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ORIGINAL ARTICLE

Hypoglycemic, hypolipidemic, and hepatoprotective effects of *Polyscias fulva* (Hiern) Harms ethanolic bark extract in streptozotocin-induced diabetic Wistar rats

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Abstract

Background *Polyscias fulva* (Hiern) Harms stem bark is used in traditional folk medicine in Kenya for diabetes mellitus and obesity management. This study sought to examine the antidiabetic effects of ethanolic stem bark extract of *P. fulva* in streptozotocin (STZ)–induced diabetic Wistar albino rats.

Methods Diabetes in rats was induced by intraperitoneal injection of STZ (50 mg/kg bwt) in experimental groups. Rats were divided into five groups ($n = 5$ per group): group 1, control; group 2, diabetic untreated rats; groups 3 and 4, diabetic rats on 200 and 400 mg/kg bwt/day of extract, respectively; and group 5, diabetic rats on metformin (100 mg/kg bwt/day). The rats received oral treatments daily for 21 days, and fasting blood glucose levels and body weights were determined weekly. Liver histopathological analysis and malondialdehyde (MDA) assay as well as serum analysis of lipid profile, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total proteins (TP), albumin (ALB), and globulins were performed at the end of the treatment period.

Results Extract had significant hypoglycemic and hypolipidemic effects in the diabetic rats compared with diabetic untreated rats ($p < 0.05$). Serum levels of ALP, ALT, and AST were significantly lowered, while TP and ALB were elevated in the extract-treated diabetic rats compared with diabetic untreated rats. The levels of liver MDA of extract-treated rats were significantly lowered compared with those of the diabetic untreated group. Extract treatment reversed liver pathological changes observed in the diabetic untreated group.

Conclusion This study has provided insights into the potential of the stem bark of *P. fulva* as an alternative medicine for diabetes mellitus.

Keywords Antidiabetic · *Polyscias fulva* · Streptozotocin · Bark · Rat

Introduction

The people affected worldwide with diabetes mellitus (DM) was estimated in 2017 to be 451 million, and the figures were projected to rise to 693 million by 2045 [1]. Hyperglycemia has been implicated in the onset and progression of DM and causation of severe complications through various mechanisms including induction of oxidative stress, decreased nitric oxide bioavailability, glucose autoxidation, and non-enzymatic protein glycation [2, 3]. Currently, pharmacological remedies have not fully addressed DM and its associated complications [4]. This high level of DM treatment failures coupled with unpleasant side effects and enormous cost associated with diabetic therapy have generated an urgent need and desire for alternative treatments such as plant medicine [5].

Polyscias fulva (Hiern) Harms (Araliaceae) is one of the many plants widely used in traditional folk medicine in Kenya for diabetes and obesity management especially among the Nandi community, and there is need to scientifically undertake

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studies to validate claims that its stem bark has antidiabetic effects [6]. In Kenya, *P. fulva* is mainly found in the highlands and tea-growing areas and its Kenyan local names include Soiyet in the Nandi; Auoun in Keiyo and Marakwet; Mutati in Kikuyu; Aounet in Kipsigis; Mwanzu in Luhya; and Nyakom ondiek in Luo [7]. Antioxidant capacity and anti-inflammatory effects of the stem bark extract of *P. fulva* have been previously reported [8].

In this present study, we therefore sought to examine the antihyperglycemic effects of ethanolic stem bark extract of *P. fulva* in streptozotocin (STZ)–induced diabetic male Wistar albino rat model. Also, the effects of *P. fulva* bark extract on serum lipids and biochemical liver function indices as well as liver's lipid peroxidation levels and histological alterations were evaluated so as to understand the plausible mode of action of the antidiabetic potential of *P. fulva* stem bark.

Materials and methods

Plant collection and identification

The stem barks *of P. fulva* were collected in its natural habitat at Timboroa forest, Uasin Gishu County, Kenya, and were identified and authenticated by Mr. Bernard Wanjohi, a plant taxonomist at the University of Eldoret. A voucher number M.U.H/PF/0031/17 was assigned and the plant specimen kept in the herbarium at University of Eldoret.

Preparation of bark extract

The stem barks were dried at room temperature and ground when completely dry using an electric mill (Disk Mill FFc-23, China). About 500 g of the powder was extracted with 95% ethanol by maceration for 3 days [8], filtered, and evaporated to dryness at 50 °C using a rotary evaporator (Rotavapor type EL 30, model AG CH-9230, Germany). The residue obtained constituted the crude extract, and it was stored at 4 °C.

Qualitative phytochemical analysis of bark extract

The bark extract was subjected to various qualitative phytochemical tests to determine the general classes of phytochemicals present using standard procedures [9, 10].

Animals

Wistar albino male rats (*Rattus norvegicus)* weighing about 140–180 g and aged 6–8 weeks were obtained from the Department of Biological Sciences, University of Eldoret. The rats were kept in wire cages of rack type with 5 animals per cage. Standard conditions were maintained (12 h dark and 12 h light circle; 25 ± 5 °C; 40–60% humidity), and the rats were allowed to acclimatize for 1 week before experimentation. The animals were fed with standard rodent chow pellet (Unga Farmcare, East Africa Limited, Nakuru, Kenya) and given free access to drinking water.

Induction of diabetes

Rats were fasted for 18 h and on access to drinking water ad libitum. Diabetes was induced for the experimental groups by single intraperitoneal injection of freshly prepared STZ (Wako Pure Chemical Industries Ltd., Japan) at a concentration of 50 mg/kg bwt [11] in 100 μl ice-cold 0.1 M sodium citrate buffer (pH 4.5). The normal group was injected with 100 μl of 0.1 M citrate buffer. The rats were given 5% glucose solution overnight to overcome drug-induced hypoglycemia. Fasting blood glucose (FBS) was determined using a glucometer (Wellion CALLA Light, Med Trust, Germany) from tail vein blood. Rats that had FBS ≥ 13.9 mmol/l after 5 days were considered diabetic.

Experimental design

The formula for calculation of sample size for the comparison of two groups that was used was according to Charan and Kantharia [12]. Male Wistar albino rats were randomly divided into 5 groups of 5 animals each as follows:

Group 1: Normal control rats administered with 100 μl distilled water (vehicle)

Group 2: STZ-induced diabetic rats untreated but administered with 100 μl distilled water (vehicle)

Group 3: STZ-induced diabetic rats treated with 100 μl of 200 mg/kg bwt/day of extract

Group 4: STZ-induced diabetic rats treated with 100 μl of 400 mg/kg bwt/day of extract

Group 5: STZ-induced diabetic rats treated with 100 μl of 100 mg/kg bwt/day of metformin (standard drug)

Animal treatment

A 100 μl water suspension of the bark crude extract of *P. fulva* at a concentration of 200 and 400 mg/kg bwt/day and metformin (Glucophage, Lipha Pharma Ltd., UK) at 100 mg/kg bwt/day was orally administered daily for 21 days according to Cheng et al. [13]. The basis for the administration of the standard drug, metformin, is its novel mechanism for plasma glucose-lowering action in STZ-induced diabetic rats. FBS and fasting body weights (FBWTS) for each rat was taken on day 0, 7, 14, and 21. Dosing was adjusted weekly as per the weekly body weights recorded. Following an overnight fast after the 21 days treatment period, the rats were euthanized under mild anesthesia of chloroform to minimize stress and pain during sacrificing and blood was collected through cardiac puncture. Serum was separated by centrifugation

(centrifuge model EBA 21 from Hettich Company Limited, Germany) and frozen at − 20 °C for analysis of biochemical parameters. The liver was excised and the first portion was frozen at − 20 °C for lipid peroxidation analysis, while the second portion was fixed in 10% formalin for histopathological analysis.

Serum analysis of lipid profile and liver function indices

Total cholesterol (T.CHOL), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TGs) were analyzed in serum and for lipid profile. For liver function tests, serum alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total proteins (TP), albumin (ALB), and globulins (GLB) were analyzed. These tests were done according to the standard operating procedures of COBAS INTEGRA 400 plus auto-analyzer (Roche Diagnostics, Mannheim, Germany).

Lipid peroxidation assay in liver tissues

Determination of malondialdehyde (MDA) levels, an index of lipid peroxidation in liver tissues, was done as described by Alam et al. [14].

Histopathological analysis of liver tissues

Processing of liver tissues was done according to the standard operating procedures of STP 120 automatic tissue processor. After tissue processing, a microtome (SLEE medical model GmbH) was used to cut into 4-μm-thick paraffin sections and then stained with hematoxylin and eosin [15]. Specimens were then examined for histopathological changes under a light microscope at × 40 (model CX21FSI, Olympus Corporation, Japan). The examination, analysis, and interpretation of the results were done by a histopathologist.

Statistical analysis

All quantitative data was expressed as mean ± standard error mean (SEM). Statistical analysis was by paired Student's *t* test and ANOVA. The value of $p < 0.05$ was considered to be statistically significant.

Results

Qualitative phytochemical analysis

Tannins, anthraquinones, terpenoids, saponins, flavonoids, and steroids were detected in the crude bark ethanolic extract of *P. fulva* upon qualitative phytochemicals analysis while alkaloids were absent.

Fasting blood sugar and body weight

Before treatment (day 0), all STZ-injected rats were diabetic with FBS levels significantly higher than normal control rats ($p < 0.001$) as shown in Table 1. However, upon treatment with 200 and 400 mg/kg of *P. fulva* bark extract, and 100 mg/kg of metformin for 21 days, there was significant reduction in the mean FBS levels when compared with diabetic untreated group ($p = 0.001$). The mean body weights for the normal control rats had an overall trend of increase across the study period while the diabetic induced groups had a declining trend (Table 1).

Serum lipid profile parameters

T.CHOL levels for the normal control rats were significantly higher than induced diabetic untreated group ($p < 0.001$) as shown in Fig. 1. In contrast, a significant reduction in T.CHOL was recorded in diabetic rats treated with 200 mg/kg of *P. fulva* when compared with the diabetic untreated group (Fig. 1). The diabetic untreated rats had a significant decrease in HDL-C levels compared with the normal control rats (Fig. 1). A significant increase in HDL-C was recorded in the diabetic rats treated with 200 as well as 400 mg/kg of *P. fulva* compared with the diabetic untreated rats. Diabetic rats treated with 200 and 400 mg/kg of *P. fulva* as well as 100 mg/kg of metformin recorded a significant decrease in LDL-C levels when compared with diabetic untreated rats. TGs levels in the diabetic untreated rats recorded a significant higher level as compared with normal control rats. Significant lower levels of TGs were recorded in diabetic rats treated with 200 and 400 mg/kg of *P. fulva* and 100 mg/kg of metformin when compared with diabetic untreated rats.

Liver function serum enzymes indices

The diabetic untreated group showed significant higher ALP, AST, and ALT levels as compared with normal control rats ($p = 0.002$, 0.001, and 0.001, respectively) as shown in Fig. 2. Among the treatment groups, significant lowest mean of ALP was recorded in diabetic rats treated with 400 mg/kg of *P. fulva* compared with diabetic untreated rats ($p = 0.002$). On the other hand, significant higher ALP levels were recorded in diabetic rats treated with 100 mg/kg of metformin when compared with diabetic untreated rats. The levels of AST and ALT were significantly reduced when diabetic rats were treated with 200 and 400 mg/kg of *P. fulva* and 100 mg/kg of metformin as compared with the diabetic untreated rats.

Table 1 Effect of *Polyscias fulva* bark extract on FBS and FBWTS

Experimental group	Duration (day)	FBS (mmol/l)	FBWTS (g)
Normal control	0	4.68 ± 0.17	151.18 ± 5.54
	7	4.44 ± 0.21	154.20 ± 5.32
	14	4.92 ± 0.32	158.60 ± 4.85
	21	4.48 ± 0.24	165.56 ± 4.47
Diabetic untreated	0	23.22 ± 2.56*	160.88 ± 5.33
	7	24.18 ± 1.85*	150.74 ± 5.06
	14	25.38 ± 1.78*	147.52 ± 4.87
	21	25.35 ± 1.14*	142.27 ± 4.49
Diabetic + 200 mg/kg extract	0	25.64 ± 1.70	158.50 ± 3.76
	7	20.30 ± 1.52#	149.06 ± 3.45
	14	17.54 ± 1.04#	146.46 ± 3.29
	21	15.76 ± 0.45#	144.58 ± 3.16
Diabetic + 400 mg/kg extract	0	25.54 ± 1.75	161.20 ± 2.31
	7	17.96 ± 0.86#	152.96 ± 3.52
	14	15.24 ± 0.63#	149.16 ± 3.47
	21	9.70 ± 0.69#	148.82 ± 3.55
Diabetic + 100 mg/kg metformin	0	30.22 ± 1.02#	166.78 ± 6.16
	7	20.48 ± 0.81#	158.74 ± 6.26
	14	15.88 ± 1.23#	155.24 ± 6.05
	21	11.08 ± 0.81#	151.52 ± 5.54

Values represent mean ± SEM; $n = 5$. *Significant difference compared with normal control, # significant difference compared with diabetic untreated group ($p < 0.05$, ANOVA). *STZ* streptozotocin, *FBS* fasting blood sugar, *FBWTS* fasting body weights

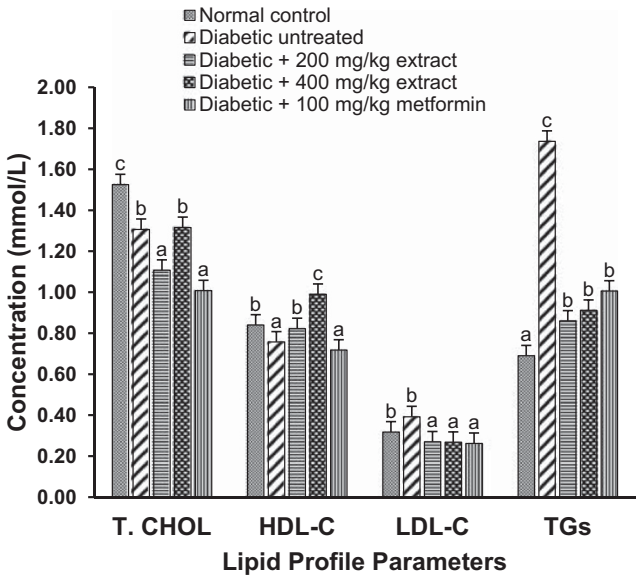

Fig. 1 Effect of *Polyscias fulva* bark extract on serum lipid profile parameters. Values represent mean ± SEM; $n = 5$. Mean values with different letters in bar graphs show statistically significant differences ($p < 0.05$, Student's t test). Total cholesterol (T.CHOL), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides (TGs)

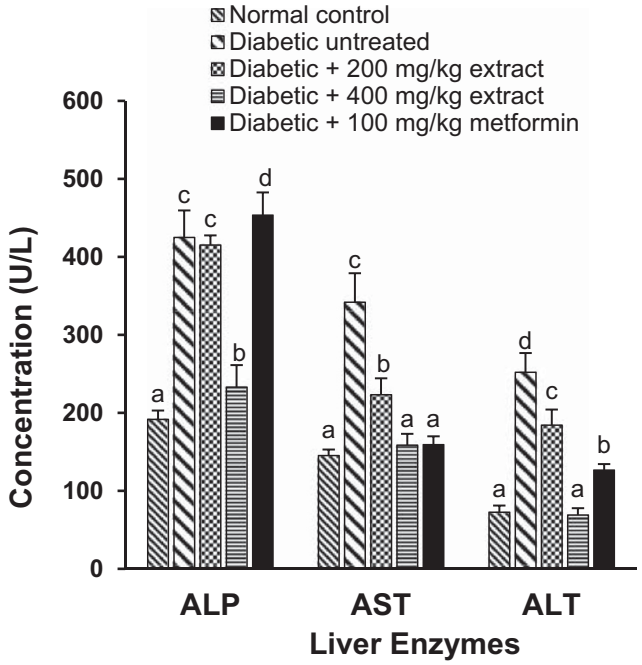

Fig. 2 Effect of *Polyscias fulva* bark extract on serum liver enzymes. Values represent mean ± SEM; $n = 5$. Mean values with different letters in bar graphs show statistically significant differences ($p < 0.05$, Student's t test). Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT)

Liver function serum proteins indices

As shown in Fig. 3, a significant increase in TP levels was recorded in the diabetic rats treated with 400 mg/kg of *P. fulva* compared with diabetic untreated rats ($p = 0.043$). The diabetic rats treated with 400 mg/kg of *P. fulva* extract recorded significant higher ALB levels than the induced untreated rats. For GLB, we found an insignificant difference among treated groups although the diabetic untreated group had higher GLB levels compared with the normal control group.

Lipid peroxidation in liver tissues

There was a significant increase in malondialdehyde levels by 57.2%, an index of lipid peroxidation, in liver tissues of diabetic untreated rats when compared with the normal control ($p = 0.008$) as shown in Fig. 4. However, diabetic rats treated with 200 and 400 mg/kg *P. fulva* and 100 mg/kg of metformin showed a significant reduction by 62.3%, 78.6%, and 49.7%, respectively, in lipid peroxidation when compared with the diabetic untreated group.

Liver histopathological analysis

Normal control group of rats showed no pathological changes as we observed normal morphology of hepatocytes and organized hepatic cell with no inflammation, fatty degeneration, and proliferation (Fig. 5a). Diabetic untreated group showed pathological changes of mild periportal chronic inflammation (arrow in Fig. 5b). Diabetic rats treated with 200 mg/kg of *P. fulva* showed improved hepatic architecture but with very mild bile duct proliferation (arrows in Fig. 5c) while those treated with 400 mg/kg of *P. fulva* showed normal hepatic architecture with prominent nucleoli (arrows in Fig. 5d) and those treated with 100 mg/kg of metformin showed normal hepatocytes morphology with prominent nucleoli (arrows in Fig. 5e).

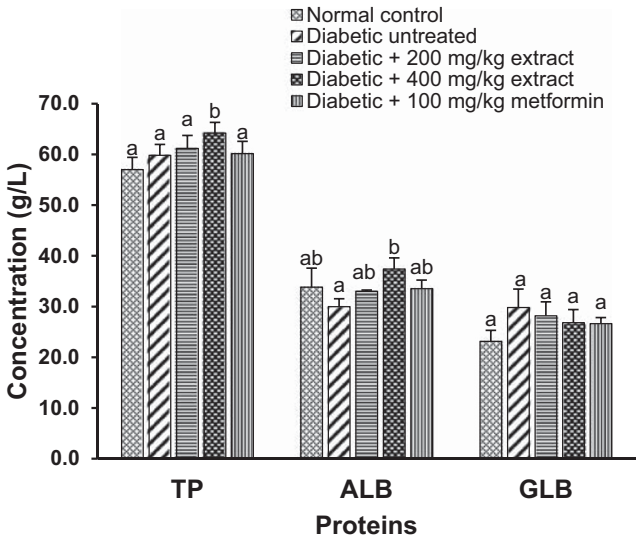

Fig. 3 Effect of *Polyscias fulva* bark extract on serum proteins. Values represent mean ± SEM; $n = 5$. Mean values with different letters in bar graphs show statistically significant differences ($p < 0.05$, Student's t test). Total proteins (TP), albumin (ALB), globulins (GLB)

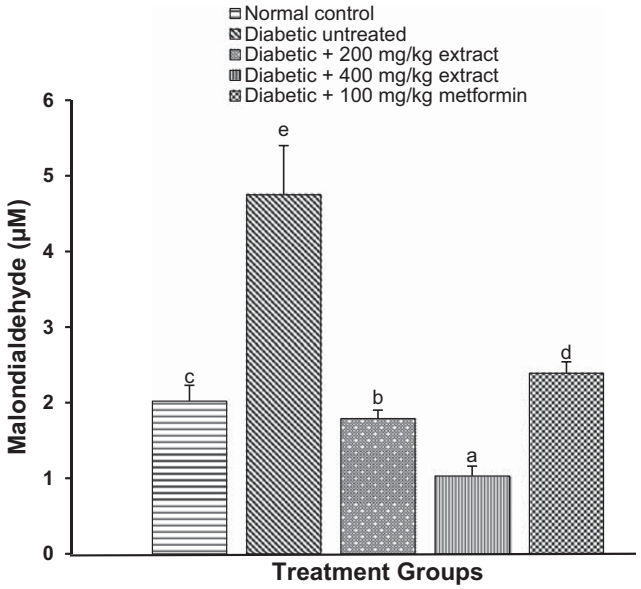

Fig. 4 Effect of *Polyscias fulva* bark extract on lipid peroxidation in liver tissues. Values represent mean ± SEM; $n = 5$. Mean values with different letters in bar graphs show statistically significant differences ($p < 0.05$, Student's t test)

Discussion

In the present study, STZ successfully induced hyperglycemia in rats, and this is postulated to be through STZ selectively destroying the pancreatic insulin secreting β-cells, leaving less active β-cells resulting in a diabetic state [11]. On the other hand, our study showed that the stem bark extract of *P. fulva* has antihyperglycemic effects in the diabetic rats which were comparable with the effects of the standard antidiabetic drug, metformin. The biochemical mechanism of anti-hyperglycemic actions of *P. fulva* bark extract might be due to an insulin mimetic effect on muscle and adipose tissues by either stimulating glucose uptake and metabolism [16], by inhibiting hepatic gluconeogenesis [17] and glycogenolysis [18], and by stimulation or regeneration process of remnant β-cells due to reduced oxidative stress [3]. These plausible anti-hyperglycemic mechanistic effects of *P. fulva* extract could also be partly attributable to the phytochemicals rich in the extract such as flavonoids, tannins, and saponins which we found present after our qualitative phytochemical analysis of the extract. The observed body weight loss in diabetic rats

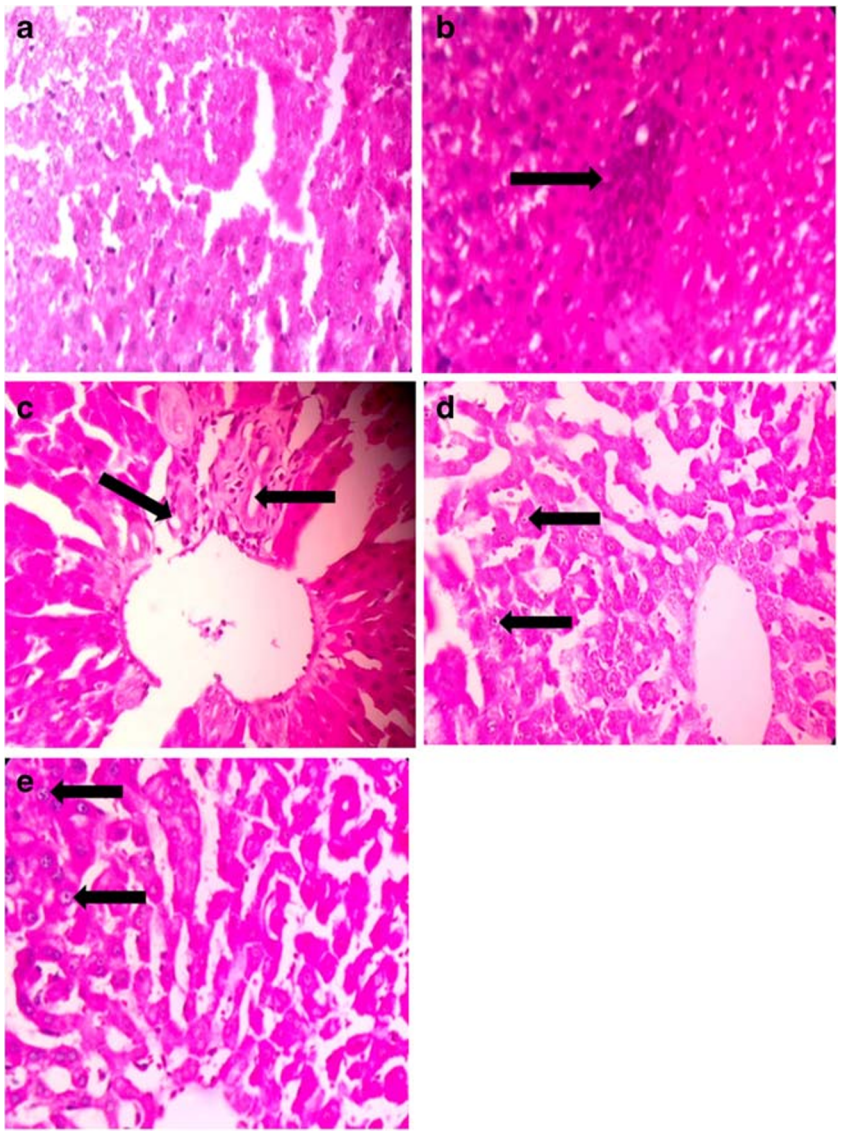

Fig. 5 Representative photomicrographs of liver sections of normal control and experimental rats (hematoxylin and eosin stained × 40). (a) Normal control, normal hepatocytes; (b) diabetic untreated rats; *arrow*, mild periportal chronic inflammation; (c) diabetic rats treated with 200 mg/kg of *Polyscias fulva* bark extract; *arrows*, mild bile duct proliferation; (d) diabetic rats treated with 400 mg/kg of *Polyscias fulva* bark extract; *arrows*, prominent nucleoli; (e) diabetic rats treated with 100 mg/kg of metformin; *arrows*, prominent nucleoli

in this study could be due to increased muscle wasting [19], dehydration, loss of carbohydrates, and the excessive breakdown of tissue proteins and fat [20].

Hypertriglyceridemia was notable in the diabetic untreated rats versus the normal control rats while a significant drop in TGs level after treatment with bark extract of *P. fulva* and metformin was also noted. STZ-induced diabetes mostly involves abnormal lipid metabolism associated with the insulin deficiency [21]. This reported hypotriglyceridemic alongside other moderate hypolipidemic effects of *P. fulva* bark extract in the diabetic state recorded in this study mechanistically is possibly imparted by the extract's phytochemicals. The reduction in LDL-C in metformin-treated group could be due to the drug's effect of potentially activating AMPK that suppresses FADS genes leading to reduction in LDL-C levels [22]. AMPK in its active form exhibits an anti-lipogenic effect and acts by suppressing hepatic expression of lipogenic enzymes (Acetyl-CoA Carboxylase 1-ACC1 and FAS). Further, active AMPK phosphorylates and inhibits ACC1/2 leading to decreased production of malonyl-CoA levels which releases the inhibitory effect on carnitine palmitoyltransferase 1A (CPT1A) and therefore favors fatty acid oxidation [23].

Lipid peroxidation is an autocatalytic free-radical-mediated destructive process whereby poly-unsaturated fatty acids in cell membranes undergo degradation to form lipid hydroperoxides including conjugated dienes and MDA [24]. In this present study, the results showed that STZ-induced diabetic rats were susceptible to lipid peroxidation versus the normal control. Prolonged exposure to hyperglycemia in diabetic state increases the generation of free radicals and reduces capacities of the antioxidant defense system which leads to oxidative stress [25]. Treatment of diabetic rats with *P. fulva* stem bark extract led to reduced lipid peroxidation. This reduction of lipid peroxidation by *P. fulva* extract could

be explained in part by its phytochemicals with known antioxidants [8].

DM is frequently associated with the elevated activities of liver toxicity marker enzymes such as ALT, AST, and ALP in serum, which might be mostly due to the outflow of these enzymes from the liver's cytosol into the bloodstream emanating from hepatocellular damage [20]. Administration of *P. fulva* bark extract and metformin reduced the AST and ALT levels in diabetic condition and a reduction of ALP in diabetic rats treated with *P. fulva* ethanolic bark extract at the highest dose. The high levels of ALP in diabetic rats treated with 100 mg/kg metformin could be due to diabetes-induced damage to the liver tissues as also observed in other studies [26]. Additionally, increased activities of ALP could have resulted from STZ that may have caused hepatic damage and distortion in membrane integrity of the cell [27]. The levels of TP and ALB were on the other hand elevated in the extract-treated diabetic rats compared with diabetic untreated rats that may be indicative of reduced biosynthetic ability of the liver for serum proteins in the untreated diabetic state [28]. *P. fulva* extract could have trapped the oxygen-related free radicals and therefore hinder their interaction with polyunsaturated fatty acids and would abolish the enhancement of lipid peroxidation processes leading to MDA generation as indicated in our results on lipid peroxidation. *P. fulva* extract could also have increased the hepatic and blood content of glutathione since higher content of glutathione in blood and liver would lead to a better tissue protection against oxidative stress [29] hence reduction in hepatotoxic effects of hyperglycemia and STZ effects.

The pathological changes observed in the liver tissues of the diabetic untreated rats could have been due to injury to the liver hepatocytes resulting from effects of STZ-induced diabetes, chronic hyperglycemia, and lipid peroxidation. The ameliorating effect of *P. fulva* extract on the derangement of serum liver function indices and its hypoglycemic, hypolipidemic, and reduction in liver's lipid peroxidation in the diabetic rats in the present study supports our improved histopathological observations. The hepatoprotective effects of *P. fulva* are also in part attributable to the rich phytochemicals in the bark extract that we found present and that has been shown to have antioxidant properties [8]. Our findings are in agreement with several studies that have shown histopathological changes in liver tissues of diabetic untreated rats, while the architecture of the liver in diabetic rats treated with plant extracts was near or similar to that of normal liver, indicating that the degenerative changes initiated by DM are improved/reversed by plant extracts in diabetic rats [30].

In conclusion, this study has shown that the phytochemical-rich ethanolic extract of *P. fulva* crude stem bark has hypoglycemic, hypolipidemic, and hepatoprotective effects in STZ-induced diabetic rats. These findings have provided important insights into the potential of *P. fulva* stem bark extract for its use as an alternative medicine in the management of diabetes mellitus.

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Data availability The data used to support the findings of this study are available from the corresponding author upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving animals Ethical approval for this study was granted by the University of Eastern Africa, Baraton's Research Ethics Committee (Reference; REC: UEAB/14/3/17). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.
2. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J. 2012;12(1):5–18.
3. Moodley K, Joseph K, Naidoo Y, Islam S, Mackraj I. Antioxidant, antidiabetic and hypolipidemic effects of Tulbaghia violacea Harv. (wild garlic) rhizome methanolic extract in a diabetic rat model. BMC Complement Altern Med. 2015;15:408.
4. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215–22.
5. Emordi JE, Agbaje EO, Oreagba IA, Iribhogbe OI. Antidiabetic and hypolipidemic activities of hydroethanolic root extract of Uvaria chamae in streptozotocin induced diabetic albino rats. BMC Complement Altern Med. 2016;16(1):468.
6. Jeruto P, Lukhoba C, Ouma G, Otieno D, Mutai C. An ethnobotanical study of medicinal plants used by the Nandi people in Kenya. J Ethnopharmacol. 2008;116(2):370–6.
7. Infonet-Biovision. Parasol tree. https://wwwinfonet-biovisionorg/EnvironmentalHealth/Trees/Parasol-tree (accessed 25th November 2018).
8. Sagnia B, Fedeli D, Casetti R, Montesano C, Falcioni G, Colizzi V. Antioxidant and anti-inflammatory activities of extracts from Cassia alata, Eleusine indica, Eremomastax speciosa, Carica papaya and Polyscias fulva medicinal plants collected in Cameroon. PLoS One. 2014;9(8):e103999.
9. Baskaran G, Salvamani S, Ahmad SA, Shaharuddin NA, Pattiram PD, Shukor MY. HMG-CoA reductase inhibitory activity and phytocomponent investigation of Basella alba leaf extract as a treatment for hypercholesterolemia. Drug Des Devel Ther. 2015;9:509–17.

10. Yusuf AZ, Zakir A, Shemau Z, Abdullahi M, & , Halima SA. Phytochemical analysis of the methanol leaves extract of Paullinia pinnata Linn. J Pharmacogn Phytother 2014;6(2):10–16.
11. Tahara A, Matsuyama-Yokono A, Nakano R, Someya Y, Shibasaki M. Hypoglycaemic effects of antidiabetic drugs in streptozotocin-nicotinamide-induced mildly diabetic and streptozotocin-induced severely diabetic rats. Basic Clin Pharmacol Toxicol. 2008;103(6):560–8.
12. Charan J, Kantharia N. How to calculate sample size in animal studies? J Pharmacol Pharmacother. 2013;4(4):303–6.
13. Cheng JT, Huang CC, Liu IM, Tzeng TF, Chang CJ. Novel mechanism for plasma glucose-lowering action of metformin in streptozotocin-induced diabetic rats. Diabetes. 2006;55(3):819–25.
14. Alam MN, Bristi NJ, Rafiquzzaman M. Review on in vivo and in vitro methods evaluation of antioxidant activity. Saudi Pharm J. 2013;21(2):143–52.
15. Rai PK, Mehta S, Watal G. Hypolipidaemic & hepatoprotective effects of Psidium guajava raw fruit peel in experimental diabetes. Indian J Med Res. 2010;131(820):e824.
16. Daisy P, Balasubramanian K, Rajalakshmi M, Eliza J, Selvaraj J. Insulin mimetic impact of Catechin isolated from Cassia fistula on the glucose oxidation and molecular mechanisms of glucose uptake on Streptozotocin-induced diabetic Wistar rats. Phytomedicine. 2010;17(1):28–36.
17. Andrade-Cetto A, Vázquez RC. Gluconeogenesis inhibition and phytochemical composition of two Cecropia species. J Ethnopharmacol. 2010;130(1):93–7.
18. Rawi SM, Mourad IM, Sayed DA. Biochemical and changes in experimental diabetes before and after treatment with Mangifera indica Psidium guava extracts. Int J Pharm Bio Sci. 2011;2(2):29–41.
19. Ravi K, Ramachandran B, Subramanian S. Protective effect of Eugenia jambolana seed kernel on tissue antioxidants in streptozotocin-induced diabetic rats. Biol Pharm Bull. 2004;27(8):1212–7.
20. Kurup SB, Mini S. Protective potential of Averrhoa bilimbi fruits in ameliorating the hepatic key enzymes in streptozotocin-induced diabetic rats. Biomed Pharmacother. 2017;85:725–32.
21. Kumar V, Anwar F, Ahmed D, Verma A, Ahmed A, Damanhouri ZA, et al. *Paederia foetida* Linn. leaf extract: an antihyperlipidemic, antihyperglycaemic and antioxidant activity. BMC Complement Altern Med. 2014;14(1):76.
22. Xu T, Brandmaier S, Messias AC, Herder C, Draisma HH, Demirkan A, et al. Effects of metformin on metabolite profiles and LDL cholesterol in patients with type 2 diabetes. Diabetes Care. 2015;38(10):1858–67.
23. Woo S-L, Xu H, Li H, Zhao Y, Hu X, Zhao J, et al. Metformin ameliorates hepatic steatosis and inflammation without altering adipose phenotype in diet-induced obesity. PLoS One. 2014;9(3):e91111.
24. Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes. 2015;6(3):456.
25. Lee J-S. Effects of soy protein and genistein on blood glucose, antioxidant enzyme activities, and lipid profile in streptozotocin-induced diabetic rats. Life Sci. 2006;79(16):1578–84.
26. Balamash KS, Alkreathy HM, Al Gahdali EH, Khoja SO, Ahmad A. Comparative biochemical and histopathological studies on the efficacy of metformin and virgin olive oil against streptozotocin-induced diabetes in Sprague-Dawley rats. J Diabetes Res. 2018;2018.
27. Adefegha SA, Oboh G, Adefegha OM, Boligon AA, Athayde ML. Antihyperglycemic, hypolipidemic, hepatoprotective and antioxidative effects of dietary clove (Szyzgium aromaticum) bud powder in a high-fat diet/streptozotocin-induced diabetes rat model. J Sci Food Agric. 2014;94(13):2726–37.
28. Thapa BR, Walia A. Liver function tests and their interpretation. Indian J Pediatr. 2007;74(7):663–71.
29. Omodanisi EI, Aboua YG, Oguntibeju OO. Assessment of the anti-hyperglycaemic, anti-inflammatory and antioxidant activities of the methanol extract of *Moringa oleifera* in diabetes-induced nephrotoxic male wistar rats. Molecules. 2017;22(4).
30. Adeyemi DO, Ukwenya VO, Obuotor EM, Adewole SO. Anti-hepatotoxic activities of *Hibiscus sabdariffa* L. in animal model of streptozotocin diabetes-induced liver damage. BMC Complement Altern Med. 2014;14(1):277.