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Comparative efficacy and safety investigation of eight antidiabetic herbal products distributed within South-Western Nigeria

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Abstract

Herbal preparations, often promoted as being natural and completely safe, are gaining popularity in the management of diabetes mellitus, despite lack of scientific data to confirm their efficacy and safety claims. This study investigated efficacy and safety of eight commercial antidiabetic herbal products. Antidiabetic activities were investigated in streptozotocin-induced diabetic rats at doses based on their labelled recommended dosages using metformin as reference drug. Body weights, blood glucose level (BGL), haematogical and biochemical parameters as well as histopathology of the kidney and lungs were assessed by standard procedures. All the samples demonstrated weight reduction ($p<0.05$), with accompanying BGL decrease ranging from 21.9 ±1.71 to 73.9 ±1.42% which was significant ($p < 0.01$) in three samples, when compared with metformin (37.9 ±7.41%). Of all the hematological indices, only WBC, platelet and eosinophil were affected by two of the samples, while for the biochemical parameters only alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels were increased ($p<0.05$) by one of the samples. Varied histopathological damages were observed with the liver, lungs and kidney tissues of treated groups. Hypoglycaemic activities were confirmed in all the samples, however, their deleterious effects on the liver, kidney and lungs calls for caution in their consumption.

Keywords: Antidiabetic; Herbal products; Blood glucose; Histopathological damage; Streptozotocin-induced

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia which occurs as a result of either deficiency in the insulin production by the pancreas or its peripheral actions or both [1,2]. The raised blood sugar over time results in serious damage to the body systems, especially the nerves and blood vessels; presenting as diseases of large blood vessels (coronary heart disease and peripheral arterial disease), small blood vessel (retinal and renal vascular disease), as well as diseases of the nerves [3]. Its prevalence is widespread and, on the increase, globally as a result of adoption of sedentary lifestyles and high caloric diets due to seeming affluence, with over 536.6 million prevalence as at 2021 and predicted to rise to over 600 million by 2030 and 783 million by 2045 [4]. In Nigeria, the current prevalence is 3.8%, with the southwestern region having 3.2% as at 2017 [5]. It is generally classified

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into insulin-dependent, non-insulin-dependent, gestational, Hybrid forms, unclassified diabetes and other specific type (monogenic diabetes, pancreatitis, trauma, infection, pancreatic cancer etc.), each of which are of different etiology [4].

There are various classes of drugs such as insulin, sulfonylureas, biguanides, α-glucosidase inhibitors and thiazolidinediones [6], currently available for the management of DM. However, these drugs are associated with several adverse effects such as hypoglycemia, weight gain, gastrointestinal disturbance, liver toxicity etc. as a result of DM being a multifactorial disease along with high cost [6]. Thus, many diabetic patients discard the use of their orthodox drugs in favour of herbal therapies alone or in conjunction with prescribed medications, many times without the knowledge of their physicians [7].

Numerous traditional herbs and their parts have been shown to have medicinal value and can be used to prevent, alleviate or cure several human diseases including Diabetes mellitus (DM) [8]. Hence, herbal preparations are gaining popularity in the treatment of Diabetes mellitus in many countries, as they are frequently considered to be less toxic, low cost and free from side effects [9,10]. Hypoglycaemic activities of a wide range of plants folklorically reported within different climes for the management of DM have been confirmed scientifically [10,11]. Their antidiabetic properties have been adduced to antioxidant activities of the component phytochemicals such as glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc. [12]. Most of the commercially available herbal preparations comprise of some of these plants extracts and their combinations.

An upsurge in the commercial production and distribution of herbal medicines globally has been reported making it a fast-growing trade projected to grow from USD 230 billion as at 2021 to USD 430 billion in 2028 [13,14]. This is further enhanced by the ease of commercial advertisements and promotion along with increased popularity in global and national herbal trado-medical fairs. However, the various controversies with regulation, safety and standardization despite the invaluable contribution of herbal therapy in healthcare shows a need for safety and quality assessment of these products [15]. Many antidiabetics herbal products containing single or combination of plant extracts have been reported and considered to be effective in the management of diabetes globally, with numerous mechanisms of actions proposed [16-18].

Integration of herbal medicine into healthcare practices is already being practiced in some countries [19-21], however, the lack of scientific and clinical data proving their efficacy and safety is a serious mitigation in many countries of which Nigeria may not be exempted [22]. Some medicinal plants widely assumed to be safe have been proven to be potentially toxic, Asteraceae, Boraginaceae and Fabaceae plant families contains pyrrolizidine alkaloids which are class or toxic alkaloids linked with hepatotoxicity [23,24]. Moreso that, inadvertent contamination by microbial or chemical agents during any of the production steps can also affect the quality, safety and efficacy of these products.

Although bioactivity of plant extracts used in the treatment of diabetes have been reported [10,25], scientific experimental data to confirm the efficacy and safety of antidiabetic herbal formulations available for sale in Nigeria market against their labelled claim is limited [16].

The aim of this study therefore, was to investigate the comparative efficacy and safety of eight commercially available polyherbal herbal products available within the southwestern part of Nigeria, in streptozotocin-induced hyperglycaemic rats.

EXPERIMENTAL METHODS

Chemicals and reagents. Metformin and Streptozotocin (Sigma Aldrich USA), alanine aminotransferase and aspartate amino-transferase kit (Randox Laboratories Ltd, UK). All reagents were of analytical grade. Eight antidiabetic herbal formulations were procured from herbal vendors in Southwestern part of Nigeria.

Herbal products profile. The herbal products for this study were selected randomly based on efficacy claims, popularity among some diabetic patients interviewed and availability to the public. The presentation of the samples was assessed, and coded and information provided on the label; country of manufacture, National Agency for Food Drug Administration and Control (NAFDAC) registration status, manufactured and expiry dates, batch number, component herb(s), dosage forms and dose were documented.

Ethical consideration: Ethical approval was obtained from animal care and use ethical committee (ACUREC), University of Ibadan (U.I) with approval number: UI-ACUREC/18/0007.

Antidiabetic activity evaluation

Experimental animals. Healthy Wistar rats of both sexes (150–200 g) obtained from the animal house of the College of Medicine, University of Ibadan were used for the study and were maintained in standard laboratory conditions (temperature: 25-30^{o}C, 12-hour light and dark cycles). The rats were allowed to acclimatized for two weeks before commencement of the study, while being fed with standard rat pellets and water *ad libitum*. Animals described as fasted were deprived of food for ≥ 16 hours, but allowed free access to water.

Induction of diabetes. Overnight fasted rats were administered freshly prepared streptozotocin (STZ) in 0.1 mol/L cold citrate buffer (pH 4.5) at dose of 55 mg/kg, intraperitonially [26]. The STZ administered animals were allowed to drink 5%w/v glucose solution overnight to overcome drug-induced hypoglycemia. The blood glucose level (BGL) of induced rats were determined using glucometer (AccuCheck®, Roche, India). Rats having persistent glycosuria and hyperglycaemia with a fasting blood glucose >200 mg/dL 72 hours after the STZ injection were considered diabetic and used for the study.

Preparation of administered herbal product solutions. known weight of each herbal products based on the labeled dosage (for two days) was coarsely powdered, macerated at room temperature with 50 ml of distilled water in a closed flask for 24 hours, shaken frequently for first 6 hours and allowed to stand for 18 hours, and there after filtered. The sample solutions were made up to 50mL volume with distilled water, stored at 8^{o}C and freshly prepared every 48 hours.

Antidiabetic evaluation. Forty previously confirmed forty diabetic rats were randomised into ten (10) groups (n = 4) with equal number of both sexes. Following an overnight fast, the extracts of the coded samples were administered twice daily for 12 days (based on the labeled dosage at 60 Kg adult weight); brand A (16.70 mg/kg), B (4.20 mg/kg), C (16.70 mg/kg), D (20.0 mg/kg), E (25.56 mg/kg), F (73.33 mg/kg), G (33.30 mg/kg) and H (33.30 mg/kg). Metformin (0.5 mL, 8.3 mg/kg BW) served as reference positive control (DPC), while diabetic negative control (DNC) and healthy rats (without DM, HC) were administered 0.5 mL distilled water. All doses were administered using oral cannula (18 gauge).

Blood glucose level (BGL) determination. Blood samples (0.25 mL) were withdrawn from the tail vein at before the treatment (0 hour), 8 hours, 24 hours, and at 3, 5, 7, and 12 days and BGL determined with a glucometer (Accuchek active®) in the morning daily

before sample administration. Percentage reductions in blood glucose levels was estimated using the following formula [27]

$$\%\ Reduction\ in\ BGL = \frac{(IBGL - TBGL)}{IBGL}\ X\ 100$$

where IBGL = Initial BGL before administration and TBGL = BGL at sampling time, T

Body weight (BW) determination: the rats were weighed before feeding and drug administration (Day 0) and at day 5, 7 and 12 using weighing balance (Mettler weighing balance, Unified National Inventory Database England). The percentage change in body weights of the rats were determined using the following formula.

$$\%\ Change\ in\ BW = \frac{(iBW - tBW)}{iBW}\ X\ 100$$

where iBGL = Initial BW @ Day 0 and tBW = BW at sampling time, t

Haematological and biochemical indices determination. Blood (2 ml) was withdrawn 24 hours after last day of sample administration (day 12) by retro-orbital venous puncture into EDTA tubes, gently mixed and used for the various haematological analysis. The haemoglobin concentration (Hb), packed cell volume (PCV), white blood cell count (WBC), red blood cell count (RBC), platelets count and differential white blood cell count (neutrophils, lymphocytes, monocyte and eosinophils) were determined using standard procedures [28].

Another 2 ml blood collected into Lithium heparinized tubes and centrifuged at 5000 revolution per min for 5 minutes. The plasma obtained was transferred into clean labelled bottles and stored at -4^{o}C prior to analysis. The plasma was used for analysis of creatinine, total bilirubin, globulin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels using Randox commercial test kits.

Histopathological evaluation. The liver, kidney and lung were harvested and preserved in sample bottles containing 10% buffered formalin solution for at least 48 h. Histopathological evaluations were carried out at the Department of Veterinary Pathology, University of Ibadan using standard procedures [29].

Statistical analysis. Results were presented as mean and standard error of the mean (SEM). To demonstrate statistical significance of data, a One-way Analysis of Variance (ANOVA) using GraphPad Prism 5 software was performed with significance set at $p < 0.05$.

RESULTS

Description and profile of the herbal products. All the samples were well packaged with good aesthetics and labels, their profile: country of manufacture, NAFDAC registration status, batch number, component herb(s), dosage form, pack size and dosage regimen are presented in Table 1. All the samples were within their shelf life as at the time of the study

Body weight determination: A significant percentage decrease ($p < 0.05$) in the body weights of all the diabetic rats was observed after drugs administration across all product-treated groups at the end of the study (Figure 1).

Antidiabetic activity. The administration of the polyherbal products and metformin for 12-day period resulted in BGL reduction ranging from 21.9 ±1.71 to 73.9 ±1.42% which was significant ($p < 0.01$) in three samples (A, B and C) when compared with metformin reference treated group (Figure 2).

Effect on haematological parameters. No significant difference in the hematological indices of the treated groups as compared to the controls (negative and positive) and healthy group, except for WBC, platelet and eosinophil were observed (Table 2). However, WBC was significantly reduced by samples C and H ($p = 0.0061$ and 0.0479 respectively) compared to the positive control. Significant reduction of platelet count ($p= 0.0493$) was observed with sample H treated group when

compared with healthy group (HC). On the other hand, sample D group caused significantly increased (p= 0.0493) platelet count, while sample H caused a decrease when compared with the untreated group (DNC).

Biochemical parameters. The AST and ALT levels for the herbal product treated groups were not significantly different from that of the metformin (positive control) and untreated groups except sample E which was increased ($p< 0.05$) (Figure 3). The varied levels of the other biochemical indices investigated; albumin, globulin, albumin/globulin ratio, total protein and creatinine were not statistically significant. However, samples A and E showed similar higher ($p < 0.05$) total bilirubin level when compared with the healthy control and untreated groups, all the other samples (B, C, D, F, G and H) were lower ($p < 0.05$) (Table 3).

Histopathological evaluation. Almost all the herbal products showed varied effects on the liver, from mild to severe portal congestion (A, B and E) to severe sinusoidal congestion, diffused vacuolar degeneration of hepatocytes and shrunken hepatocytes in samples C, F and H, and hepatic degeneration and necrosis in sample G (Plate 1). Also, kidney morphology showed mild renal cortical congestion around the interstitium and glomeruli without visible lesion in samples E and H groups, but a mild congestion of the renal cortex and mild to moderate interstitial and glomerular hemorrhage was observed in samples D and F groups respectively (Plate 2). Furthermore, three of the samples showed varied effects on the lung tissues; from severe proliferated alveolar walls and pneumocytes in samples A and D, respectively, with pulmonary congestion and severe lymphocytic cellular infiltration (sample H) and of the interstitium in sample F. (Plate 3). However, no significant change was observed in the morphology of the other organs with all the herbal product treated groups.

Table 1: Profile of the eight commercially available antidiabetic herbal products investigate

Sample	Country	Batch no	NAFDAC No.	Component herbs (As indicated on the package)	Dosage form	Weight per dosage form (g)	Pack size	Dosage Regimen
A	Nigeria	MFG/0018	A7-2358L	*Azadirachta indica, Vernonia amygdalina, Aloe bitters*	Tablets	0.5	30	2 tablets, twice daily
B	Nigeria	KDFMA1GS	A7-0466L	*Radix rehmannia preparata, Cortex montan, Fructus comi, Rhizome dioscoraea, Poria and Rhizomia alismatis*	Capsules	0.25	30	1 capsule, twice daily
C	Nigeria	FMB0028GRW	A7-0201L	*Viscum album* & Flax seeds and extract of natural *Kaolin*	Tablets	0.5	60	2 capsules, thrice daily
D	Nigeria	2016.10.0101	-	*Ginseng radix rubrie, Rehmannia glutinosa, Cortex phellodendri and Fructus lycil*	Tablets	0.3	80	12 tablets, thrice daily
E	Nigeria	-	-	*Piper nigrum*	Capsules	0.38	60	4 capsules, twice daily
F	Nigeria	-	A7-0196L	*Mangifera indica, Tridax procumbens, Viscum album, and Zingiber officinale*	Teabag	2.2	25	2 teabags, twice daily
G	China	-	-	Not stated	Teabags	2.0	20	1 teabag, daily
H	China	-	-	*Trichosanthis Radix, Lobed Kudzuvine Root, Stevia rebaudiana (Bertoni) Hemsl, Common Yam Rhizome, etc*.	Teabags	2.0	20	1 teabag, twice daily

Table 2: Effect of eight commercially available herbal products on haematological parameters in streptozotocin-induced diabetic rats

Sample	PCV (%)	Hb (g/dl)	RBC ($x10^{12}$ L)	WBC (/UI $x10^2$)	Platelet (/UI $x10^3$)	Lymphocyte (%)	Neutrophils (%)	Monocytes (%)	Eosinophils (%)	ESR (%)
HC	44.0 ±1.00	14.6 ±0.60	7.3 ±0.08	31.0 ±14.14	98.5 ±14.50	72.5 ±0.50	24.0 ±1.00	1.5 ±0.50	2.0 ±1.00	1.3 ±0.01
DNC	41.0 ±4.00	13.6 ±1.85	6.9 ±0.58	34.8 ±20.86	88.0 ±4.0	69.0 ±4.00	26.5 ±3.50	1.5 ±0.50	3.0 ±0.01	1.1 ±0.25
DPC	42.5 ±0.50	13.5 ±0.10	6.9 ±0.31	47.0 ±15.56	72.5 ± 32.5	65.5 ±5.50	33.0 ±6.00	1.0 ±0.01	0.5 ±0.50[b]	1.2 ±0.05
A	50.5 ±0.50	16.7 ±0.01	8.5±0.02	23.0 ±15.56	90.5 ±12.50	76.0 ±1.00	20.0 ±1.00[c]	1.0 ±0.01	3.0 ±0.01	1.3 ±0.10
B	37.5 ±0.50	12.4 ±0.01	6.2 ±0.03	27.0 ±56.57	104.0 ±8.00	67.5 ±1.50	30.0 ±1.00	1.5 ±0.50	1.0 ±0.01	0.8 ±0.01
C	47.0 ±1.00	16.0 ±0.20	7.9 ±0.24	19.5 ±49.49[c]	98.0 ±2.00	74.0 ±0.01	24.0 ±0.01	1.5 ±0.50	0.5 ±0.50[b]	1.4 ±0.05
D	40.0 ±0.01	13.0 ±0.01	6.5 ±0.01	24.0 ±0.01	154.0 ±0.01[bc]	72.0 ±0.01	24.0 ±0.01	1.0 ±0.01	3.0 ±0.01	1.0 ±0.01
E	42.0±11.00	13.8 ±3.60	6.9 ±1.64	20.8 ±10.61	107.00 ±25.00	72.0 ±4.00	25.0 ±4.00	2.0 ± 0.01	1.0 ±0.01	1.1 ±0.30
F	45.0 ±3.00	15.2 ±1.13	7.6 ±0.50	26.3 ±60.10	116.5 ±11.50	73.5 ±0.50	23.0 ±2.00	2.0 ± 0.01	1.5 ±1.50	1.4 ±0.15
G	38.5 ±3.53	12.5 ±0.80	6.3 ±0.19	23.0 ±70.71	118.0 ±2.00	69.5 ±2.50	28.0 ±2.00	1.0 ± 0.01	1.0 ±0.01	0.9 ±0.10
H	43.0 ±0.01	14.0 ±0.01	7.3 ±0.01	7.50 ± 0.01[c]	19.0 ±0.01[ab]	73.0 ±0.01	24.0 ±0.01	2.0 ± 0.01	1.0 ±0.01	1.5 ±0.01

Data are expressed as ± S.E.M. One-way ANOVA followed by Dunnett's Multiple Comparison test was carried out. Sig. $P < 0.05$. [a] Significance with HC; [b] Significance with DNC; [c] Significance with DPC; (± SEM).

Table 3: Effect of eight commercially available herbal products on biochemical parameters in streptozotocin-induced diabetic rats

Code	Total protein	Albumin	Globulin	Albumin/ Globulin Ratio	Creatinine	Total bilirubin
HC	6.5 ±0.50	2.8 ±0.25	3.8 ±0.25	0.8 ±0.05	0.6 ±0.05	0.3 ±0.05
DNC	7.2 ±0.15	3.1 ±0.25	4.1 ±0.10	0.8 ±0.05	0.7 ±0.05	0.2 ±0.01
DPC	7.1 ±0.25	3.1 ±0.35	4.0 ±0.10	0.7 ±0.10	0.6 ±0.10	0.4 ±0.01[ab]
A	7.1 ±0.25	3.0 ±0.40	4.1 ±0.15	0.6 ±0.05	0.7 ±0.01	0.4 ±0.05[b]
B	6.3±0.45	2.6 ±0.20	3.7 ±0.25	0.6 ±0.10	0.6 ±0.05	0.2 ±0.01[c]
C	7.6 ±0.05	3.4 ±0.10	4.2 ±0.05	0.8 ±0.05	0.7 ±0.01	0.3 ±0.05[c]
D	7.1 ±0.01	3.0 ±0.01	4.1 ±0.01	0.7 ±0.01	0.6 ±0.01	0.2 ± 0.01[c]
E	7.5 ±0.50	3.3 ±0.40	4.2 ±0.10	0.8 ±0.05	0.7 ±0.05	0.4 ± 0.01[ab]
F	7.0 ±0.50	2.7 ±0.10	4.3 ±0.10	0.6 ±0.05	0.6 ±0.01	0.3 ±0.05[c]
G	6.2 ±0.85	2.6 ±0.10	3.6 ±0.75	0.7 ±0.10	0.6 ±0.07	0.2 ± 0.01[c]
H	7.2 ±0.01	3.3 ±0.01	3.9 ±0.01	0.8 ±0.01	0.6 ±0.01	0.2 ± 0.01[c]

Data are expressed as ± S.E.M. One-way ANOVA followed by Dunnett's Multiple Comparison test was carried out. Sig. $P < 0.05$. a Significance with HC; b Significance with DNC; c Significance with DPC; (± SEM).

DISCUSSION

The challenges of managing DM have led to the search for alternatives remedies including herbal preparations which are used by most patients. In Nigeria, many antidiabetic polyherbal formulations with claims of efficacy and safety are widely distributed and consumed. The present study was conducted to comparatively assess the efficacy and safety of eight selected polyherbal antidiabetic formulations sold in southwestern part of Nigeria in order to ascertain their labelled claims. Standard bioassay procedures were used to assess the antidiabetic activity and safety of the preparations in rodent model of diabetes mellitus.

Four of the eight selected commercially available herbal products which were observed to contain various plant ranging from one to six and have national drug regulatory agency (NAFDAC) certification number ending with L indicating 'listed status' (Table 1). There packaging in terms of dosage form, aesthetics and labels were quite impressive.

The induction of diabetes symptomatically by the significant increase in water intake and reduced feed intake in the diabetic rats compared to healthy rats was confirmed by BGL above 200mg/dL. These symptoms are well known markers of type 2 diabetes in both human and animal models which are direct consequence of insulin deficiency [30] with attendant impact on the body weight of the rats. Decreased body weights ($p < 0.05$) of diabetic rats across the groups agrees with diabetic symptoms after

induction using streptozotocin due to degradation of structural proteins and muscle wasting (Figure 1).

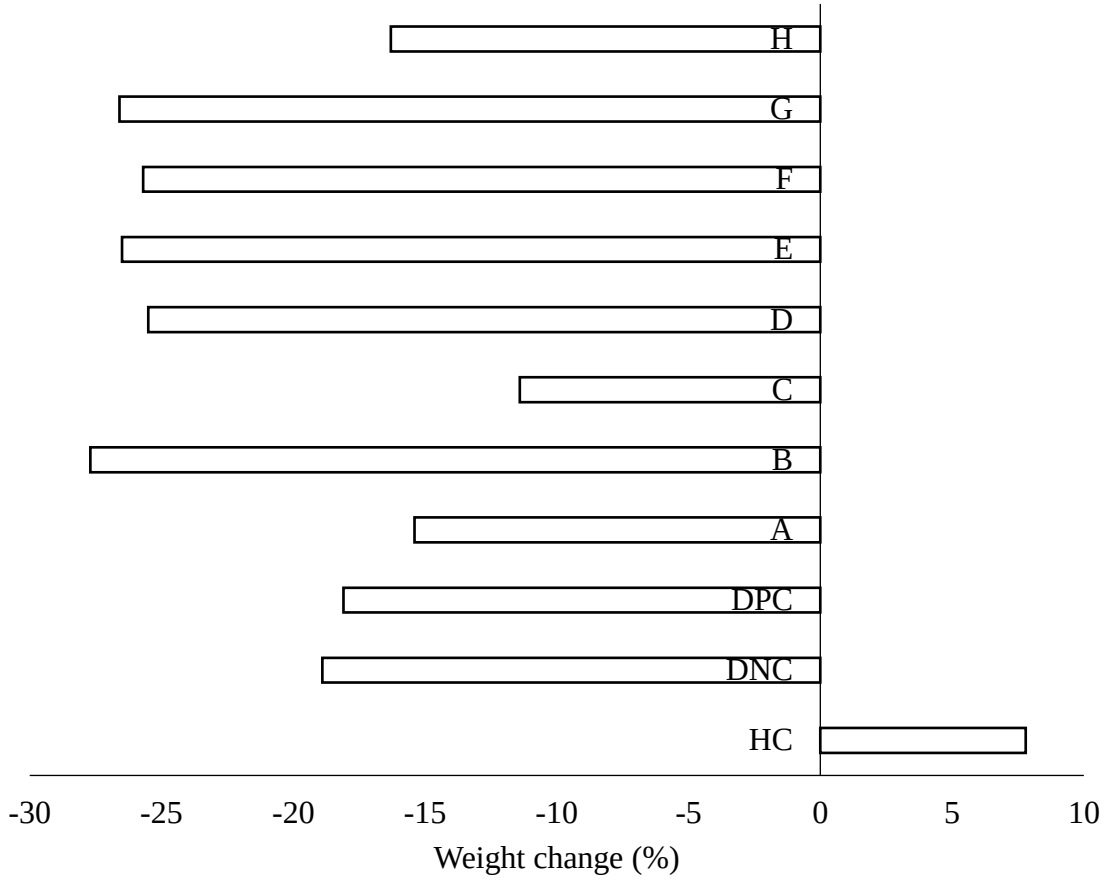

Figure 1: Effect of eight commercially available herbal products on body weights of streptozotocin-induced diabetic rats *(-ve = weight reduction, +ve = weight increase)*

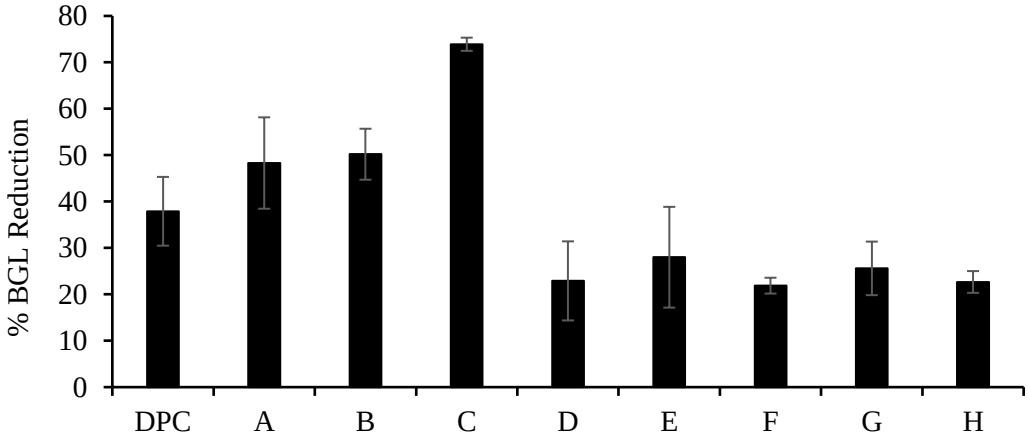

Figure 2: Effect of eight commercially available herbal products on blood glucose level in streptozotocin-induced diabetic rats

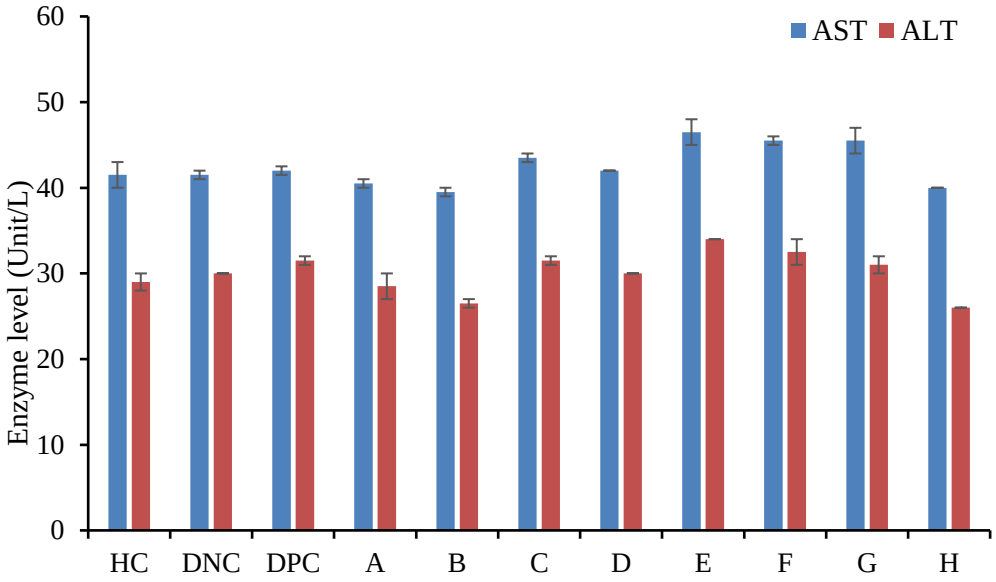

Figure 3: Effect of eight commercially available herbal products on AST and ALT levels of streptozotocin-induced diabetic rats

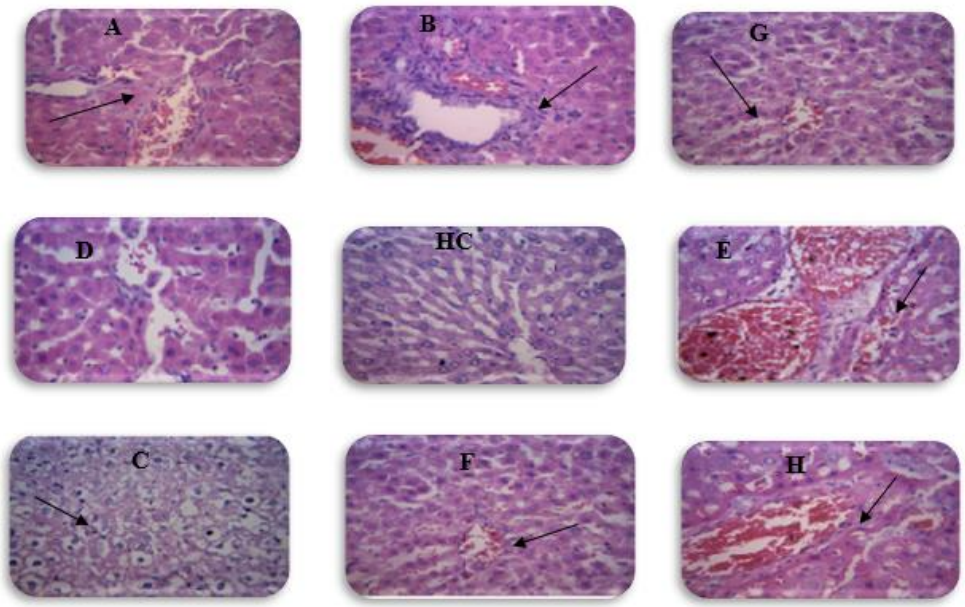

Plate 1: Photomicrograph sections of liver tissues following administration of eight antidiabetic herbal products and healthy control (HC), showing normal morphology in HC, mild portal congestion and periportal cellular infiltration in A, moderate to severe portal congestion with mild periportal cellular infiltration in B and E , mild to moderate diffuse hepatic degeneration and necrosis in G, moderate diffuse vacuolar degeneration of the hepatocytes in C, severe portal, central venous and sinusoidal congestion; diffuse hepatic degeneration and shrunken hepatocytes in F, moderate to severe portal, central venous and sinusoidal congestion in H treated groups, no significant visible lesion in D. (Haematoxylin & Eosin, x 200)

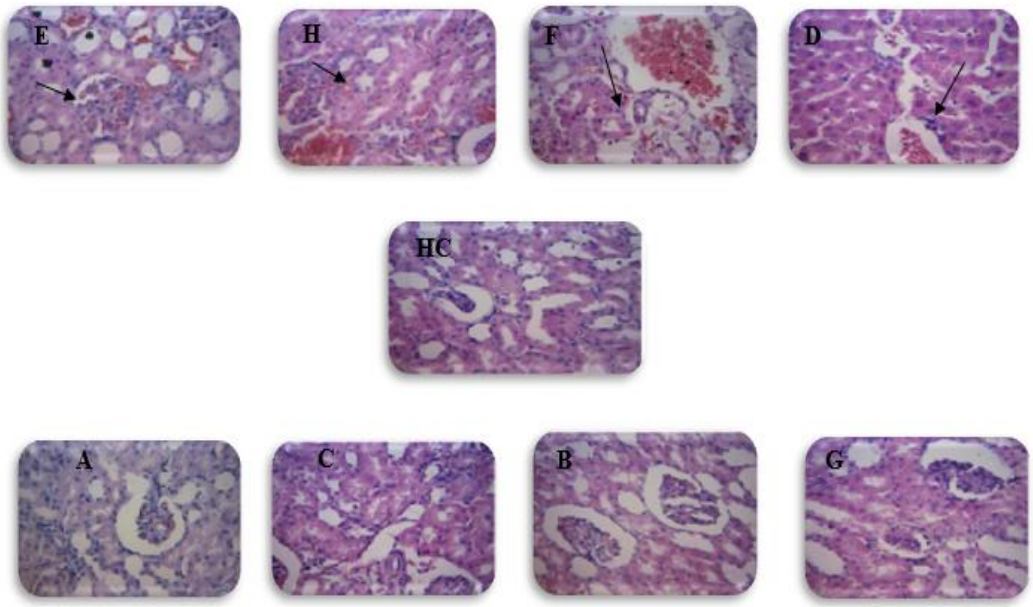

Plate 2: Photomicrograph sections of the kidney following administration of eight antidiabetic herbal products and healthy group (HC), showing normal morphology in HC, mild renal cortical congestion around the interstitium and glomeruli without visible lesion in E and H, mild congestion at the renal cortex in D, mild to moderate interstitial and glomerular hemorrhage in F treated groups, no visible lesion were observed in A, B, C and G. (Haematoxylin & Eosin, x 200)

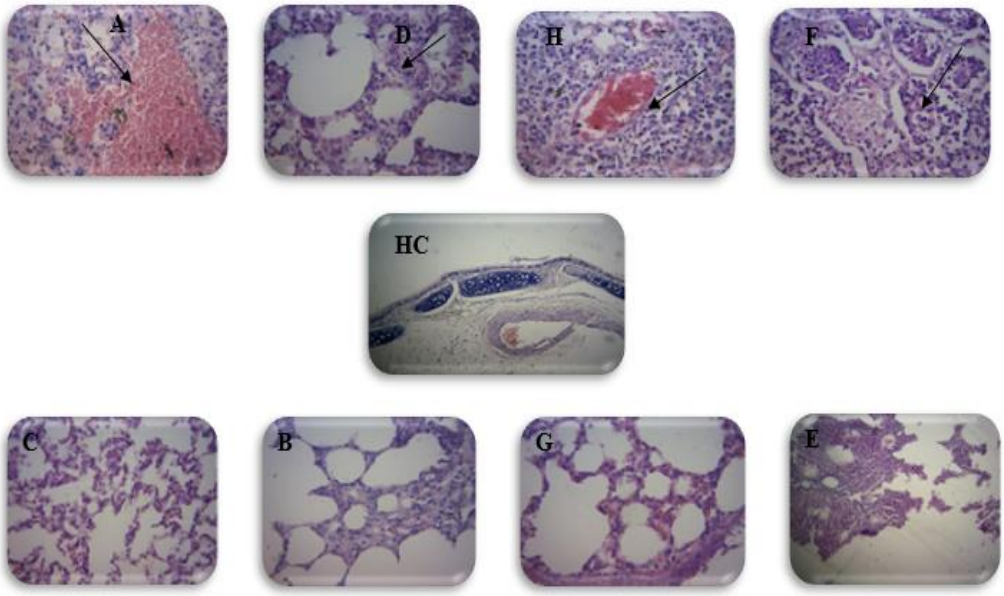

Plate 3: Photomicrograph sections of lung following administration of eight antidiabetic herbal products and healthy group (HC), showing normal morphology in HC, hemorrhage into the alveoli surrounded by severely proliferated alveolar walls in NCH, mild diffuse proliferation of alveolar pneumocytes in DT, severe pulmonary congestion through severe infiltration of the interstitium and alveolar spaces by mono nuclear cells in NBS, large foci of severe lymphocytic cellular infiltration of the interstitium and alveolar spaces in PHD treated groups and no visible lesion were observed in B, C, E and G. (Haematoxylin & Eosin, x 200)

The induction of diabetes symptomatically by the significant increase in water intake and reduced feed intake in the diabetic rats compared to healthy rats was confirmed by BGL above 200mg/dL. These symptoms are well known markers of type 2 diabetes in both human and animal models which are direct consequence of insulin deficiency [30] with attendant impact on the body weight of the rats. Decreased body weights ($p < 0.05$) of diabetic rats across the groups agrees with diabetic symptoms after induction using streptozotocin due to degradation of structural proteins and muscle wasting (Figure 1). The reduction in body weight of the treated groups compared to untreated (DNC) group suggests the inability of the herbal drug products to curb the muscle wasting and structural protein degradation in the diabetic rats. This may indicate absence of weight gain effects usually associated with antidiabetics such as sulphonylureas [31].

All the herbal preparations showed hypoglycaemic activity; three samples exhibiting significant percentage BGL reduction ($p< 0.01$), two of which exhibited significantly higher hypoglycaemic activities than the metformin group, while one was comparable (Figure 2). Hypoglycaemic activities of plants and herbals have been adduced to the presence of flavonoids, alkaloids and phenolics as a result of their antioxidant properties [32,33. The variations in the activities may be linked to the differences in the component plant extracts in the herbal products, which have been earlier reported to possess antidiabetic activities. The hypoglycaemic activities of these herbal products may be linked to the presence of phytochemicals such as flavonoids, alkaloids and phenolics which has been previously reported [34].

Hematological parameters are important indices of the physiological and pathological status for both animals and humans [35] which along with immunity changes has been linked to oxidative damage in diabetes mellitus [36]. Generally, there was no difference in the hematological indices of the treated groups as compared with the healthy, untreated and positive controls except in WBC, platelet and eosinophils (Table 2) which were however within the normal reference range in experimental rats [37].

Liver and kidney are internal organs which have several functions whose dysfunction causes leakage of biochemical substances into the blood circulatory system [38] resulting in their increased levels. Serum marker enzymes such as ALT and AST have diagnostic significance in routine clinical evaluation of hepatic damage [39,40], by xenobiotics or any other hepatotoxin [41]. All the biochemical indices did not show significant difference ($p> 0.05$) except AST, ALT and total bilirubin levels with some of the samples (Table 3, Figure 3). The increased release of ALT and AST into the blood could be linked to hepatic necrosis development in diabetes mellitus and hepatotoxicity or heart damage [42].

Of all the samples, only one group exhibited significant increase ($p<0.01$) in AST and ALT levels when compared with healthy and untreated groups, while only AST levels were significantly higher ($p= 0.0366$ and 0.0360 respectively) with two groups compared with untreated and metformin reference drug. Increased plasma AST concentration level observed in one group compared to healthy rats though not significant, showed need for caution in its consumption.

Increased total bilirubin and conjugated bilirubin indicates a compromise in the normal liver function [35]. The high AST, ALT and bilirubin levels for metformin is in agreement with previous reports [20]. The elevation of the liver enzymes caused by some of the samples indicates a predisposition to heart and liver damage.

The varied adverse histopathological implications of these herbal products on the liver, kidney and lungs (Plates 1, 2 and 3) call for caution in their consumption. The basis for the observed potential negative implications in some of the herbal products may not be farfetched. Some of the component plants extracts in these herbal products earlier associated with some adverse effects includes Aloe vera (genotoxicity, carcinogenicity), *Xathium sibiricum* (liver damage), Allismatis Rhizoma (nephrotoxicity), *Phellodendri cortex* (toxicity due to Berberine), *Viscum album* (arched back, dyspnoea, coma, death) [43,44,45,46,47]. Although some of the formulations contains plant extracts with reported activity in reversing toxicity; *Cortex montan, Lycii Fructus* and *Tridax procumbens* [48,49,50], possibility of chemical interactions between component biochemicals from different plant extracts used in the sample formulations could also contribute to the untoward effects.

Conclusion. All the herbal products investigated showed antidiabetic activity with two samples demonstrating better hypoglycaemic activity than the reference metformin, while another one was comparable. However, the varied effect of these herbal products on some biochemical parameters, and the damage caused to the liver, lungs and kidney within the short period of administration by some of the products, calls for caution in their consumption at chronic level associated with the management of diabetes mellitus.

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