Original Research Article

Anti-Hyperglycemic and Anti-Hyperlipidemic Potentials of Methanol Leaf Extracts of *Aframomummelegueta* and *Piper guineense*

Aim: The study investigated the anti-hyperglycemic and anti-hyperlipidemic potentials of methanol extracts of *Piper guineense* and*Aframomummelegueta* leaves with a view to utilizing the plants in the treatment and management of cardiovascular disorders.

Methodology: Twenty-eight healthy albino rats were randomly divided into seven equal groups: Group I received normal saline (2 ml/kg bwt); Group II received a single dose of alloxan(150 mg/kg bwt) intraperitoneally; Group III received alloxan (150 mg/kg bwt) + glibenclamide(5 mg/kg bwt);Group IV received alloxan (150 mg/kg bwt) +PG (200 mg/kg bwt); Group V received alloxan (150 mg/kg bwt) + PG (400 mg/kg bwt); Group VI received alloxan (150 mg/kg bwt) + AM 200 (mg/kg bwt); Group VII received alloxan (150 mg/kg bwt) + AM (400 mg/kg bwt). The blood glucose level was determined before and after treatment with the extracts. The lipid: (total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were estimated using the Randox diagnostic kits.

Results: The results revealed that alloxan was able to induce hyperglycemia at 150 mg/kg bwt and post-treatment with *P. guineense*and *A. melegueta* at 200 mg/kg and 400 mg/ kg bwt were able to significantly lower the blood glucose level which was quite apparent in AM treated groups. Also, the extracts at 200 mg/kg and 400 mg/kg were able to bring a significant ($p < 0.05$) reduction in TC, TG and LDL concentrations when compared to the alloxan treated group with the highest reduction in AM treated groups.

Conclusion: These results revealed that the methanol extract of *P. guineense*and *A. melegueta*elicited anti-hyperglycemic and anti-hyperlipidemic potentials of the extracts with the highest effect observed in *A. melegueta* treated rats.

Keywords:-Anti-hyperglycemic, Anti-hyperlipidemic, *Piper guineense* and *Aframomummelegueta*

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder and is becoming a global health concern because of the increase in its prevalence. However, hyperglycemia and hyperlipidemia are some of the factors indicating this metabolic syndrome[1]. Hyperglycemia is a condition in which an excessive amount of glucose circulates in the blood plasma. Diabetic neuropathy may be a result of long-term hyperglycemia. Hyperlipidemia is characterized by abnormal elevation in plasma triglyceride, cholesterol and low density lipoprotein-cholesterol (LDL-c) and very low lipoprotein - cholesterol (VLDL-c) and has also been reported to be the most prevalent indicator for susceptibility to atherosclerotic heart disease [2]. Also, high blood glucose levels are associated with low level of high-densitylipoprotein cholesterol (HDL-c) and increase of LDL-c cholesterol, thus increasing risk of coronary heart diseases. Therefore, it is vital to manage both diabetes and lipid levels [3]

The increase in demand for cheapertherapeutics with no/minimum side effects is stimulating interest in studying the use of natural products for the treatmentand management of diseases [4]. The medicinal values of these plants are usually due to the presence of phytochemicals [5].

*P.guineense*belongs to the family Piperaceae commonly known as West African Black Pepper. It is a climbing plant climbing up to 12m high by its adventitious rootlets. It is known with different vernacular names in Nigeria which include 'Uziza' in Igbo, and 'Iyere' in Yoruba.The seeds are smooth and are prolate-elliptically shaped. The seeds, leaves and sometimes the stems are used in preparing soup. It imparts "heat" and a spicy pungent aroma to food.The plant is utilized for a variety of purposes which include human dietaries,preservative, bio-control agent as well as traditional medicine [6].

Previous phytochemical studies of *P. guineense*seed extract revealed the presence of various substances such as alkaloids, flavonoids, tannins triterpenoids, cardiac glycosides and saponins[7]. Pharmacological and physiological studies of *P. guineense*extract showed depolarizing neuromuscular blocking action, insecticidal properties, sexual behavioural effect and antifungal activity [8]and edema in gastrointestinal tract, urinary bladder and adrenal glands and immunotoxicological effects [9].

*Aframomummelegueta*K. Schum belongs to the ginger family(Zingiberaceae) and it is commonly known as grains of paradise or alligatorpepper [10]. It is variously known locallyas *oseoji*in Igbo, ataareinYoruba, and *cittáá*in Hausa of Nigeria.The seeds of *A. melegueta*have been variously reported to be rich in carbohydrates, crude fibre, and bulk minerals [11] suggesting it to be of good nutritional quality, and hence justifying itsincorporation into diet. The report of [12, 13],NMR and GC-MS analyses of the chloroformextract of the seeds and essential oils from various plant parts,respectivelyshow the plant to be rich in secondary metabolites such as modifiedgingerols, paradols and shogaols. These

metabolites account for some of peppery taste of the seeds [14]. The use of *A. melegueta* in traditional medicine in treating diabetes has been age long. The essential oils, polyphenol profile andantioxidant activity of *Aframomummelegueta*, have been reported[15,17,18,19]. It is usedmedicinally to treat many diseases including measles, leprosy; tostop lactation and post-partum haemorrhage, as antidiarrhea andantiinflammatory activity which may be due to prostaglandininhibition, and membrane stabilizing activity respectively[20].

Many studies have been carried out on the seeds of these plants but there is dearth of scientific information on the leaves of these plants. Hence, this study investigated the anti-hyperglycemia and the anti-hyperlipidemic effects of the leaf extracts of*A. melegueta* and *P. guineense.*

2. MATERIALS AND METHODS

2.1 Chemicals

All chemicals and drugs used were obtained commercially and of analytical grade.

2.1.1 Collection of plantmaterials

The leaves of *A.melegueta and P.guineense*werecollected in February, 2015 at Okuku, Odo-Otin local government, Osun State, Nigeria. It was identified and authenticatedat IFE herbarium(17525),ObafemiAwolowo University, Ile- Ife.

The methanolic extracts of *A. melegueta* and *P. guineense* were separately prepared. The leavesweredried under shade and ground intopowder. Typically, the powder (200g) was macerated in 2.5 Lmethanol (70%) at room temperature for 72h. It was then filteredusing muslin cloth. The filtrates were allowed to settle, decanted and filtered using filtration assembly.Thefiltrateswere evaporatedusing rotary evaporator and then freeze dried using lypholizer. The extracts were storedin air tight container in a refrigerator until used.

2.2 Experimental Animals

Adult female and male albino rats (28) weighing between 120-150 g were obtained from the Animal House, Faculty of Pharmacy, ObafemiAwolowo University, Ile-Ife. The rats werehoused in polyethylene cages at the Animal House, Department of Biochemistry, Adeleke University, Ede and were kept under standard conditions; food and water were supplied *ad libitum*. They were allowed to acclaimatized for a period of 14 days.

2.3 Grouping and Treatment of Animals

The ratswere randomly assigned into seven groups of four ratsin each group as follows:

Group I: Control (Normal saline)

Group II: Alloxan Treated (150 mg/kg bwt)

Group III: Alloxan + Glibenclamide (5mg/kg bwt)

Group IV: Alloxan + PG (200 mg/kg bwt)

Group V: Alloxan + PG (400 mg/kg bwt)

Group VI: Alloxan + AM (200 mg/kg bwt)

Group VII: Alloxan + AM (400 mg/kg bwt)

The extracts and the reference drug (Glibenclamide) were administered orally. The doses of the extract was determined according to the acute toxicity study carried out by []

2.4 Induction of *Diabetes* and Treatment with the Extracts

The animals were allowed to fast overnight and diabetes was induced by a single intra-peritoneal injection of alloxan monohydrate (150 mg/kg bwt). Increase glucose level was monitored 3 days after injection by measuring the tail vein blood glucose level using glucometer. The induced rats were orally treated with the extracts for 7 days.

2.5 Determination of Blood Glucose Levels

The level of blood glucose was determined according to the method described by [21]before and after treatment with the extract and standard drugby using a glucometer. The rats were subjected to fasting for 12-18 h with free access to water prior to the administration of the extract and the blood glucose level was measured. After the last treatment with the extracts, the animals were fasted overnight and the blood samples were collected for the determination of the blood glucose concentration.

2.6 Sacrificing and Preparation of Blood Plasma

The rats were sacrificed under mild anasthesia with ether, 24 h after the last treatment (oral administration of extracts and drug). Blood was collected by cardiac puncture into bottles containing anticoagulant (trisodium citrate, 3.8% w/v) and mixed gently. Blood plasmawas prepared using standard procedure as reported and modified by Bode and Oyedapo [22]. Blood sample was centrifuged on Bench Centrifuge Model 90-2 (Searchtech Instrument England, UK.) at3000 rpm for 10 min. The supernatant (plasma) was collected into sterile bottles, labeled and stored in freezer for biochemical analyses.

2.7 Estimation of Plasma Lipid Profiles

Plasma lipid profiles: triacylglycerol (TG), total cholesterol (TC), High density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), were estimated spectrophotometrically using Randox assay kits.

2.8 Statistical analysis

The data were statistically analyzed using t-test and ANOVA with the aid of SARSsoftware package. The level of statistical significance was also compared using Duncan's multiple range test $p < 0.05$.

3. RESULTS

Yield of the Extract

3.1 The methanol leaf extract obtained from 500g of powdered leaf weighed 5.6g which was 1.12% of the starting material.

4.1.2 The methanol leaf extract obtained from 500g of powdered leaf weighed 97.69g which was 19.5% of the starting material.

3.1 Blood Glucose Level

In Table 1is the summary of the initial and final concentrations of blood glucose. After induction of hyperglycemia with alloxan monohydrate, there was a significant increase (P<0.05) in blood glucose level of other experimental groups when compared with the normal control group. After treatment the extracts at 200 mg/kg and 400 mg/kg, the blood glucose level was significantly reduced (P<0.05) when compared to the alloxan treated rats. This indicated the anti-hyperglycemic potentials of the extracts.

Table 1:Effects of Methanol Leaf Extract of*P. guineense* and *A. melegueta*on Blood Glucose Concentration (mg/dl) of Alloxan-induced Hyperglycemic Rats

Treatment Group	Initial Blood Glucose (mg/dl)	FinalBlood Glucose (mg/dl)	% Change
Control	80.50 ± 2.02	75.75 ± 1.11	5.90
Alloxan Treated	79.25 ± 0.85^{b}	199.00 ± 1.68^{a}	151.10
Alloxan + Gilbenclamide (5mg/kg bwt)	59.25 ± 0.48^{a}	95.75 ± 0.85^{b}	61.60
Alloxan + *P. guineense* (200 mg/kg bwt)	68.25 ± 0.35^{a}	137.75 ± 2.66^{b}	101.83
Alloxan + *P. guineense*(400 mg/kg bwt)	75.50 ± 1.09^{b}	114.50 ± 3.07^{b}	51.66
Alloxan + *A. melegueta*(200 mg/kg bwt)	79.50 ± 0.87^{b}	65.50 ± 1.96^{b}	-17.61

Alloxan + *A. melegueta*(400 mg/kg bwt)	74.25 ± 0.91^{b}	72.25 ± 1.58^{b}	2 .69

Each value represented mean ± SEM, n = 4 readings. Values with different superscript alphabet are significantly different at $P<0.05$.

3.2 Lipid Profiles

In Table 2 is the summary of the effect of the extracts on the plasma lipid profilse of alloxan-induced hyperglycemia rats. There was significant increase in the concentrations of TC, TG and LDL-c but a decrease in HDL-c of the alloxan treated group when compared to the control group.However, treatment with the extracts at 200 and 400 mg/kg bwt caused a significant reduction in the concentrations of TC, TG and LDL-c but an increase in HDL-c.

Table 2: The Effectsof Methanol Leaf Extract of*P. guineense* and *A. meleguetaon* LipidProfile (mmol/L)of Alloxan-induced HyperglycemicRats

Treatment Group	TC(mmol/L)	TG(mmol/L)	HDL(mmol/L)	LDL(mmol/L)
Control	5.99 ± 0.003	1.61 ±0.001	4.54 ± 0.001	0.714 ± 0.008
Alloxan Treated	15.82 ± 0.019[a]	4.89 ± 0.002[a]	0.02 ± 0.001[a]	13.58 ± 0.019[a]
Alloxan + Gilbenclamide (5mg/kg bwt)	8.253 ± 0.019[b]	1.96 ± 0.310[b]	3.27 ± 0.019[b]	4.09 ± 0.014[c]
Alloxan + PG (200 mg/kg bwt)	9.448±0102[b]	3.862±0.021[b]	2.266±0.387[b]	5.426±0.061[b]
Alloxan + PG (400 mg/kg bwt)	7.318±0.018[b]	2.008±0.003[b]	4.364±0.017[b]	5.426±0.061[b]
Alloxan + AM (200 mg/kg bwt)	9.35 ± 0.046[b]	0.961 ± 0.032[b]	6.95 ± 0.04[b]	1.05 ± 0.10 [b]
Alloxan + AM (400 mg/kg bwt)	8.411 ± 0.062[b]	2.381 ± 0.02[b]	7.12 ± 0.002[b]	0.214 ± 0.07[b]

Values are mean ± SEM of four determinations. Values with different superscript alphabet are significantly different at P<0.05.

4. Discussion

The study evaluated anti-hyperglycemia and anti-hyperlipidemic effects of *A. melegueta* and *P. guineense* leaf extracts at 200 mg/kg bwt and 400 mg/kg bwt.The dose was chosen based on the reports of previous studies [23, 24, 25].After the administration of alloxan monohydrate, there was significant increase ($p < 0.05$)in the blood glucose level of the alloxan-treatedgroup when compared to the normal control group(Table 1).Elevated value of fasting blood glucose concentration observed in alloxan treated ratsmay be due to the toxic effect of alloxan on islet beta cells of the pancreas through its ability to induce reactive oxygen species (ROS) formation, resulting in the necrosis of the pancreas and loss of capacity of the pancreas to secrete insulin resulting to hyperglycemia [26,27,28].

Chronic exposure to hyperglycemia is the primary casual factor in the pathogenesis of diabetic complications and cause changes in vascular tissue which promote atherosclerosis [29). Our findings is in agreement with the report of earlier studies that administration of alloxan at the dose of 250mg/kg was able to increase to elevate the fasting blood sugar levels [21, 29]. However, post-treatments with

P.guineense and *A. melegueta* at 200 mg/kg and 400 mg/ kg bwt extracts were able to significantly lower theblood glucose respectively when compared to the alloxan treated group.

Both extracts compared favorably with the reference drug, Glibenclamide and the highest effect was observed in *A. Melegueta* at 200 mg/kg bwt. The observed anti-hyperglycemia activity of these extracts may be attributed to the presence of phytochemicals such as: total phenols, flavonoids, alkaloids,tannins, terpenoids, and saponins in the plants that have been known to have anti-hyperglycemic activity[30].The presence of these bioactive compounds was earlier reported by our previous studies [10, 31].Studies also reported that flavonoids have anti-hyperglycemic properties because they stimulate glucose uptake in peripheral tissues and attenuate oxidative stress during diabetic conditions [32, 33].Flavanoids have been reported to be actively involved in the restoration of pancreatic β-cell and insulin secretion.A large number of alkaloids have been isolated from numerous medicinal plants and investigatedfor their possible anti-hyperglycemic activity [34].Saponinsare known to be efficiently involved in the restoration of pancreatic β-cell and insulin secretion[32, 35].

One of the associated metabolic disorders of diabetes is dyslipidemia which is one of the risk factors of diabetes [36]. Hypercholesterolemia and hypertriglyceridemia have been reported to occur in alloxan treated rats [37, 38].The elevated values for lipid profile: TC, TG, LDL-cholesterol, observed in the alloxan induced diabetic rats could be partly due to increased intestinal biosynthesis of cholesterol because diabetes shifted the major site of cholesterogenesis from the liver to the small intestine leading to hypercholesterolemia[39]. Severe diabetes mellitus due to insulin deficiency might be accompanied with a reduced LDL-receptor resulting to high concentration of serum LDL cholesterol in diabetic subjects [40].

The results of the extracts treated groups revealed a significant reduction in the levels of total cholesterol, triglyceride, LDL but an increase in HDL when compared to the alloxan-treated group. The anti-hyperlipidemic effect was more apparent in the *A. melegueta* treated group at 200 and 400 mg/kg bwt. This revealed the anti-hyperlipidemic activityof the plant extracts. The ability of*A. melegueta* and *P. guineense* to ameliorate the lipid profile may be attributed to the presence of phytochemicals in the plants. Epidemiological studies have shown that bioactive compounds such as flavonoids intake are inversely related to mortality from coronary heart diseases and the incidence of heart attacks [41].

In conclusion, the results of this study revealed that the plant extracts elicited anti-hyperglycemic effect and normalized the lipid profile of diabetic rats. This study showed that these spices do not just impact

flavour to foods, but may be sources of bioactive substances useful in the treatment and management of diabetes and related disorders.

Ethical Approval:

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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