastroenteritis, diabetes, vaginal discharge, to regulate menstrual cycle and to tighten or
60 tone vaginal walls after child birth [13, 14, 15,16, 17].

61 In recent times reports from medicinal plants research indicate that extracts from some plants are
62 hepatotoxic or hepatoprotective. However, liver function tests are commonly used in clinical practice to
63 screen for liver diseases, monitor the progression of known disease, and monitor the effects of potentially
64 hepatotoxic drugs. Individuals with type 2 diabetes have high incidence of liver abnormalities than
65 individuals who do not have diabetes and anti-diabetic agents have generally been shown to decrease
66 alanine aminotransferases levels as tighter blood glucose level is achieved [18].

67 There are reports on anti-hyperglycemic effects of *P. guajava* leaf extracts [5, 6, 17] but, scanty reports
68 are available on the effect on liver enzymes on using aqueous extract of *P. guajava* leaf in treatment of
69 alloxan-induced diabetic rats. Therefore, this study was carried out to determine the effect of treatment of
70 alloxan induced diabetic rats with aqueous extract of *P. guajava* leaf on blood glucose level and liver
71 enzymes.

72 2. MATERIALS AND METHODS

73 2.1 Collection and Preparation of Plant Materials

74 The fresh leaves of *P. guajava* were collected from Umuinem Village, Okigwe in Okigwe Local
75 Government Area, Imo State-Nigeria in January, 2012. The Botanical identification of the plant specimen
76 was carried out at the department of Plant Science and Biotechnology (PSB), Faculty of Biological and
77 Physical Sciences, Abia State University Uturu. Samples of the specimen were deposited in the
78 Herbarium of the same University. The fresh leaves of *P. guajava* collected were sorted and all dead
79 matter and unwanted particles were discarded. The leaf were air dried for two weeks and grounded into
80 powder using electric blender and the powder was stored in an air tight container in the laboratory. A total
81 of 200g of the ground powder was weighed out and soaked in 1000mls of distilled water for two days at
82 room temperature. The mixture was filtered using (NO. 1) Watman filter paper. The filtrate was dried at a
83 temperature of 30°C in an incubator to produce gel-like extract that weighed 20g. The extract was then
84 diluted with distilled water into 200mg/kg, 150mg/kg and 100mg/kg body weight.

85 2.2 Animal Treatments

86 A total of 36 male albino rats weighing between 120 -135g were purchased from the animal house of
87 Department of Biochemistry, Abia State University Uturu-Nigeria. The rats were randomly divided into 6
88 groups of 6 rats in each group. Groups A, B and C were the test group, group D was the normal control,
89 Group E the untreated control and group F extract control. The rats were acclimatized for 10 days before
90 the commencement of the experiment. The animals in both test and control group were allowed free
91 access to food (rat pellets) and water *ad libitum*, throughout the experimental period. Good hygiene was
92 maintained by constant cleaning and removal of faeces and spilled feed from cages daily. The weights of
93 the rats were taken every day throughout the period of the experiment.

94 The blood glucose of the rats was determined before induction of diabetes. Groups A, B, C and E were
95 induced by a single intraperitoneal injection of freshly dissolved alloxan monohydrate (100mg/kg) using
96 normal saline maintained at 37°C as vehicle to rats fasted for 15hrs. Diabetic states were confirmed by
97 measuring the fasting glucose concentration after 5days of injection and were compared with the initial
98 blood glucose level. Rats with blood glucose level of 13mmol/l and above were used for the study. The

99 groups D and F were given the same quantity of normal saline. The animals were administered aqueous
100 extracts of *P. guajava* leaf through gastric tube for four weeks according to their body weight as follows.

- 101 i. Group A were treated with 200mg/kg body weight of the extract after the injection of alloxan.
- 102 ii. Group B were treated with 150mg/kg body weight of the extract after the injection of alloxan.
- 103 iii. Group C were treated with 100mg/kg body weight of the extract after the injection of alloxan.
- 104 iv. Group D were treated with distilled water in place of extract after no injection of alloxan.
- 105 v. Group E were treated with distilled water in place of extract after the injection of alloxan.
- 106 vi. Group F were treated with 150mg/kg body weight of the extract after no injection of alloxan.

107
108 All the animal processes involved in the handling and the experiment were carried out in accordance with
109 the guidelines of Animal Ethical Committee of Faculty of Biological and Physical Sciences, Abia State
110 University Uturu-Nigeria.

111

112 2.3 Collection and Analysis of Blood Specimen

113 The animals were fasted overnight, anaesthetized with chloroform vapour and dissected for blood
114 collection. Blood samples were collected by cardiac puncture into plain and fluoride-oxalate treated
115 sample bottles. The blood samples were allowed to clot and were spun in bench centrifuge (MSE
116 England) at 3000rpm for 5min to obtain sera. The serum samples were separated into another set of plain
117 sample tubes and stored in the refrigerator at -4°C until required for the enzyme analysis. The blood
118 glucose levels were determined by the glucose oxidase enzymatic method (Trinder, 1969). Colorimetric
119 end point method was used to determine serum alkaline phosphatase (ALP) [20]. Serum aspartate
120 aminotransferase (AST) and serum alanine aminotransferase (ALT) activities were determined using
121 Reitman and Frankel [21] method. All assays were carried out within 24hrs of the sample collection.

122 2.4 Statistical Analysis

123 All data were analyzed using Analysis of Variance (ANOVA) and means were compared for significance
124 using Duncan's Multiple Range Test (DMRT) at $P < 0.05$.

125 3. RESULTS

126 The average weights of alloxan-induced diabetic rats treated with aqueous extract of *P. guajava* leaf are
127 as shown in table 1. A significant ($P < 0.05$) decrease in average weight of the rats in test groups A, B, C
128 and untreated diabetic control (group E) were observed after 5days post alloxan-induction. After 28 days
129 of post treatment the average weight of the animals in groups A, B, C, D and F increased significantly
130 ($P < 0.05$) compared to group E (untreated diabetic control).

131 **Table 1.** Average weights of alloxan- induced diabetic rats treated with aqueous extract of *P. guajava* leaf
 132 measured in gram.

Duration	Group A	Group B	Group C	Group D	Group E	Group F
Pre- induction	130.72±22.31 ^a	135.65±28.42 ^a	140.00±26.81 ^a	132.90±27.12 ^a	130.92±25.32 ^a	138.20±26.32 ^a
5days Post- induction	121.20±21.48 ^a	128.45±26.32 ^a	132.05±26.21 ^a	143.62±30.66 ^a	122.50±21.53 ^a	145.42±25.08 ^b
Post- treatment	208.51±30.02 ^b	210.60±28.38 ^b	205.30±28.05 ^b	222.32±32.86 ^b	96.82±16.41 ^a	215.74±28.52 ^b

133 *Values are mean ± standard deviation of six determinations. Values in rows with different superscript*
 134 *alphabets are significant (P<0.05).*

135 The effect of aqueous extract of *P. guajava* leaf on the blood glucose level of alloxan-induced diabetic
 136 rats (Table 2) show that at 5 days post-induction of alloxan, the blood glucose level of groups A, B, C and
 137 E increased significantly (*P*<0.05) in relation to groups D and F which were not induced with alloxan
 138 monohydrate. The blood glucose levels of the test groups decreased significantly (*P*<0.05) compared to
 139 untreated diabetic control (group E) after 28 days of the extract administration.

140 **Table 2.** Effect of aqueous extract of *P. guajava* leaf on the blood glucose level of alloxan-induced
 141 diabetic rats measured in mmol/l.

Duration	Group A	Group B	Group C	Group D	Group E	Group F
Pre-induction	8.89±0.10 ^a	9.03±0.11 ^a	9.21±0.17 ^a	9.14±0.07 ^a	9.28±0.12 ^a	9.30±0.08 ^a
5days Post- induction	13.88±0.09 ^b	13.72±0.16 ^b	14.40±0.09 ^b	9.10±0.14 ^a	14.12±0.10 ^b	9.04±0.09 ^a
Post- treatment	8.68±0.14 ^a	8.45±0.13 ^a	8.67±0.12 ^a	9.31±0.17 ^a	15.23±0.14 ^b	8.82±0.17 ^a

142 Values are mean \pm standard deviation of six determinations. Values in rows with different superscript alphabets are
143 significant ($P<0.05$).

144 Table 3 shows the liver enzyme activities of alloxan- induced diabetic rats treated with aqueous extract of
145 *P. guajava* leaf. It was observed that after induction and administration of the aqueous extract, there was
146 no significant change in ALP, AST and ALT activities of the test groups compared to both extract control
147 (group F) and normal control (group D). However a significant ($P<0.05$) decrease was observed when the
148 test groups were compared to the untreated diabetic control (group E).

149 **Table 3.** Liver enzyme activities of alloxan-induced diabetic rats treated with aqueous extract of
150 *P.guajava* leaf (U/L).

Liver enzymes	Group A	Group B	Group C	Group D	Group E	Group F
ALP	40.33 \pm 1.76 ^a	38.62 \pm 1.50 ^a	39.71 \pm 1.50 ^a	40.23 \pm 1.51 ^a	43.87 \pm 1.35 ^a	38.90 \pm 1.20 ^a
AST	42.87 \pm 1.70 ^a	43.70 \pm 1.78 ^a	41.68 \pm 1.53 ^a	44.96 \pm 2.97 ^a	46.20 \pm 2.35 ^a	42.08 \pm 1.25 ^a
ALT	24.84 \pm 2.24 ^a	26.85 \pm 2.14 ^a	24.01 \pm 2.80 ^a	25.73 \pm 1.86 ^a	32.80 \pm 2.40 ^b	25.36 \pm 2.64 ^a

151 Values are mean \pm standard deviation of six determinations. Values in rows with different superscript alphabets are
152 significant ($P<0.05$).

153

154 4. DISCUSSION

155 Varieties of plants are known to be of economic and medicinal value and those plants that are of
156 medicinal value are often used as herbal remedy for the restoration and maintenance of good health.
157 Medicinal plants usually have phytochemicals as part of its constituents. The phytochemicals include
158 alkaloids, anthocyanins, carotenoids, essential oils, fatty acids, lecithins, phenols, saponins, tannins,
159 triterpenes and vitamin C [10, 12]. It has been reported that the presence of phenolic compounds, gallic
160 acid, catechins and quercetin in *P. guajava* leaf significantly inhibited the glycation of proteins such as
161 albumin, suggesting their use for prevention of diabetes complication [22]. The presence of high amount
162 of phenolic compounds with antioxidant activity in the leaf of *P. guajava* leaf was also reported by Haida
163 *et al.* [23]. Deguchi and Miyazaki [6] reported that the consecutive injection of aqueous extract of *P.*
164 *guajava* leaf have the potential to improve diabetes symptoms such as hyperglycaemia, nephropathy and
165 insulin resistances in diabetic animal models and/or clinical trials.

166 The result showed a significant ($P<0.05$) decrease in body weight of group E compared to other groups.
167 However, it has been shown that weight loss is one of the symptoms of diabetes mellitus [7] and group E
168 was not treated with *P. guajava* leaf which therefore led to the increase in severity of the disease and
169 then the significant weight loss. The observed decrease in blood glucose level of the alloxan- induced
170 diabetic rats after treatment with aqueous extracts of *P. guajava* may be attributed to the presence of
171 tannins, flavonoids, triterpenoids, alkaloids, and other chemical compounds in the plant. These
172 compounds which have been shown present in *P. guajava* leaf [24] have been reported to be responsible
173 for hypoglycaemic activity in *Mormordica charantia* [25] and *Mormordica foedum* [26]. The lowering of
174 glucose levels by aqueous extract of *P. guajava* may also be due to the high content of quercetin in *P.*
175 *guajava* leaf extract thereby confirming its usefulness for diabetic patients [5] as was suggested by Cheng
176 *et al.* [27] that quercetin in aqueous extract of *P. guajava* leaf promotes glucose uptake in liver cells, and
177 contributes to the alleviation of hyperglycemia in diabetes. The marked decrease in blood glucose level of
178 the alloxan- induced diabetic rats by *P. guajava* appear to suggest that its main mechanism of action may
179 not be due to potentiation of insulin release from pancreatic cells since alloxan induce diabetes by
180 destroying β -cells and impairing renal function. Hence, the extract may have effect in the control of non-
181 insulin dependent diabetes mellitus. The observed hypoglycaemic effect of aqueous extract of *P. guajava*
182 on normoglycaemic rats (group F) is a pointer that the effect could possibly be due to increase peripheral
183 glucose utilization and inhibition of the proximal tubular reabsorption mechanism for glucose in the kidney
184 [28].

185 Liver function tests are commonly used to screen for liver diseases, monitor the progression of known
186 disease and monitor the effects of potentially hepatotoxic drugs [18]. Liver function test is also used to
187 find out if a medicinal plant is hepatotoxic or hepatoprotective. The present study showed that there were
188 no significant ($P<0.05$) change on alkaline phosphatase (ALP), aspartate aminotransferase (AST) activity
189 in test groups compared to control but, significant ($P<0.05$) decrease was observed in alanine
190 aminotransferase (ALT) activity in test group compared to untreated diabetic control after the
191 administration of aqueous extract of *P. guajava* leaf on alloxan –induced diabetic rats. This may be as a
192 result of flavonoids present in the extract. Flavonoids are indicated in the protection against allergies,
193 inflammation, free radicals, platelet aggregation, microbes, ulcer, hepatotoxins, virus and tumors [29, 30,
194 31].

195 It was also suggested that the hepatoprotective effect of *P. guajava* extracts may be due to the action of
196 various contents of the extracts especially the flavonoids which have been found to have anti-oxidative
197 effects [32]. The observed decrease in ALT activity may be attributed to ant-diabetic constituents of the
198 extract which generally decrease ALT levels as tighter blood glucose level are achieved [18]. Since the
199 aqueous extract of *P. guajava* leaf did not show any interference with the functional integrity of the liver
200 tissues, it is suggested that the aqueous extract be used as liver tonic.

201 **5. CONCLUSION**

202 This study indicated that the aqueous extract of *P. guajava* possess hypoglycaemic properties with no
203 **side** effect on the selected liver enzyme activities hence, lend pharmacological credence to the suggested
204 folkloric, ethnomedical uses of the plant in the management of adult-onset, type 2 diabetes mellitus in
205 some rural African communities.

206

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209 **COMPETING INTERESTS**

210

211 Authors have declared that no competing interest exists.

212

213 **AUTHORS' CONTRIBUTIONS**

214

215 This work was carried out in collaboration of the Authors. Authors IE and CCO designed the study and
216 wrote the protocol. Authors VCU, AEU and CCO managed the literature search and wrote the first draft of
217 the manuscript. Author VCU and CCO performed the statistics. Authors CCO, VCU and AEU managed
218 the analyses of the study. All the authors read and approved the manuscript.

219 **CONSENT**

220 Not applicable.

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