

RESEARCH ARTICLE

Influence of coadministration of metformin and methanolic stem extract of *Anisopus mannii* N.E.Br. (*Apocynaceae*) on glucose homeostasis and lipid profile in streptozotocin/nicotinamide-induced diabetic ratsAminu Chika¹, Amina Yahaya¹, Abubakar Amali Muhammad², Muhammad Bashiru Abdulrahman³¹Department of Pharmacology and Therapeutics, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria, ²Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria, ³Department of Chemical Pathology and Immunology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, NigeriaCorrespondence to: Aminu Chika, E-mail: chika.aminu@udusok.edu.ng

Received: September 01, 2019; Accepted: September 23, 2019

ABSTRACT


Background: *Anisopus mannii* (AM) N.E.Br. (*Apocynaceae*), a plant traditionally used for the treatment of diabetes mellitus in Northwestern Nigeria, is often prescribed as an adjunct to conventional treatment of diabetes mellitus. **Aims and Objectives:** The objective was to investigate the influence of coadministration of the stem of AM and metformin on glucose homeostasis and lipid profile in rats. **Materials and Methods:** Following departmental ethics committee permission, two doses (200 mg/kg and 600 mg/kg) each of the aqueous and methanolic stem extracts of AM were administered to glucose-loaded normal rats, and the influence of the coadministration of the most effective of the doses tested (200 mg/kg of methanolic stem extract) with metformin (50 mg/kg) for 28 days on glucose homeostasis and lipid profile was investigated in streptozotocin/nicotinamide-induced diabetic rats. **Results:** When coadministered, metformin reduced the fasting glucose-lowering effect of the AM extract, whereas the extract reduced the degree of elevation of the skeletal muscle glycogen content by metformin. Furthermore, both the extract and metformin, when combined in diabetic rats, reduced each other's beneficial effects in (a) improving glucose tolerance, as evidenced by reduction in the total area under the oral glucose tolerance test curve; (b) reducing fasting blood levels of total cholesterol, low-density lipoprotein cholesterol and triglycerides; and (c) increasing hepatic glycogen content. **Conclusion:** This study revealed that metformin (50 mg/kg) and the methanolic stem extract of AM (200 mg/kg) had a potentially negative influence on each other's beneficial effects on glucose homeostasis and lipid profile in diabetic rats.

KEY WORDS: *Anisopus mannii*; Metformin; Streptozotocin; Diabetic Rats; Coadministration

INTRODUCTION

The world has recently witnessed a dramatic increase in demand for herbal products.^[1] These products are commonly

used concurrently with conventional drugs, particularly by patients suffering from chronic disorders.^[2] For example, conventional antidiabetic drugs are often coadministered with herbal products, resulting in an increased risk of herb-drug interactions. A study involving outpatients visiting a diabetic clinic at Lagos State University Teaching Hospital, Nigeria revealed that about one-third of the participants consumed herbal products concurrently with antidiabetic agents and that a majority of such patients kept their physicians in the dark about the practice.^[3] Although it may be beneficial (by helping to reduce otherwise uncontrolled blood glucose back to normal), the consequence of such

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2019.9.0931023092019001	

National Journal of Physiology, Pharmacy and Pharmacology Online 2019. © 2019 Aminu Chika, *et al.* This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material for any purpose, even commercially, provided the original work is properly cited and states its license.

practice may also be harmful by reducing the effect of the conventional antidiabetic drugs or increasing the risk of their adverse effects (such as hypoglycemia).^[4] Metformin is the most widely prescribed antidiabetic drug globally, and it is the only antidiabetic agent which has been shown to reduce overall as well as cardiovascular mortality.^[5]

Anisopus mannii (AM) N.E.Br. (*Apocynaceae*) is a medicinal plant used traditionally to treat diabetes mellitus in Northwestern Nigeria. It is known as “kashe zaki” or “sakayau” in Hausa, the dominant language in Northern Nigeria. The plant is also prescribed by herbalists as an adjunct to conventional treatment of diabetes mellitus to improve the well-being of the patients (personal communication). Some previous studies have documented the antihyperglycemic and antihyperlipidemic properties of extracts from the stem and leaves of the plant.^[6-9] However, no previous study has evaluated the influence of an extract of the plant on the antidiabetic activity of metformin.

The present study is aimed at determining the effect of coadministration of the stem extract of AM with metformin on serum levels of glucose and hepatic and skeletal muscle contents of glycogen, as well as plasma levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in streptozotocin/nicotinamide-induced diabetic rats.

MATERIALS AND METHODS

Drugs and Chemicals

Glucose standard, streptozotocin powder, metformin hydrochloride, and nicotinamide powder were purchased from Sigma-Aldrich Inc. USA. Glucose oxidase reagent and kits for the assay of TC, HDL-C, and LDL-C as well as TG were procured from Randox Laboratories Ltd. (Crumlin, UK). Glucometer (Accu Chek Active) of Roche Diagnostics, Germany was obtained from a reputable chemical store. All chemicals used were of analytical grade.

Plant Material

A mature whole plant of AM was collected from the forests of Achida, Sokoto State Nigeria. The plant name was verified in the Plant List database (<http://www.theplantlist.org>). Taxonomic identification and authentication were performed by Abdulazeez Salihu of botany unit of the Department of Biological Sciences, Faculty of Science, Usmanu Danfodiyo University Sokoto. A specimen with voucher no. UDUH/ANS/0141 was deposited at the herbarium of the department for future reference.

Preparation of Plant Extracts

The whole plant of AM was shade dried until constant weight was observed, and then the stem was separated from the leaves.

The dried stem was ground to a powder using pestle and mortar, and the powder was divided into two portions, weighing 50 g each. Each portion was macerated using 250 ml of either water or 99% methanol for 48 h with frequent shaking. The aqueous extraction was performed in a refrigerator at 4°C, while the methanolic extraction was done at room temperature. Each of the extracts was filtered twice: using a clean, sterile, white muslin cloth, and then employing Whatman filter 1. The filtrate was then subjected to evaporation under reduced pressure using rotary evaporator at 35°C. The resultant semisolid mass of methanolic extract or reduced volume of aqueous extract was finally dried in an aerated oven at 40°C. The percentage yield of the two dried extracts was calculated (10.98% and 17.66% for the aqueous and the methanolic extracts, respectively), and the extracts were stored in a freezer at -4°C until ready for use.

Animals

Male Wistar rats aged 5–6 weeks and weighing 100–120 g were procured from the Pharmacology Department, University of Jos, Nigeria. They were acclimatized for 2 weeks on standard commercial chow (Vital feeds, Jos, Nigeria) and water *ad libitum*. The animals were maintained and handled according to the recommendations of internationally accepted guidelines.^[10] Permission to conduct the study was obtained from the Animal Ethics Committee, Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University Sokoto.

Induction of Diabetes Mellitus

Male Wistar rats were injected intraperitoneally with 65 mg of streptozotocin prepared in citrate buffer (pH 4.5, 0.1 M) 15 min after injection of 150 mg/kg of nicotinamide (10 ml/kg) (dissolved in normal saline). The same process was repeated daily for 2 days. Following an 8 h fast, plasma glucose was determined 1 week after the last injection using a standardized glucometer (Accu Chek® Active). Rats with a plasma glucose concentration of 198–252 mg/dl (moderate diabetes) were selected for the study.^[11]

Experimental Procedures

The study was divided into two experiments: the optimization experiment in normal rats and the herb-drug combination experiment in streptozotocin/nicotinamide-induced diabetic rats. For both experiments, the same volume of treatment relative to body weight (10 ml/kg) was administered to each animal orally by gavage needle.

Determination of the Effect of AM Extract on Oral Glucose Tolerance Test (OGTT) in Normal Rats and Dose Optimization

A total of 48 normal rats were randomly divided into six groups of eight animals each and were assigned to the

following treatments following an 8 h fast. Two groups were administered with either distilled water or metformin (50 mg/kg) to serve as negative and positive controls, respectively. Additional two groups were administered with low dose aqueous extract (LDAE) or high dose aqueous extract (HDAE) at 200 mg/kg or 600 mg/kg, respectively. Another two groups were treated with low dose methanolic extract (LDME) or high dose methanolic extract (HDME) at 200 mg/kg or 600 mg/kg, respectively. Thirty minutes after each treatment, oral glucose (2 g/kg) was administered to the animals in each group, and blood glucose was determined using standardized Accu Check glucometer at -30 min (just before the administration of each treatment), 0 min (just before glucose loading), and then at 30 min, 60 min, and 120 min after glucose loading.

Of the four tested doses and methods of extraction of AM stem, the LDME (200 mg/kg) was selected for the next phase of the experiment, as it was found to be as effective as the HDME (600 mg/kg) and more effective than either the low dose (200 mg/kg) or the high dose (600 mg/kg) aqueous extracts.

Determination of the Effect of Coadministration of AM Extract and Metformin in Diabetic Rats

A total of 40 rats (8 normal and 32 successfully induced diabetic rats) were randomly assigned to five groups. One group represents diabetic vehicle-administered control group, administered with distilled water. Two groups were treated with either the extract (200 mg/kg) or metformin (50 mg/kg) singly. Another diabetic group was administered with the extract in combination with metformin. The last group for the experiment is the normal vehicle-treated control group (randomly selected before the induction).

Collection of Blood and Tissue Samples, Measurement of Body Weight, and Determination of Biochemical Parameters in Diabetic Rats

OGTT was performed on days 0, 14, and 28. Following an 8 h fast, the animals in each were administered with their respective treatments. Thirty minutes afterward, oral glucose (2 g/kg) was administered to the animals, and blood

glucose was determined using standardized Accu Check glucometer at -30 min (just before the administration of each treatment), 0 min (just before glucose loading), and then at 30 min, 60 min, 90 min, and 120 min after glucose loading.

Body weights of the animals were assessed at baseline, 2 weeks, and 4 weeks post-treatment. At the end of the study (day 29), the fasted rats were anesthetized with chloroform vapor in a gas jar. The animals were then dissected; the liver and femur skeletal muscle tissues were excised, and their glycogen content determined by the method of Kemp and Van Heijningen.^[12] The glycogen concentration was determined from a standard curve in terms of glucose equivalents using the glucose oxidase method (Glucose oxidase reagent, Randox Laboratories Ltd., Crumlin, UK).

Blood samples were also taken to determine plasma lipid profile of the rats at the end of the study (day 29). TC, HDL-C, LDL-C, and TG were assayed using Standard Randox Diagnostic kits according to the manufacturers' instructions.

Statistical Analysis

Data were analyzed using GraphPad Prism and summarized as mean \pm Standard error. The significance of the difference between means was tested using one-way ANOVA with Tukey Kramer post-test. $P < 0.05$ was considered significant.

RESULTS

Effect of AM Extract on OGTT in Normal Rats

Of the extracts and the doses tested, LDME was found to be the most effective in reducing the total area under the curve (AUC) of the OGTT, as shown in Figure 1. The potency of the LDME (% reduction in the total AUC = 11.4%) was significantly higher than that of LDAE (% reduction in the total AUC = 2.5%) and HDAE (% increase in the total AUC = 4.1%), but comparable to that of HDME (% reduction in the total AUC = 10.6%) and the standard drug metformin (% reduction in the total AUC = 9.6%).

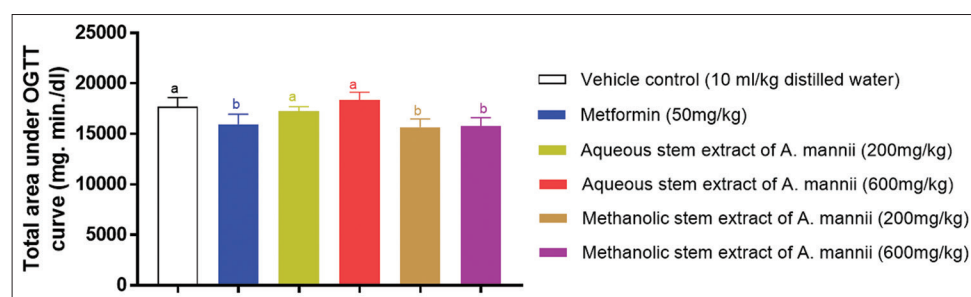


Figure 1: Comparison of the effect of the various stem extracts and doses of *Anisopus mannii* on the total area under the curve of oral glucose tolerance test in normal rats. Treatment means with different lower case letters are significantly different at $P < 0.05$

Effect of Coadministration of AM Extract and Metformin on OGTT, Tissue Glycogen Content, Body Weight, and Lipid Profile in Diabetic Rats

Intraperitoneal injection of streptozotocin/nicotinamide resulted in a significant elevation in the mean blood glucose level within the acceptable range of 198–252 mg/dl for the majority (83.3%) of the induced rats.

A significant reduction in the total AUC of OGTT was found at baseline in the rats treated with either metformin or the AM extract ($P < 0.05$; Table 1), but not in the rats treated with the metformin extract combination, when compared with the vehicle-treated diabetic group of animals. The reduction was significantly greater when either metformin or the extract was given singly than when the two were coadministered ($P < 0.05$; Table 1).

Following 2 weeks of treatment, the groups of rats treated with the AM extract or metformin, singly or in combination, demonstrated a significant reduction in the total AUC of OGTT compared to the vehicle-treated diabetic control ($P < 0.05$; Table 1). The reduction was significantly greater when either the conventional drug or the extract was given singly than when the two were combined ($P < 0.05$; Table 1).

A significant reduction in the fasting blood glucose level was also demonstrated in the group of rats administered with either the extract or metformin singly ($P < 0.05$), but not in the group treated with the extract in combination with metformin [Table 1]. The reduction was significantly larger when the extract (but not metformin) was given singly than when coadministered with metformin ($P < 0.05$; Table 1).

At day 28, the groups of rats treated with either metformin or the AM extract, singly or in combination, showed a significant reduction in the total AUC of OGTT and reduction in fasting blood glucose level ($P < 0.05$ for all) compared to the vehicle-treated diabetic group. However, compared to treatment with metformin or the extract as a monotherapy, administration of metformin-extract combination was not associated with any significant reduction in the total AUC of OGTT or reduction in fasting level of blood glucose [Table 1].

A significant increase in glycogen contents of the liver and skeletal muscles was demonstrated in the groups treated with either the AM extract or metformin, singly, or a combination ($P < 0.05$; Figure 2). The combined effect of metformin and the extract on liver glycogen content was significantly smaller than that of metformin or the AM extract administered alone ($P < 0.05$ for each; Figure 2). In contrast, the effect of the

Table 1: Effect of methanolic stem extract of AM alone or in combination with metformin on fasting blood glucose and OGTT in diabetic rats

Group	FBG level (mg/dl)			Total area under OGTT curve (mg/dl×min)		
	0 week	2 weeks	4 weeks	0 week	2 weeks	4 weeks
Normal control	78.38±2.74 ^b	74.00±2.10 ^d	74.13±1.43	15834.00±960.00 ^c	14919.00±329.10 ^d	14689.00±279.90 ^c
Negative control	216.13±5.98 ^a	237.60±6.75 ^a	258.60±6.77 ^a	55044.00±1528.00 ^a	56374.00±910.60 ^a	58849.00±919.20 ^a
Positive control (50 mg/kg)	223.13±6.74 ^a	211.00±7.49 ^{b^c}	182.80±4.07 ^b	48684.00±834.90 ^b	43733.00±1275.00 ^c	41803.00±1199.00 ^b
Extract (200 mg/kg)	207.50±4.95 ^a	197.10±4.90 ^c	179.00±5.10 ^b	50229.00±582.40 ^b	46427.00±746.80 ^c	41083.00±619.40 ^b
Extract (200 mg/kg) +Metformin (50 mg/kg)	234.38±5.62 ^a	224.90±4.81 ^{ab}	192.40±4.17 ^b	54609.00±665.40 ^a	51113.00±1047.00 ^b	41220.00±801.60 ^b

Values represent means±standard error ($n=8$). Different superscripts in the same column denote significant difference between treatment means at $P < 0.05$, FBG: Fasting blood glucose, OGTT: Oral glucose tolerance test, AM: *Anisopus mannii*

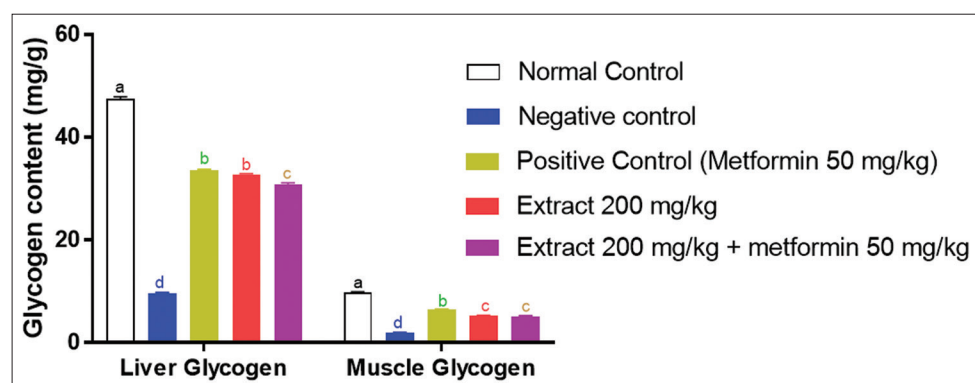


Figure 2: Effect of the methanolic stem extract of *Anisopus mannii* alone or in combination with metformin on the content of liver and skeletal muscle glycogen in streptozotocin/nicotinamide-induced diabetic rats. Treatment means with different lower case letters are significantly different at $P < 0.05$

herb-drug combination on skeletal muscle glycogen content was significantly smaller ($P < 0.05$) than that of metformin, but not the AM extract ($P > 0.05$), when given singly [Figure 2].

There was no significant difference in body weight between the treatment groups at baseline ($P > 0.05$; Table 2).

By week 2 post-treatment, the vehicle-treated diabetic control group showed significantly lower body weight than the normal control group, and this continues throughout the experiment ($P < 0.05$; Table 2). The three groups of rats treated with either metformin or extract, singly or in combination demonstrated a bodyweight which was significantly higher than that of the vehicle-treated control but lower than that of the normal control group ($P < 0.05$; Table 2).

Rats treated with either the AM extract or metformin, alone or in combination, showed a significant reduction in the fasting blood levels of TG, TC, and LDL-C, compared to the vehicle-treated

diabetic control ($P < 0.05$ for each). However, following concurrent administration of the standard drug metformin with the AM extract, the plasma levels of the features mentioned above were significantly higher than that of metformin or the extract administered alone ($P < 0.05$ for each; Figure 3).

In addition, rats treated with either AM extract or metformin, singly or in combination, demonstrated a significant elevation in the fasting blood level of HDL-C when compared to the vehicle-treated diabetic control group ($P < 0.05$ for each). The effect of metformin and the extract in combination was significantly larger than that of the extract ($P < 0.05$) but not that of metformin ($P > 0.05$) when administered alone [Figure 3].

DISCUSSION

In this study, two doses each of the two stem extracts (aqueous and methanolic) of AM were tested in glucose-loaded normal

Table 2: Effect of methanolic stem extract of AM alone or in combination with metformin on body weight of diabetic rats

Group	Bodyweight (g)		
	Baseline (Before induction of diabetes)	Post-treatment	
		2 weeks	4 weeks
Normal control	108.25±1.70 ^a	126.25±2.36 ^a	143.38±1.78 ^a
Negative control	109.88±2.25 ^a	93.13±1.71 ^c	73.38±1.89 ^d
Positive control (50 mg/kg)	112.00±2.20 ^a	110.00±2.49 ^b	125.75±2.73 ^b
Extract (200 mg/kg)	109.88±2.47 ^a	114.13±2.59 ^b	119.25±2.57 ^{bc}
Extract (200 mg/kg) +Metformin (50 mg/kg)	109.25±2.31 ^a	108.25±2.30 ^b	116.25±2.49 ^c

Values represent mean±standard error ($n=8$). Different superscripts in the same column denote significant difference between treatment means at $P < 0.05$, AM: *Anisopus mannii*

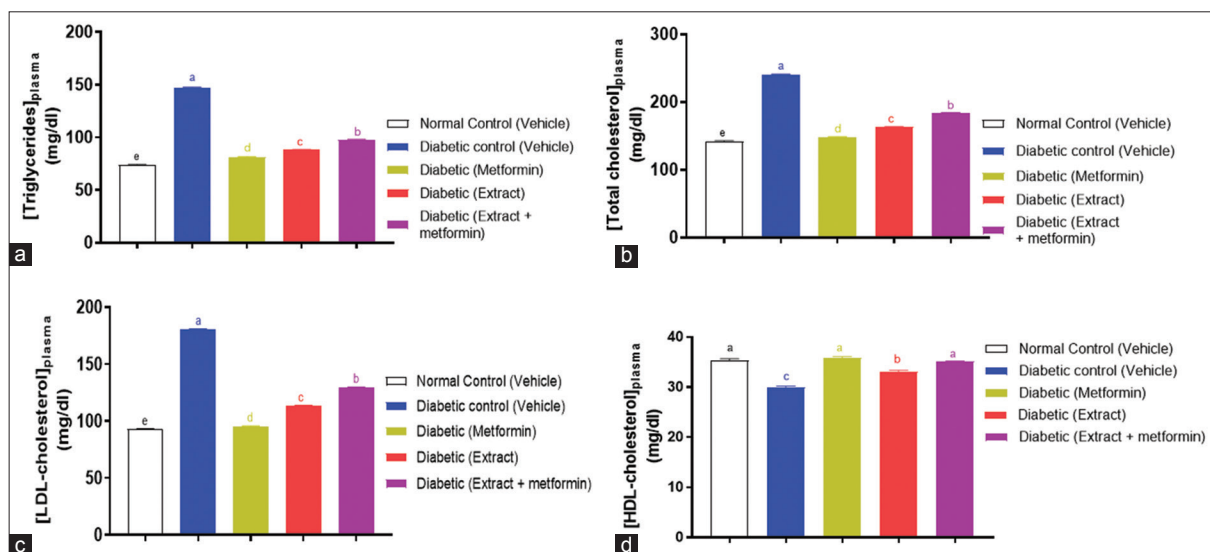


Figure 3: Effect of the methanolic stem extract of *Anisopus mannii* alone or in combination with metformin on lipid profile in diabetic rats. (a) Plasma triglyceride concentration at the end of the study (day 29). (b) Plasma total cholesterol concentration at the end of the study (day 29). (c) Plasma low-density lipoprotein cholesterol concentration at the end of the study (day 29). (d) Plasma high-density lipoprotein cholesterol concentration at the end of the study (day 29). Treatment means with different lower case letters are significantly different at $P < 0.05$

rats, of which only the methanolic stem extract produced an improvement in glucose tolerance as evidenced by a significant reduction in the total area under the OGTT curve compared to the vehicle. In that respect, the methanolic extract at low dose (200 mg/kg) was as effective as the same extract at high dose (600 mg/kg); it was therefore chosen for further testing in streptozotocin/nicotinamide-induced diabetic rat one of the most commonly used rodent models of type 2 diabetes mellitus.^[13] Intraperitoneal injection of streptozotocin and nicotinamide in rats resulted in hyperglycemia, reduced content of glycogen in the liver and skeletal muscles, as well as weight loss and alteration in lipid profile. The presence of some of these features in this animal model of diabetes mellitus has been previously documented.^[13,14] Streptozotocin acts by damaging the β -cells of the pancreas through DNA alkylation.^[15] On the other hand, nicotinamide possesses the ability to inhibit cellular death, thus protecting and ameliorating the damage to the pancreas by streptozotocin.^[14] Treatment with either metformin or the AM extract resulted in the amelioration of the above-mentioned features induced by streptozotocin/nicotinamide. In addition, treatment with methanolic stem extract of AM caused a significant elevation in the glycogen content of the liver and skeletal muscles as compared to the vehicle-treated diabetic control group. When combined, metformin reduced the fasting glucose-lowering effect of the extract, whereas the extract reduced the degree of elevation of the skeletal muscle glycogen content by metformin. Furthermore, both the extract and metformin, when coadministered in diabetic rats, reduced each other's beneficial effects in (a) improving glucose tolerance, as evidenced by reduction in the total area under the OGTT curve; (b) reducing fasting blood levels of TC, LDL-C, and TG; and (c) increasing glycogen content of the liver.

The observed effectiveness of the methanolic stem extract of AM in reducing blood glucose in hyperglycemic rats provides additional support to the findings of other researchers, who had previously demonstrated antidiabetic properties of extracts from the plant.^[6-9] The findings of the current study also agree with the results of prior research by Osibemhe *et al.*,^[16] which reported that aqueous stem extract of AM possesses antihyperlipidemic properties in diabetic rats. Our team previously reported a high yield of tannins (most abundant phytoconstituent), alkaloids, saponins, and flavonoids in the methanolic stem extract of AM used in this study.^[17] Such phytoconstituents have been known to confer potential benefit in the treatment of diabetes.^[18-20] Any of these phytochemicals, singly or in combination may have contributed to the observed antidiabetic activity of the extract. The ability of metformin to reduce fasting blood glucose in this experimental model of diabetes agree with findings from other studies.^[21,22] It is documented that the action of metformin does not depend on the activity of the β cells of the pancreas.^[21] The glycogen-elevating effect of the extract as observed in this study may be due to an increase in

glycogenesis or a decrease in glycogenolysis secondary to an increase in insulin secretion or insulin sensitivity by tissues or both.^[23] The finding that metformin (50 mg/kg) and the methanolic stem extract of AM (200 mg/kg) had a potentially negative influence on each other's beneficial effects on glucose homeostasis and lipid profile in diabetic rats agree with previous research which documented that concurrent use of herbal products with standard antidiabetic drugs could result in a negative effect in the form of loss of glucose control.^[24] It has been documented that tannins (which is the most abundant class of phytochemicals in the extract) reduce the absorption of some drugs by forming non-absorbable complexes with some drugs,^[25] culminating in the reduction of the absorption of both the drug and the tannins present in the extract. This may be one of the possible mechanisms behind the observed reduction in the antidiabetic activity of both metformin and the extract when the two are coadministered. However, interference of the metformin-extract combination on other pharmacokinetic parameters (distribution, metabolism, and excretion) or pharmacodynamics of metformin or the extract is also plausible.

The current study is the first to report the potentially negative influence of the coadministration of the methanolic stem extract (at 200 mg/kg) with metformin. One of the limitations of this study is that only one dose of the extract (200 mg/kg) was investigated in streptozotocin/nicotinamide-induced rats. Higher doses were not investigated because they seem to be not superior in efficacy to the lower dose, based on findings from the preliminary study in glucose-loaded normal rats. Furthermore, although the safety of an extract from the stem of AM administered for 28 days at doses ranging between 100 and 400 mg/kg has been documented,^[9] no published study has demonstrated the safety of repeated administration of a stem extract of the plant at higher doses. The authors, however, acknowledge the possibility that the optimal dose may be lower than 200 mg/kg.

CONCLUSION

This study revealed that the coadministration of metformin (50 mg/kg) and methanolic stem extract of AM (200 mg/kg) resulted in attenuation of each other's beneficial effects on glucose homeostasis and lipid profile in diabetic rats through yet unknown mechanisms. Concurrent use of extracts from the stem of AM with metformin should therefore be discouraged. There is need for further research to confirm and investigate the mechanism(s) of the observed findings.

ACKNOWLEDGMENTS

The authors are grateful to the laboratory staff of the Departments of Pharmacology and Toxicology, Chemical Pathology and Immunology and Biochemistry, Usmanu Danfodiyo University Sokoto for their technical help.

REFERENCES

- Dhikav V. Drug utilization study of drugs of complementary and alternative system of medicine in patients with chronic painful musculo-skeletal conditions. *Open J Pharmacol Pharmacother* 2018;2:1-6.
- Handley MA, Quan J, Chao MT, Ratanawongsa N, Sarkar U, Emmons-Bell S, *et al.* Use of complementary health approaches among diverse primary care patients with Type 2 diabetes and association with cardiometabolic outcomes: From the SF bay collaborative research network (SF bay CRN). *J Am Board Fam Med* 2017;30:624-31.
- Ogbera AO, Dada O, Adeyeye F, Jewo PI. Complementary and alternative medicine use in diabetes mellitus. *West Afr J Med* 2010;29:158-62.
- Abubakar AR, Chedi BA, Mohammed KG, Haque M. Drug interaction and its implication in clinical practice and personalized medicine. *Natl J Physiol Pharm Pharmacol* 2015;5:1-5.
- Nesti L, Natali A. Metformin effects on the heart and the cardiovascular system: A review of experimental and clinical data. *Nutr Metab Cardiovasc Dis* 2017;27:657-69.
- Zaruwa MZ, Manosroi A, Akihisa T, Manosroi W, Rangdaeng S, Manosroi J, *et al.* Hypoglycemic activity of the *Anisopus mannii* N. E. Br. Methanolic leaf extract in normal and alloxan-induced diabetic mice. *J Complement Integr Med* 2013;10:37-46.
- Manosroi J, Zaruwa MZ, Manosroi A. Potent hypoglycemic effect of Nigerian anti-diabetic medicinal plants. *J Complement Integr Med* 2011;8:1-6.
- Tijjani MB, Auwal MS, Mairiga IA, Saka S, Shuaibu A, Hambagda M. Acute toxicity, phytochemical, hypoglycaemic and antidiabetic activity of the aqueous stem extract of *Anisopus mannii* (Asclepiadaceae) on wistar strain albino rats. *Afr J Anim Biomed Sci* 2012;7:50-8.
- Sani D, Sanni S, Ngulde SI. Hypoglycaemic effect of aqueous stem extract of *Anisopus mannii* in normal rats. *Afr J Pharm Pharmacol* 2009;3:481-4.
- National Research Council. Guide for the Care and Use of Laboratory Animals. 8th ed. Washington, DC: National Academy Press; 2011.
- Taha H, Arya A, Paydar M, Looi CY, Wong WF, Vasudeva Murthy CR, *et al.* Upregulation of insulin secretion and downregulation of pro-inflammatory cytokines, oxidative stress and hyperglycemia in STZ-nicotinamide-induced Type 2 diabetic rats by *Pseudeuvaria monticola* bark extract. *Food Chem Toxicol* 2014;66:295-306.
- Kemp A, Van Heijningen AJ. A colorimetric micro-method for the determination of glycogen in tissues. *Biochem J* 1954;56:646-8.
- Ghasemi A, Khalifi S, Jedi S. Streptozotocin-nicotinamide-induced rat model of Type 2 diabetes (review). *Acta Physiol Hung* 2014;101:408-20.
- Pauzi N, Muhammad AA, Fakurazi S, Arulselvan P, Ahmad Z. Preliminary study of the optimization of protocol for development of Type 2 diabetic model in rats. *Indian J Sci Technol* 2013;6:4960-5.
- Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia* 2008;51:216-26.
- Osibemhe M, Lawal N, Umar D, Omaji GO, Jibiya SA. Effect of aqueous extract of *Anisopus mannii* stem in alloxan-induced diabetic rats. *Sci World J* 2017;12:7-10.
- Chika A, Yahaya A. Effect of coadministration of glibenclamide and methanolic stem extract of *Anisopus mannii* N.E.Br. (*Apocynaceae*) on glucose homeostasis and lipid profile in streptozotocin/nicotinamide-induced diabetic rats. *Natl J Physiol Pharm Pharmacol* 2019;9:1045-51.
- Teotia S, Singh M. Hypoglycemic effect of *Prunus amygdalus* seeds in albino rabbits. *Indian J Exp Biol* 1997;35:295-6.
- Tiong SH, Looi CY, Hazni H, Arya A, Paydar M, Wong WF, *et al.* Antidiabetic and antioxidant properties of alkaloids from *Catharanthus roseus* (L.) G. Don. *Molecules* 2013;18:9770-84.
- Galleano M, Calabro V, Prince PD, Litterio MC, Piotrkowski B, Vazquez-Prieto MA, *et al.* Flavonoids and metabolic syndrome. *Ann N Y Acad Sci* 2012;1259:87-94.
- Michael UA, David BU, Theophine CO, Philip FU, Ogochukwu AM, Benson VA, *et al.* Antidiabetic effect of combined aqueous leaf extract of *Vernonia amygdalina* and metformin in rats. *J Basic Clin Pharm* 2010;1:197-202.
- Prabhakar PK, Prasad R, Ali S, Doble M. Synergistic interaction of ferulic acid with commercial hypoglycemic drugs in streptozotocin induced diabetic rats. *Phytomedicine* 2013;20:488-94.
- Sruthi T, Satyavati D, Maheswara RC, Srilatha N. Estimation of glycogen content in liver, skeletal muscle and cardiac muscle of niddwin, a polyherbal formulation in alloxan induced diabetic rats. *Pharm Innov* 2014;2:56-60.
- Fakeye TO, Oladipupo T, Showande O, Ogunremi Y. Effects of coadministration of extract of *Carica papaya* Linn (family Caricaceae) on activity of two oral hypoglycemic agents. *Trop J Pharm Res* 2007;6:671-8.
- Issa FH, Al-Habori M, Chance ML. Effect of khat (*Catha edulis*) use on the bioavailability, plasma levels and antimalarial activity of chloroquine. *Sultan Qaboos Univ Med J* 2016;16:e182-8.

How to cite this article: Chika A, Yahaya A, Muhammad AA, Abdulrahman MB. Influence of coadministration of metformin and methanolic stem extract of *Anisopus mannii* N.E.Br. (*Apocynaceae*) on glucose homeostasis and lipid profile in streptozotocin/nicotinamide-induced diabetic rats. *Natl J Physiol Pharm Pharmacol* 2019;9(11):1145-1151.

Source of Support: Nil, **Conflict of Interest:** None declared.