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ANTIDIABETIC POTENTIALS OF POLYHERBAL (*Citrullus colocynthis, Curculigo pilosa, and Gladiolus pssitacinus*) EXTRACT IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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Abstract

The art of preparing concoction/decoction using collection of medicinal plants is very common for treatment of ailment in folk medicine. The study explored the antidiabetic potentials of polyherbal extract (PHE) prepared from *Citrullus colocynthis*, *Curculigo pilosa* and *Gladiolus pssitacinus*. Phytochemical profiling, *in vitro* antioxidant and antidiabetic properties of the PHE were evaluated. Diabetes mellitus (DM) was induced by (i.p) administration of streptozotocin (50 mg/kg). Fasting blood glucose (FBG) and body weight (BW) were monitored in diabetic rats during administration of PHE for 28 days. Effects of treatment on lipid profiles and different markers of liver and kidney functions were determined. Also concentrations of lipid peroxides (LPO), nitric oxide (NO), glutathione (GSH) and activity of superoxide dismutase (SOD) were determined in kidney and liver tissues. The results showed that PHE has phenolic (90.64 mg/100g GAE) and flavonoids (63.97 mg/100g QUE) contents. It also exhibited *in vitro* antioxidant and inhibitions of amylase and glucosidase. Treatment of diabetic rats with PHE reduced significantly ($p<0.05$) their FBG. Lipid profiles and serum level of liver and kidney function markers were positively modulated in treated diabetic rats. Levels of LPO and NO were decreased with oral administration of PHE while GSH and activity of SOD were increased. This study has shown that polyherbal extract possesses antidiabetic potential thereby justifying it usage in traditional medicine for management of DM.

Keywords: Antioxidant capacity, Fasting blood glucose, Polyherbal extract, Traditional medicine

Introduction

A metabolic disorder, diabetes mellitus (DM) is gradually becoming a door-door disease with a global incidence of about 600 million. This disease is characterized by persisted elevated glucose concentration in blood caused by either insensitivity to insulin secretion or inadequate insulin secretion (Anjorin *et al.*, 2024). It has been postulated as one of the predisposing causes of kidney damage, blindness, amputation and cardiovascular diseases (IDF, 2023). One of the reasons attributed to the predominant occurrence of DM is over-dependence on energy dense diet that lacks antioxidant components (Karigidi and Olaiya, 2021). An important hallmark in etiology of all complications of DM is oxidative stress. Enhanced glucose concentration (hyperglycemia) has been reported to generate

free radicals through formation advanced glycation end-products, increased polyol flux and activation of protein kinase C isoforms (Papachristoforou *et al.,* 2020). Due to multifaceted nature of this disease, traditional practitioners usually used combination of herbs (polyherbal) for its treatment. One example of polyherbal extracts explored to treat DM in folk medicine of Yoruba tribe of Nigeria contains *Citrullus colocynthis, Curculigo pilosa and Gladiolus psittacinus***.**

Citrullus colocynthis (CC) is a member of Cucurbitaceae. Its fruit is popularly called Bitter apple or Bitter gourd in English and Baara in Yoruba tribe of Nigeria. This plant is notable for the treatment of Asthma, Jaundice and DM in herbal practice. The antidiabetic potential of its pulp has been documented (Ghauri *et al.,* 2020).

Curculigo pilosa (CP) is a prominent member of Curculigo species in hypoxidaceae genus. Its rhizome is popularly called African crocus in English and Epakun in Yoruba tribe of Nigeria. This rhizome is very prominent in the traditional treatment of DM that some ethnomedicinal surveys have listed it as one of the plant species used in treatment of DM (Ofuegbe and Adedapo, 2015, Soladoye *et al.,* 2012). It has been shown to reduce fasting blood glucose and modulate oxidative stress in diabetic rats (Karigidi and Olaiya 2020, Karigidi *et al* 2020).

Gladiolus psittacinus (GP) belongs to Iridaceae family. It is called Maid of the mist in English and Baaka in Yoruba tribe of Nigeria. It is locally used for cold, asthma, venereal diseases and DM. Like CP, it has been listed by ethnomedicinal surveys as one of the plant species used in treatment of DM (Ofuegbe and Adedapo 2015, Soladoye *et al* 2012). Study of Karigidi *et al* (2023) has shown that its can modulate streptozotocin induced diabetes in rats. Previously, the lethal doses (LD_{50}) of the botanicals (*Citrullus colocynthis, Curculigo pilosa and Gladiolus psittacinus*) have been reported (Olaiya and Karigidi, 2016).

Despite the uses of many polyherbal decoction/ concoction in the treatment/management of many ailments in folk medicine, there is paucity of systematic studies to justify and unraveling their uses and mechanisms. Therefore, this study aimed at evaluating the phytochemical and antidiabetic potential of polyherbal extract (PHE) made from *Citrullus colocynthis, Curculigo pilosa and Gladiolus psittacinus* in streptozotocin-induced diabetic rats.

Materials and methods

Plant material

Citrullus colocynthis (CC)*, Curculigo pilosa* (CP) *and Gladiolus psittacinus* (GP) corms were bought from Okitipupa local market (6°33'N 4°43'E), Ondo state, Nigeria. The samples were identified and authenticated at the Herbarium arena. The Vouchers (OAUSTECH/H/696, OAUSTECH/H/676, and OAUSTECH/H/656, respectively) was kept in their herbarium.

Preparation of Corn steep liquor (CSL)

The protocol of Karigidi and Olaiya (2020) was used to prepare CSL. Briefly, 1000 g of dried-corn was solvated in 4 L of boiled water for 3 days. Thereafter, the solvated corn was pulverized and filtered with cheese cloth. The filtrate was permitted to settle for 24 h and the supernatant was separated as CSL.

Preparation of polyherbal extract

Five hundred grams (fresh weight) of CC (350 g)*,* CP (100 g) and GP (50g) (7:2:1) were pounded together using mortar and pestle until they formed a homogenous mixture. The moist mixture was soaked in 5.5 L of Corn steep liquor and shaken intermittently for 48 hours. Thereafter, the mixture was filtered and the extract was dried with rotary evaporator to give a yield of 50.54 g (10.11%) termed as polyherbal extract (PHE).

Determination of bioactive, antioxidant and antidiabetic potentials of PHE (*in vitro*)

Total phenolics of the PHE were evaluated using the protocol of Kim *et al.,* (2003). Total flavonoids of the PHE were assayed with the protocol of Park *et al.,* (2008). Total antioxidant capacity (TAC) of the PHE was evaluated according to the protocol of Prieto et al (1999). DPPH scavenging effect of PHE was assayed using the procedure of Gyamfi *et al.,* (1999). Ferric reducing antioxidant power (FRAP) of the PHE was assayed with Benzie and Strain (1996).

***In vitro* enzyme's inhibition assays**

Amylase and glucosidase inhibition potentials of PHE were assayed as described by Worthington (1993) and Apostolidis *et al* (2007), respectively.

Phytochemical profiling of the extract using HPLC (Finger printing)

The phytochemical profiling was done using the procedure of Ojo *et al* (2018). Exactly, 5 µL (0.8 mg/mL) of the extract was injected into the HPLC to generate comparable peaks (area and profile) for the analyte(s). Spotting of the phytocomponents was accomplished by correlating the height of PHE to the standard spectra. The calculation of concentration of the analyte in extract was done as follows:

Concentration of analyte in extract = {height of the analyte in PHE × height of the standard spectra}/ peak area of standard analyte

Animal study

Male Wistar rats (118-122) g were bought from the Physiology Department. The animals were permitted fourteen days to acclimatize. They were placed standard pellet diet and water *ad libitum*. The animal care was done as ratified by the Research Ethics Committee (OAUSTECH/ETHC-BCH/2023/001) in accordance with the guidelines of National Institute of Health (NIH Publication No. 80-23)

Induction of diabetes mellitus

Briefly, DM was induced in fasted rats using a single 50 mg/kg of (i.p.) streptozotocin (STZ) freshly prepared in cold citrate buffer (0.1 M, pH 4.5). Hyperglycemia was determined three days after STZ administration using glucometer. Rats with FBG greater than 250 mg/dL were chosen for the study (Karigidi *et al* 2023).

Experimental design

Diabetic rats were classified into 5 groups of least 6 rats each.

Grouping	Description
Control	Healthy rats treated with distilled water
Dcontrol	Diabetic rats administered only distilled water
PHE1	Diabetic rats administered PHE (75 mg/kg)
PHE11	Diabetic rats administered PHE (150 mg/kg)
DGBLC	Diabetic rats administered Glibenclamide (5 mg/kg)

Body weight and blood glucose concentration measurements were done using weighing balance and glucometer, respectively. Polyherbal extract (PHE) was given orally for 28 days. The rats were euthanized with Sodium pentobarbitone after treatment.

Preparation of homogenate

Renal and hepatic tissues were harvested, homogenized with phosphate buffer (0.1 M, pH 7.4) and centrifuged for 10 min at 10,000×g. The supernatant was used for determination of oxidative stress markers and antioxidant status. The concentration of protein was assayed using the protocol (Bradford 1976).

Determination of serum parameters

Cholesterol and HDL-cholesterol concentrations were determined using the protocol (Allain *et al* 1974), triglycerides were evaluated with procedure (Jacobs and Van-Denmark 1960). Atherogenic index and cardiac risk ratio were calculated using (Ikewuchi and Ikewuchi 2009) and (Takasaki 2005) methods, respectively. Urea and Creatinine were assayed with the Bartels and

Bohmer (1972) and Weatherburn (1967) protocols, respectively. Alkaline phosphatase was determined with the procedure of Rec GSCC (DGKC) (1972) while aspartate and alanine transaminases were determined using the protocol of Reitman and Frankel (1957)

Determination of markers of oxidative stress

Lipid peroxide (LPO) was assayed using the procedure of Farombi et al (2000). Nitric oxide (NO) was evaluated with the procedure of Green *et al* (1982). Reduced glutathione (GSH) was assayed using the method of Jollow *et al* (1974). Superoxide dismutase (SOD) was quantified with the procedure of Misra and Fridovich (1972)

Statistical analysis

Data are expressed as the mean ± SD. Analysis of variance (ANOVA) $p < 0.05$ was used to establish the significance of differences between the means. Graph pad prism was used for charts drawing

Results

Phytochemical profiling of PHE using HPLC fingerprinting was shown in Table 1. Curculin (0.21 mg/g), Quercetin (0.72 mg/g), Kaempferol (0.29 mg/g) and Rutin (0.25 mg/g) are the most abundant phytochemicals identified. Contents of total phenolics, flavonoids and antioxidant parameters (TAC and FRAP) are presented as Table 2. *In vitro* scavenging potential against DPPH and inhibition of physiological enzymes (α-amylase and α-glucosidase) are shown in Figure 1. The effects of PHE on FBG and BW of diabetic rat are presented in Table 3. There was significant increment in the FBG and reduction of BW of diabetic rats. Treatment with PHE significantly produced dose dependent reduction in FBG and improved BW in the diabetic rats treated with PHE. Figure 2 presented the effect of PHE on lipid profiles (cholesterol, HDL-cholesterol and triglycerides) of diabetic rats. There were increases in total cholesterol and triglycerides levels while HDL-cholesterol was lowered in diabetic rats. Calculated atherogenic index

Table 1: Phytochemicals identified in the PHE using HPLC DAD

	Phytochemical	mg/g
1	Coumarin	**0.09**
2	Curculin	**0.21**
3	Curculigenin A	**0.06**
4	Gallic acid	**0.02**
5	Catechin	**0.02**
6	Beta-sitosterol	**0.01**
7	Stigmasterol	**0.01**
8	Nicotiflorin	**0.01**
9	Cinnapic acid	**0.01**
10	Quercetin	**0.72**
11	Kaempferol	**0.29**
12	Rutin	**0.25**
13	Sinapic acid	**0.01**
14	Ferulic acid	**0.01**
15	Hesperidin	**0.01**
16	Daucosterol	**0.01**
17	Phloerizin	**0.01**
18	Pomiferin	**0.01**
19	Scanderin	**0.01**

Table 2: Phenolics, flavonoids, TAC and FRAP of the PHE

Phenolics (mg/ 100g GAE)	90.64±3.69
Flavonoids (mg/ 100g QAE)	63.97±2.07
TAC (mg/ 100g AAE)	11.46±0.99
FRAP (mg/ 100g $Fe^{2+}E$)	25.80±1.83

Values are means of three determinations

Table 3: Body weight and fasting blood glucose of polyherbal treated diabetic rats

	Body weight (g)		Fasting blood glucose (mg/dL)	
	Initial	Final	Initial	Final
Control	143.20±6.30	177.60±6.11	97.20±7.60	97.80±7.82
Dcontrol	146.60±5.13	114.60±4.45 [a]	284.40±24.03	310.20±47.01 [a]
PHE 1	146.80±3.70	153.60±8.04 [ab]	306.20±28.15	169.00±26.68 [ab]
PHE 11	148.40±4.04	159.80±4.77 [ab]	316.60±43.01	152.40±7.70 [ab]
DSTGLB	145.40±9.15	162.50±8.07 [ab]	290.20±27.02	117.60±8.84 [ab]

Values were Mean ± SD. [a] $p < 0.05$ when experimental groups were compared with control group, [b] $p < 0.05$ when diabetic control was compared with treated groups. Control= Healthy rats given distilled water. Dcontrol= Diabetic rats given distilled water. DCCP1= Diabetic rats given 75 mg/kg PHE. DCCP11= Diabetic rats given 150 mg/kg PHE. DSTGLB= Diabetic rats given 5 mg/kg Glibenclamide

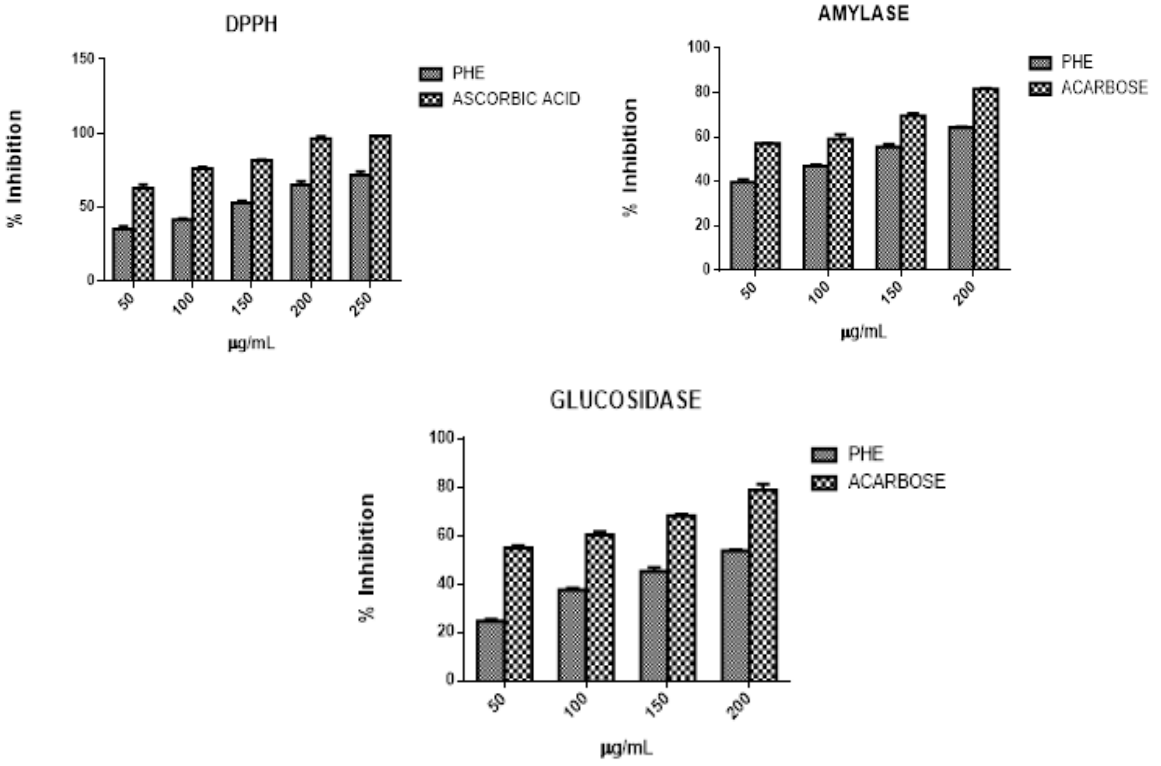

Figure 1: DPPH scavenging activity and inhibition potential against amylase and glucosidase of PHE

and cardiac risk ratio were also elevated in the diabetic rats. Oral administration of PHE significantly modulated the lipid profile and calculated atherogenic index and cardiac risk ratio positively. The effect of PHE on biomarkers of liver and kidney function is presented in Figure 3. These biomarkers (AST, ALT, ALP, creatinine and urea) were elevated in diabetic control group but their levels were lowered in groups treated with PHE. Figure 4 presented the effect of PHE on lipid peroxidation (LPO), nitric oxide generation (NO), glutathione level (GSH) and activity of superoxide dismutase (SOD). The LPO and NO levels were significantly enhanced while GSH and SOD were significantly lowered in liver and kidney tissues of diabetic rats. Oral treatment with PHE significantly lowered LPO and NO while GSH and SOD were significantly increased in hepatic and renal tissues of treated diabetic rats.

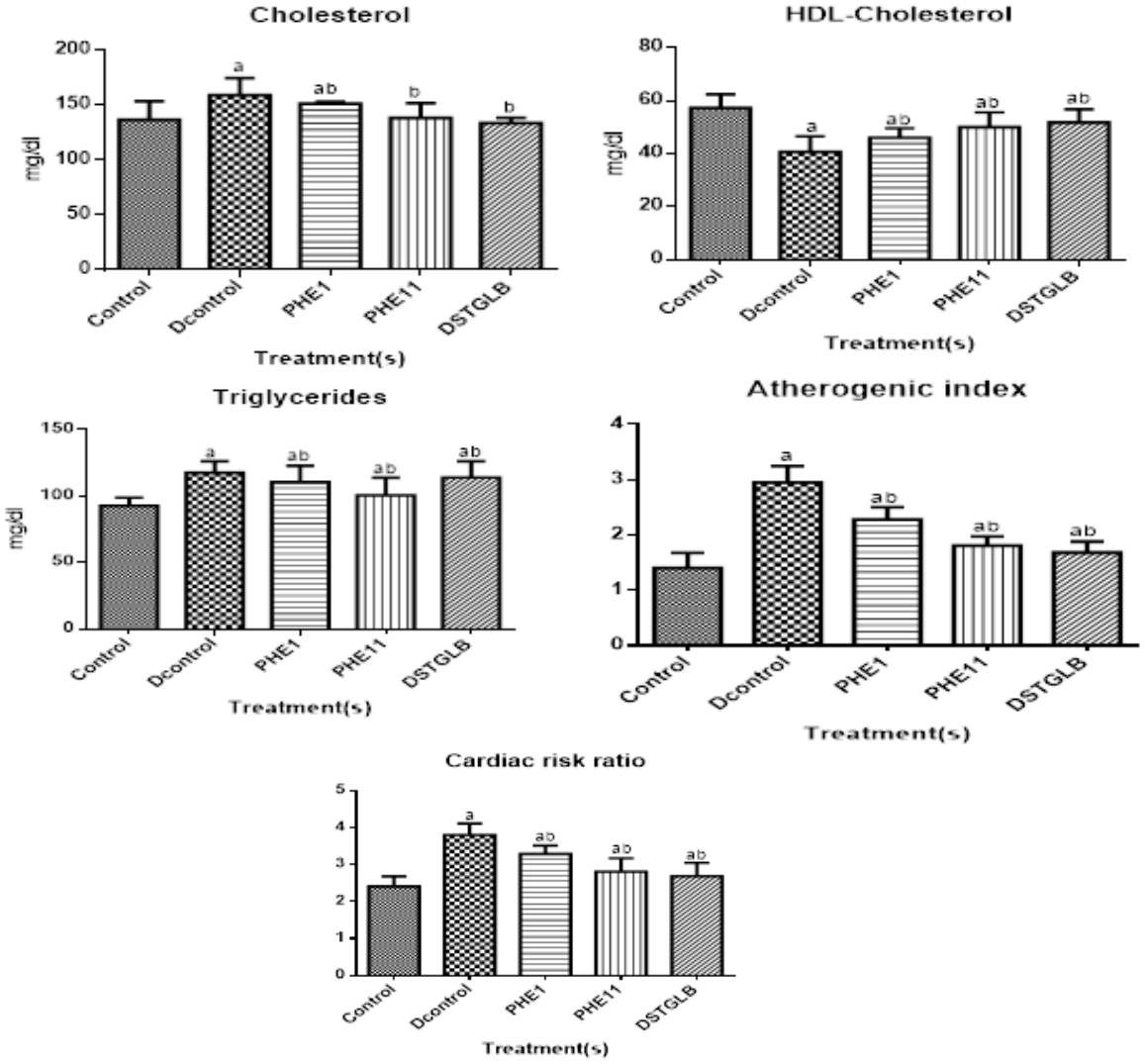

Figure 2: Effect of PHE on lipid profiles of streptozotocin-induced diabetic rats. [a] $p < 0.05$ when diabetic group was compared with control group, [b] $p < 0.05$ when diabetic control was compared with treatment groups**.** Control= Healthy rats given distilled water. Dcontrol= Diabetic rats administered distilled water. PHE1= Diabetic rats administered PHE (75 mg/kg). PHE11= Diabetic rats administered PHE (150 mg/kg). DSTGLB= Diabetic rats administered Glibenclamide (5 mg/kg)

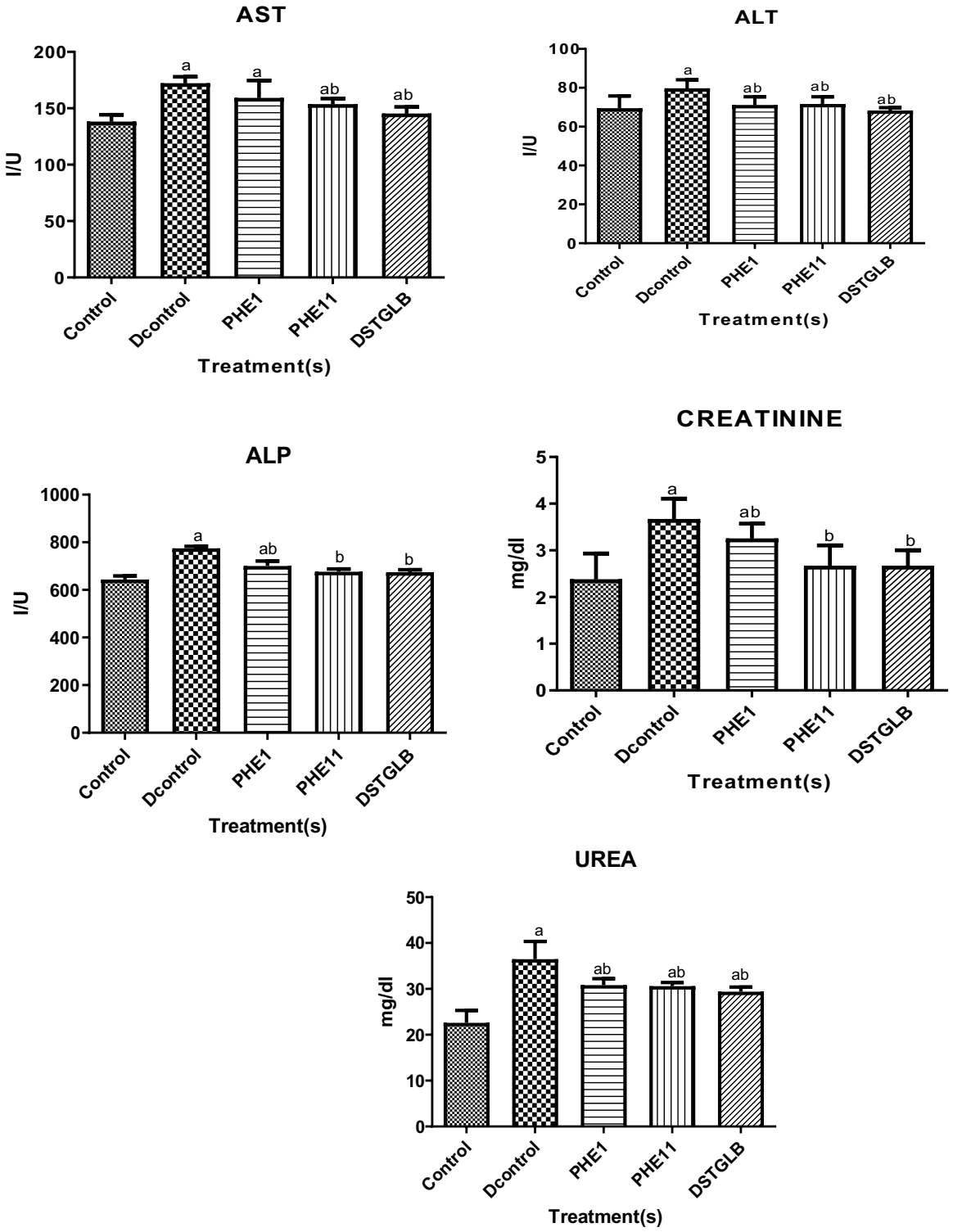

Figure 3: Effect of PHE on liver and kidney function markers of streptozotocin-induced diabetic rats. [a] $p < 0.05$ when diabetic group was compared with control group, [b] $p < 0.05$ when diabetic control was compared with treatment groups**.** Control= Healthy rats given distilled water. Dcontrol= Diabetic rats administered distilled water. PHE1= Diabetic rats administered PHE (75 mg/kg). PHE11= Diabetic rats administered PHE (150 mg/kg). DSTGLB= Diabetic rats administered Glibenclamide (5 mg/kg)

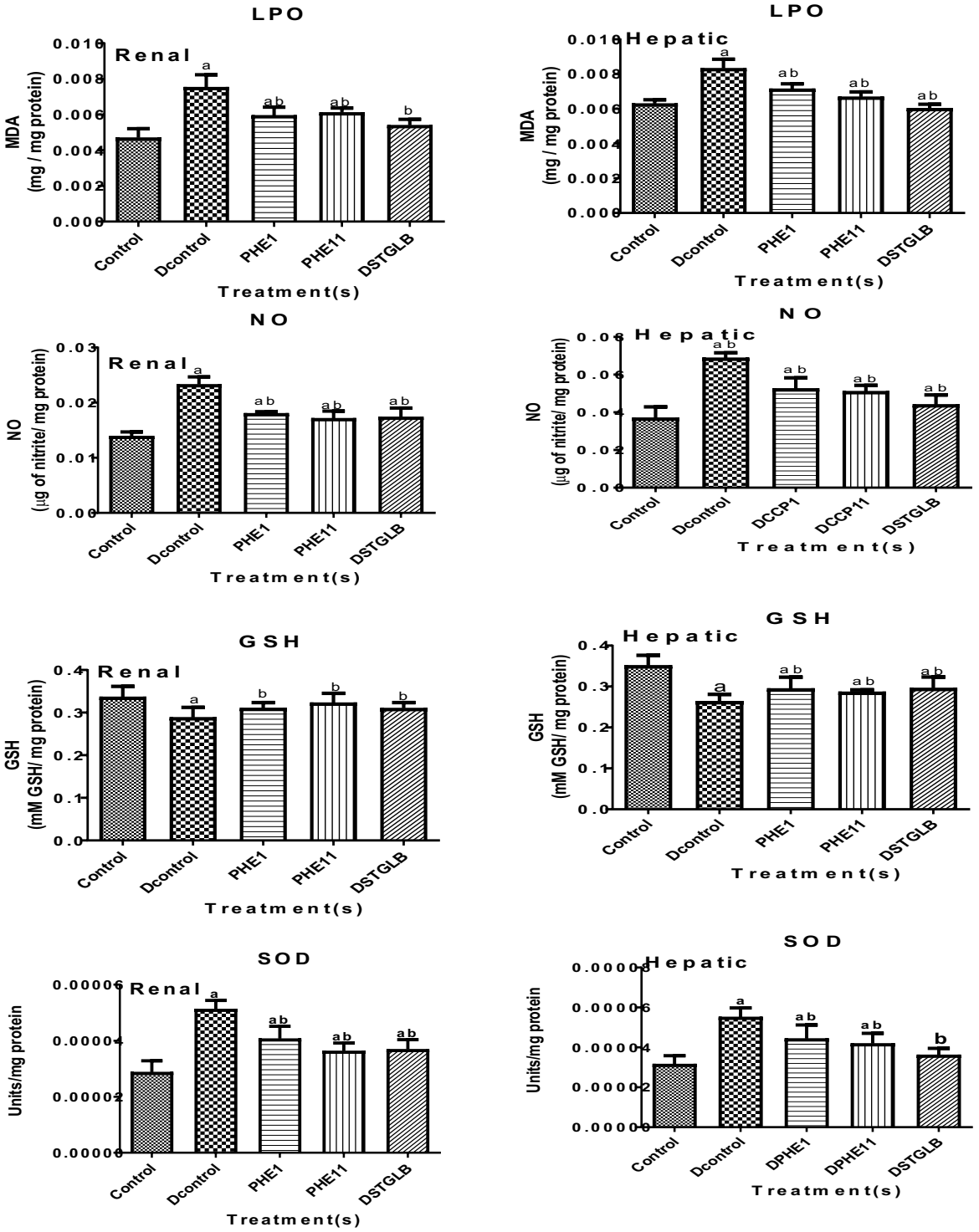

Figure 4: Effect of PHE on renal and hepatic oxidative stress markers of streptozotocin-induced diabetic rats. [a] $p < 0.05$ when diabetic group was compared with control group, [b] $p < 0.05$ when diabetic control was compared with treatment groups. Control= Healthy rats given distilled water. Dcontrol= Diabetic rats administered distilled water. PHE1= Diabetic rats administered PHE (75 mg/kg). PHE11= Diabetic rats administered PHE (150 mg/kg). DSTGLB= Diabetic rats administered Glibenclamide (5 mg/kg)

Discussion

Polyherbal formulation has been the mainstay of traditional medicine since time immemorial, for example it is the bedrock of ancient Ayurvedic system of medicine in India (Acharyya 2000). It is postulated that a collection of many medicinal plants may possess greater efficacy and fewer side effect since each plant is distinct and may complement each other (Resmi and Anju 2023). In the present study; phytochemical contents, *in vitro* antioxidant potential, ability to repress the activities of α-amylase and α-glucosidase and antidiabetic effects of polyherbal formulation in streptozotocin-induced diabetic rats were explored. The use of herbal plants for treatment of maladies is based on presence of secondary metabolites which exhibited many biological activities such as antioxidant, antidiabetic, antimicrobial, antihypertensive and anticancer. This indicates that secondary metabolites such phenolics and flavonoids of PHE might be responsible for its antidiabetic effects; as many polyphenolic-rich extracts have been reported to exhibit antidiabetic effects (Nunez *et al* 2023, Paun *et al* 2024). The *in vitro* antioxidant and antidiabetic potentials of PHE might serve as pointer that the extract might control glucose homeostasis and oxidative stress in diabetic animals.

Streptozotocin, an alkylating agent is used to stimulate DM in experimental rats. The STZ has a molecule of glucose with a nitrosourea moiety which is believe to be responsible for its cytotoxic action. This glucose molecule directs the drug to the pancreatic β-cell, where it damaged the pancreas and subsequent elevated glucose level in the blood of rats (Kottaisamy *et al.,* 2021). The reduction in FGB of the diabetic rats upon PHE administration might be linked to the potential of PHE to repair damaged β-cell and exert glycemic control in diabetic rats. This improved glycemic control which made glucose available for energy generation might be responsible for body weight gain in treated diabetic as fat are not mobilized for energy generation.

As proven in literature, DM usually led to disorderliness in fat metabolism; cholesterol and triglyceride levels are enhanced (Anjorin *et al* 2023, Karigidi *et al* 2023). When insulin level is depleted, an enzyme "lipase" is activated which catalyzed the release of fatty acids from adipose tissue to meet energy demands. The uses of fatty acids for energy usually give rise to excessive acetyl CoA which is the precursor for cholesterol in the body. Also, the excessive fatty acids in the body can be esterified to glycerol to produce triglyceride in the body. The decreased cholesterol and triglyceride concentrations in diabetic rats upon treatment with PHE might be attributed to improved glucose homeostasis and improved insulin secretion. This will prevent activation of lipase, release of fatty acid and subsequent availability of acetyl CoA for cholesterol production. This result indicated that PHE might prevent cardiovascular complications in DM.

Diabetes mellitus has been shown to cause hepatic and renal damage (Yedjou *et al* 2023, Ferguson and Finck 2021). There were increases in biomarkers of hepatic (AST, ALT and ALP) and renal (creatinine and urea) damage in diabetic rats. Upon treatment with PHE, the concentrations of these biomarkers were reduced indicating the hepatic and renal protective ability of the PHE.

One of the prominent investigative mechanisms of organs' damage in DM is oxidative stress. It occurs when the rate of generation of free radicals overwhelm the antioxidant status in the body (Charlton *et al* 2021, Moh *et al* 2023). In DM, excessive glucose concentration leads to generation of free radical which depletes antioxidant

system. In this study, lipid peroxide and nitric oxide generations were enhanced in hepatic and renal tissues of diabetic rat but lowered upon administration of PHE. The potential of PHE to mitigate the generation of these biomarkers in diabetic rats might be attributed to the ability of PHE to exert better glucose homoeostasis thereby reducing the formation of free radicals or to the antioxidant potential of PHE which mitigate the production of free radicals. The increment in concentration of GSH and activity of SOD in treated diabetic rats might be ascribed to reduced generation of free radicals.

Fingerprinting of the polyherbal extract revealed the availability of some phytochemicals (gallic acid, quercetin, kaempferol, and rutin) with antioxidant and antidiabetic potentials (Hong *et al* 2023, Alshehri 2023, Cai *et al* 2023, Rahmani *et al* 2023)

Conclusions

The study has clearly showed that polyherbal extract made from *Citrullus colocynthis, Curculigo pilosa* and *Gladiolus psittacinus* has ability to modulate glucose concentration and lipid metabolism in diabetic rats. Also it reduced generation of free radicals (lipid peroxides and nitric oxides) and improved antioxidant system in liver and kidney of diabetic rats

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Conflict of interest

None was declared

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