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ANTIDIABETIC EFFECT OF *CLEOME RUTIDOSPERMA* DC AND *SENECIO BIAFRAE* (OLIV. & HIERN) EXTRACTS IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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ABSTRACT: The present study was carried out to investigate the effects of oral administration of aqueous extracts of *Cleome rutidosperma* leaves and *Senecio biafrae* roots on blood glucose, biochemical parameters, lipid profile, antioxidant enzymes activity and hepatic glucose regulating enzyme activities in Streptozotocin (STZ)-induced diabetic rats. STZ was administered as a single dose (60mg/kg wt, i.p.) to induce diabetes. The effects of the extracts were compared with the standard drug Glibenclamide (600µg/kg b.wt). The aqueous extract of both plants at different doses (125mg/Kg, 250mg/Kg and 500mg/Kg) administered orally to the diabetic rats for 28 days, produced significant ($p < 0.05$) decrease in the level of blood glucose, feed and water intake as well as serum cholesterol, triacylglycerols, low density lipoprotein (LDL), creatinine, urea, bilirubin and activity of liver marker enzymes such as AST, ALT, ALP and TBARS in liver and kidney. Treatment also produced significant ($p < 0.05$) increase in body weight, PCV, High density lipoprotein (HDL), Superoxide dismutase (SOD), Catalase (CAT), Glutathione-S-Transferase (GST) and Glutathione Reductase(GR). Administration of both extracts to STZ-diabetic rats accelerated hepatic glucokinase activity and inhibited gluconeogenesis enzymatic activity (glucose-6-phosphatase). Comparatively, the aqueous extract of *Cleome rutidosperma* leaves showed better activities than the *Senecio biafrae* roots aqueous extract. The present investigation suggests that *Cleome rutidosperma* leaves and *Senecio biafrae* roots aqueous extracts exhibit antihyperglycaemic, antihyperlipidaemic and antioxidant effects and consequently could prevent various complications of diabetes. The study has also provided evidence for the traditional usage of the plants in the control of diabetes.

INTRODUCTION: Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic disorder of carbohydrate, fat and protein metabolism that results from defects in both insulin secretion and/or insulin action.

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The disease is associated with reduced quality of life and increased risk factors for morbidity and mortality.

The long term hyperglycemia is an important factor in the development and progression of micro- and macrovascular complication, which include cerebrovascular,[1] neuropathy, nephropathy and cardiovascular diseases [2]. According to Palanduz *et al*., [3] diabetic complications are associated with over production of free radicals and accumulation of lipid peroxidation by products.

However, an array of enzymatic antioxidants, superoxide dismutases (SOD), catalase (CAT) defense mechanism are involved in the protection of free radicals induced oxidative damage.

Several drugs such as biguanides, sulfonylurea and thiazolidenediones are presently available to reduce hyperglycemia in diabetes mellitus [4]. The use of these drugs has accompanying side effects [5]. Hence, the search for safer and more effective hypoglycemic agents has continued. Ethnobotanical information indicates that plant species are used in the traditional management of diabetes [6]. The medicinal plants may provide the useful source of new oral hypoglycemic compounds for the development of pharmaceutical entities or as dietary adjunct to existing therapies [7].

Plants are endowed with various phytochemical molecules such as vitamins, terpenoids, phenolic, lignins, stilbenes, tannins, flavonoids, quinones, coumarins, alkaloids, amines, betalains, and other metabolites which are rich source of free radical scavengers [8]. They are also antioxidant compounds which possess anti-inflammatory, antiatherosclerotic, antitumor, antimutagenic, anticarcinogenic, antibacterial, and antiviral activities [9]. Ingestion of natural antioxidants has been associated with reduced risks of cancer, cardiovascular disease, diabetes, and other diseases associated with ageing. Phytochemicals isolated from plant sources have been used for the prevention and treatment of cancer, heart disease, diabetes mellitus and high blood pressure [10].

Cleome rutidosperma DC is a low-growing herb, up to 70 cm tall, found in waste grounds and grassy places with trifoliate leaves and small, violet-blue flowers, which turn pink as they age. The plant is native to West Africa, from Guinea to Nigeria, Zaire and Angola. It has become naturalized in various parts of tropical America as well as Southeast Asia. *Cleome rutidosperma* has been well studied by different researchers. The analgesic, antipyretic, anti-inflammatory, locomotory, antimicrobial, diuretic, laxative antioxidant, and antiplasmodial activities of the plant have already been reported [11].

Cleome rutidosperma is traditionally used in the treatment of paralysis, epilepsy, convulsions, spasm, earache, pain and skin disease.

Senecio biafrae (Oliv. & Hiern) is a perennial climbing herb which naturally occurs in African forest zones, from Guinea to Uganda. It is one of the green leafy vegetables consumed in Sierra Leone, Ghana, Benin, Nigeria, Cameroon and Gabon. Also, leaves of *Senecio biafrae* contain various secondary metabolites such as dihydroisocoumarins, terpenoids, sesquiterpenes or amino acids [12]. *Senecio biafrae* is equally known for its therapeutic virtues, notably in Nigeria where it is used in the treatment of diabetes or pulmonary defects [13]. The leaves and stems of *Senecio biafrae* are used either macerated in water or in palm wine by traditional healers to treat cases of women infertility [14].

This study was undertaken, based on our previous findings on the antihyperglycemic effect of *Cleome rutidosperma* leaves and *Senecio biafrae* roots, to further evaluate their antdiabetic activities using the aqueous extracts in STZ-induced diabetic rats. Also determined in this study are the effects of the extracts on carbohydrate metabolizing enzymes, renal and hepatic functions in rats, as well as *in vivo* antioxidant activities.

MATERIALS AND METHODS:

Reagents and Chemicals: All reagents and chemicals used were of analytical grade purchased from Sigma Chemical Company, St. Louis, Missouri, USA. The assay kits for the analyses of serum biochemical and lipid profile parameters were obtained from Randox Laboratories Limited, Ardmore, Co Antrim, UK.

Plant materials: The plants (*Cleome rutidosperma* and *Senecio biafrae*) were collected from Abraka in Delta State, Nigeria and Akoko in Ondo State, Nigeria, respectively in January 2013. They were identified by Dr. H. A. Akinnobosun of the Herbaruim Unit, Department of Plant Science, University of Benin, Benin City Edo State-Nigeria, where voucher specimens were deposited with numbers: UBHc0148 and UBHs0149.

Experimental Animals: Male Wistar Albino rats weighing 120-200g were obtained from National Veterinary Research Institute (NVRI) Vom, Jos, Plateau State, Nigeria. The animals were allowed 3 weeks of acclimatization before commencement of experiment. They were fed on standard laboratory diet (Vital Feed Nig. Ltd, Jos, Nigeria) and water *ad libitum* throughout the experiment.

Treatment and Extraction of plant samples: The plant samples were washed with distilled water and air-dried at room temperature, cut into small pieces and pulverized into fine powder using pestle and mortar. They were first extracted with petroleum ether and then distilled water by cold maceration method. Fifty grams powder of the plant was soaked in 200 ml of distilled water in airtight conical flask with daily shaking for three days at room temperature and were first filtered through double layered muslin cloth and then filtered through Whatman No 1filter paper and the filtrates were collected into airtight bottle. The filtrate was concentrated at 50^{o}C using water bath and the dried extract was stored in the refrigerator at 4^{o}C till further use.

Induction of Experimental Diabetes: Streptozotocin was dissolved in 10 mM citrate buffer pH 4.5. The rats (diabetic control and test rats) were injected intra-peritoneally with portions (1μL/g) of this solution at a dose of 60mg per kg body weight after an overnight fast. 3 days after development of diabetes, the rats with plasma glucose more than 200 mg/dl were considered as diabetic rats and were allowed for 2 weeks diabetic stabilization before being used for the experiment.

Antidiabetic Evaluation of Aqueous Plant Extracts: In order to investigate and compare the antidiabetic potential and sub-chronic toxicity of the two plant aqueous extracts, a total of 77 rats (56 diabetic rats and 21 normal rats) were divided into eleven groups of 7 rats each as follows:

Group A: Normal untreated rats

Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract

Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract

Group D: Diabetic control rats

Group E-G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.

Group H-J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae*.

Group K: Diabetic rats given reference drug, glibenclamide (600 μg/kg of body weight).

Rats in control group were given distilled water, while those in the treatment groups were given three different doses as stated above via the oral route for 28 days. Water and feed intake were measured daily while body weights of the rats, FBG and PCV were determined weekly and at the end of the study (day 29), the rats were euthanized in an airtight glass chamber saturated with chloroform and after opening up the rats surgically, blood samples were collected for the analyses below. Also, the organs (liver and kidney) were carefully excised, blotted and weighed. One gram (1 g) and half gram (0.5g) respectively of the liver and kidney was homogenized in 10 ml and 5ml respectively of 0.01 M phosphate buffer, pH 7.4, and centrifuged at 3,000xg to collect supernatant; which was used as organ extract.

Hepatic and renal function analyses: The activities of serum transaminases (ALT and AST), alkaline phosphatase, albumin, total protein and bilirubin (total and direct) were assayed using Randox assay kits by methods of Reitman and Frankel [15], Sood [16], Doumas *et al*. [17], Gornall *et al*. [18], Jendrassik and Grof [19] and Trinder [20], respectively.

Lipid profile analyses: The lipid profile assays were done using Randox kits: Serum total triacylglycerols concentrations, total cholesterol level and HDL-cholesterol concentrations were measured by the methods as described in the manuals of the kits, while the Serum LDL-cholesterol level was calculated by the method described in the manual of the Randox HDL-cholesterol kit.

Measurement of Carbohydrate Metabolizing Enzymes: Carbohydrate metabolizing enzymes in the liver were assayed by standard procedures:

Hepatic glucokinase activity was assayed by the method of Brandstrup *et al*. [21].

Liver glucose-6-phospatase activity was determined according to the method of Baginsky *et al*. [22].

Assay for Oxidative stress markers: Oxidative stress markers were determined in the supernatant fraction of the liver and kidney homogenates of each rat according to standard methods:

Glutathione reductase was assayed by the procedure of David and Richard [23], Glutathione S-transferase activity was assessed by the method of Habig *et al*., [24]. The concentration of TBARS in the tissues was estimated by the method of Nichans and Samuelson [25], while Catalase activity was determined by the method of Aebi [26]. The method of Misra and Fridovich [27] was used to estimate the superoxide dismutase (SOD) activity in the organs.

Statistical analysis: Data are reported as mean ± SD and were analyzed using ANOVA followed by Tukey Kramer multiple comparison test in Graphpad Prism, version 6.0 0 (Graph Pad Software, San Diego, CA, USA).and values of P< 0.05 were considered significant.

RESULTS:

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on weekly water and feed intake in streptozotocin-induced diabetic rats. Figure 1 shows the effect of aqueous extract of the extracts on weekly water intake in both normal and diabetic rats. There was significant increase ($p<0.05$) in water intake in diabetic control group, while the extracts of both plants significantly ($p<0.05$) prevented this diabetes-induced polydipsia. Although, there were slight differences in the weekly water intake among the diabetic treated rats and the normal control group, these were not significant ($p<0.05$). Similarly, there was significant increase ($p<0.05$) in the feed intake in diabetic control group, but treatment with both plant extracts and the standard drug, also prevented the diabetes-induced polyphagia significantly ($p<0.05$) as shown in **figure 2**. Also, no significant ($p<0.05$) difference was observed among the diabetic treated rats and normal control rats.

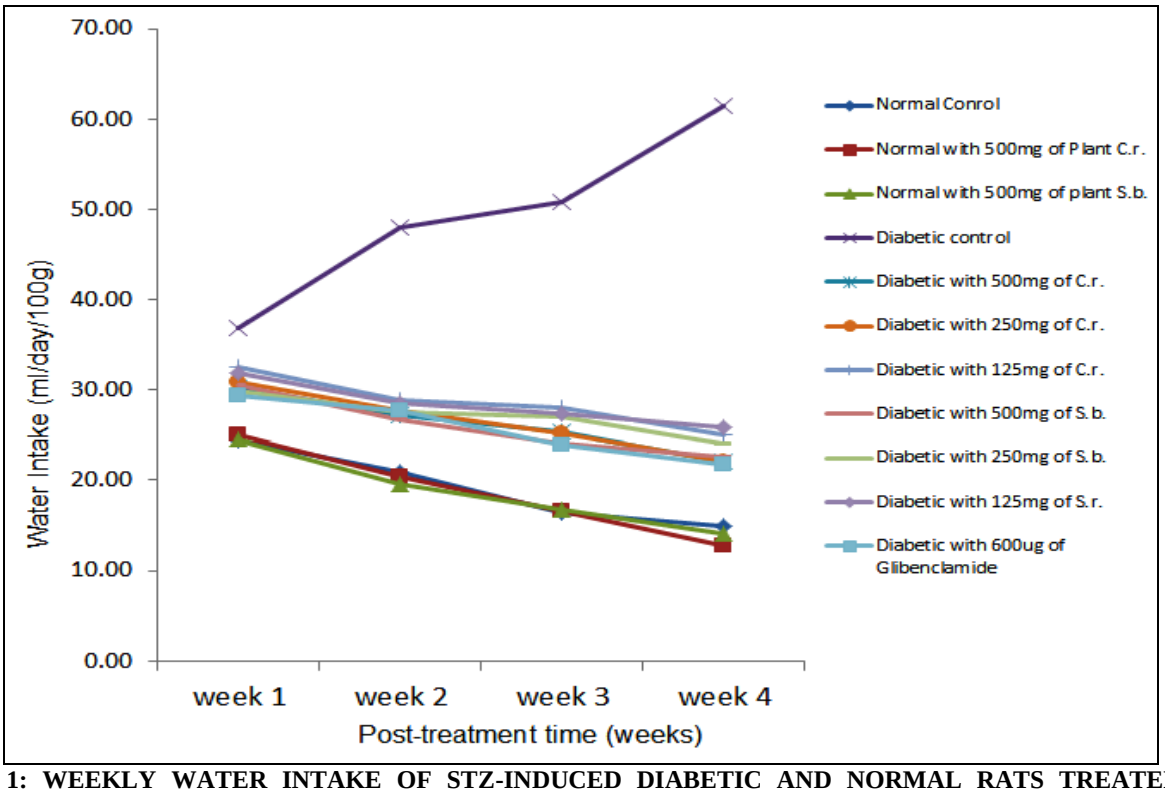

FIGURE 1: WEEKLY WATER INTAKE OF STZ-INDUCED DIABETIC AND NORMAL RATS TREATED WITH VARIOUS DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* (C.r.) AND *SENECIO BIAFRAE* (S.b.)

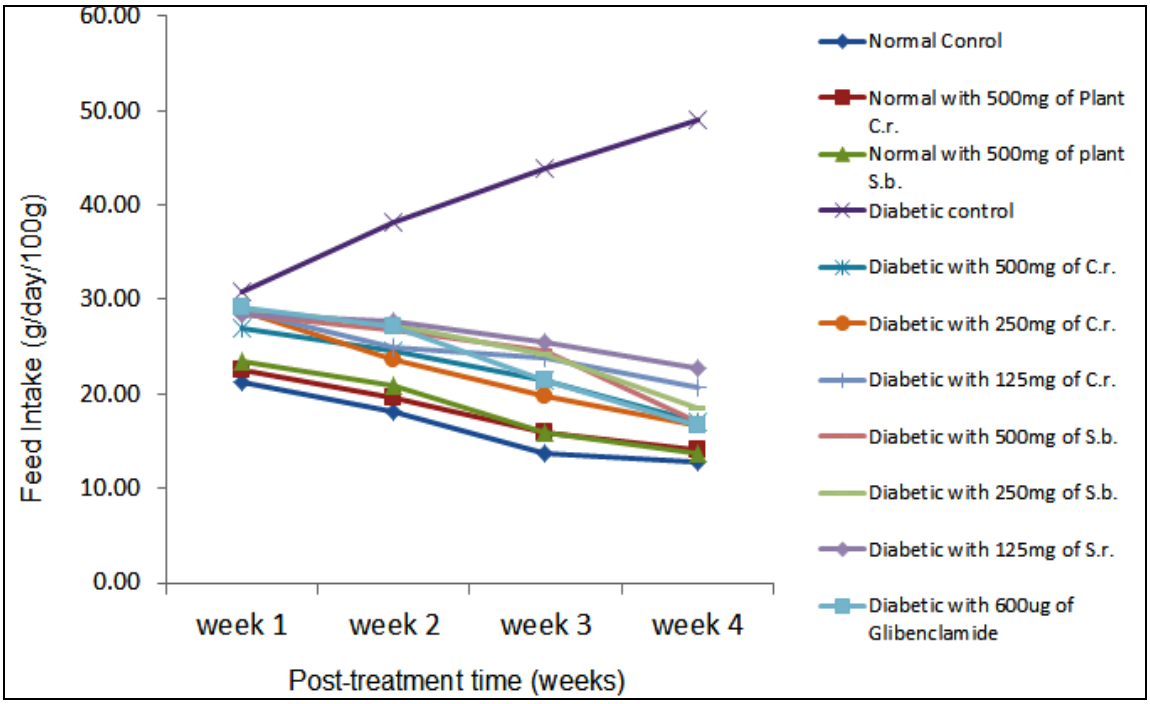

FIGURE 2: WEEKLY FEED INTAKE OF STZ-INDUCED DIABETIC AND NORMAL RATS TREATED WITH VARIOUS DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* (C.r.) AND *SENECIO BIAFRAE* (S.b.).

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on weekly body weight in streptozotocin-induced diabetic rats. Although, significant increases were seen in the water and feed intakes for the diabetic control group (above), however, a significant ($p<0.05$) weight loss was observed in this group. This weight loss which is usually associated with STZ diabetic rats was nevertheless reversed to a considerable extent by treatment with both plant extracts and the standard drug (**figure 3**).

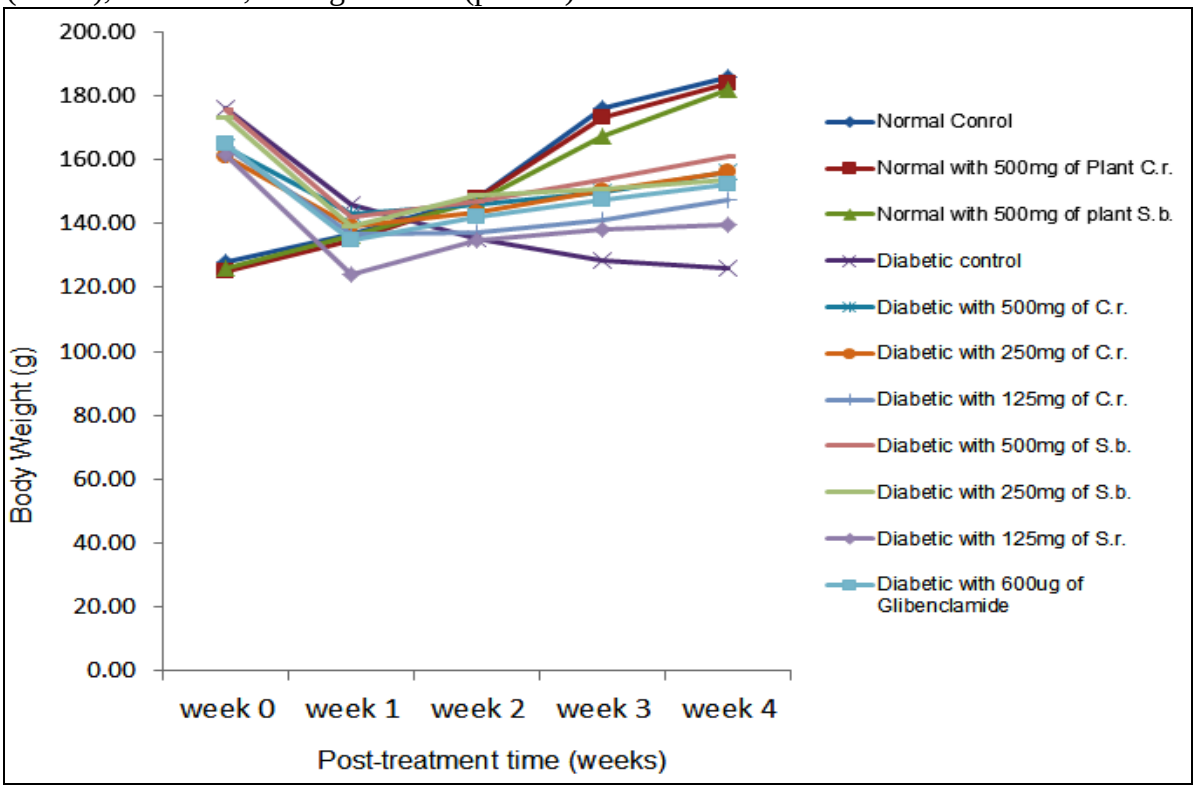

FIGURE 3: WEEKLY BODY WEIGHTS OF STZ-INDUCED DIABETIC AND NORMAL RATS TREATED WITH VARIOUS DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* (C.r.) AND *SENECIO BIAFRAE* (S.b.)

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on weekly fasting blood glucose in streptozotocin-induced diabetic rats: The effect of the aqueous extracts of both plants on fasting blood glucose is shown in **figure 4**. There was significant (P<0.05) increase in fasting blood glucose for the diabetic control group when compared with the normal control. On the other hand, steady significant (P<0.05) decrease in FBG was observed in all treated groups when compared with the diabetic control group, from week one up to week four post treatment . The maximum blood glucose lowering effect of both plant extracts and standard drug on diabetic rats was observed at week four. The percentage blood glucose reduction (**Table 1**) of the different doses of the two plant extracts at week four were from 12.28±8.37 to 57.77±5.05 for *Cleome rutidosperma* and 3.03±5.19 to 46.43±7.55 for *Senecio biafrae* respectively, while the standard drug, glibenclamide reduced the blood glucose level by 44.74±9.24%. On the contrary, there was a steady increase of FBG in the diabetic control group throughout the experimental period. Thus the extracts had greater blood glucose lowering effect than the standard drug, glibenclamide at 500mg/kg body weight for both plant extracts.

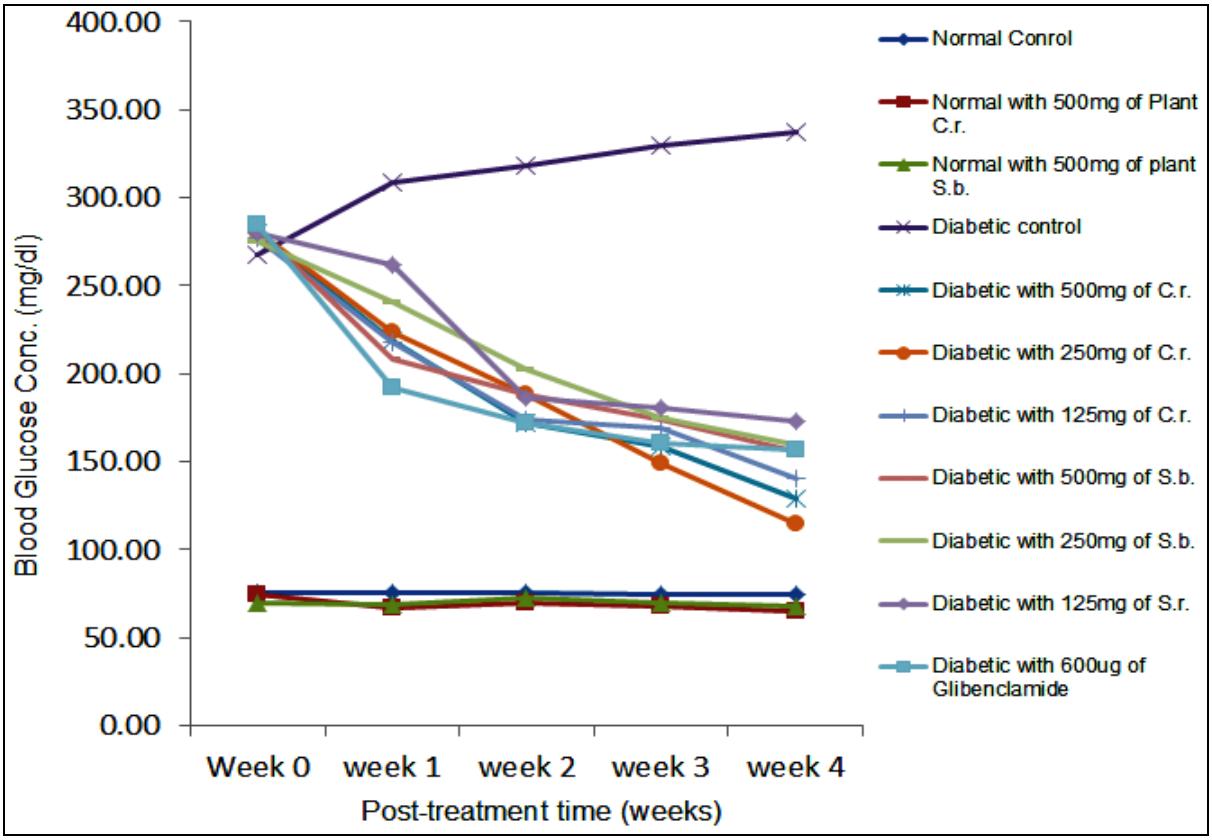

FIGURE 4: WEEKLY FASTING BLOOD GLUCOSE OF STZ-INDUCED DIABETIC RATS TREATED WITH VARIOUS DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* (C.r.) AND *SENECIO BIAFRAE* (S.b.)

TABLE 1: PERCENTAGE DECREASE IN FBG AT WEEK 4 AFTER TREATMENT WITH VARIOUS DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* AND GLIBENCLAMIDE

GROUP	% Decrease in FBG at Week 4 post-treatment *Cleome rutidosperma*	GROUP	% Decrease in FBG at Week 4 post-treatment *Senecio biafrae*
A	1.38±4.64[a]	A	1.38±4.64[a]
B	12.28±8.37[b]	C	3.03±5.19[a]
D	-30.44±17.57[c]	D	-30.44±17.57[b]
E	55.00±3.54[b]	H	46.43±7.55[c]
F	57.77±5.05[b]	I	42.76±5.36[c]
G	47.20±9.24[b]	J	42.76±5.36[c]
K	44.74±9.24[b]	K	44.74±9.24[c]

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different (p<0.05). Negative value means an increase in FBG.

Where Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.,Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on weekly PCV profile in streptozotocin-induced diabetic rats: As shown in **figure 5**, the PCV of the untreated diabetic animals were significantly lower (P<0.05) than those of either the normal control group or those given different doses of both plant extracts (*Cleome rutidosperma* and *Senecio biafrae*) and that of diabetic rats treated with the standard drug, glibenclamide. There were however no significant differences among the diabetic rats treated with either plant extracts or the normal control rats.

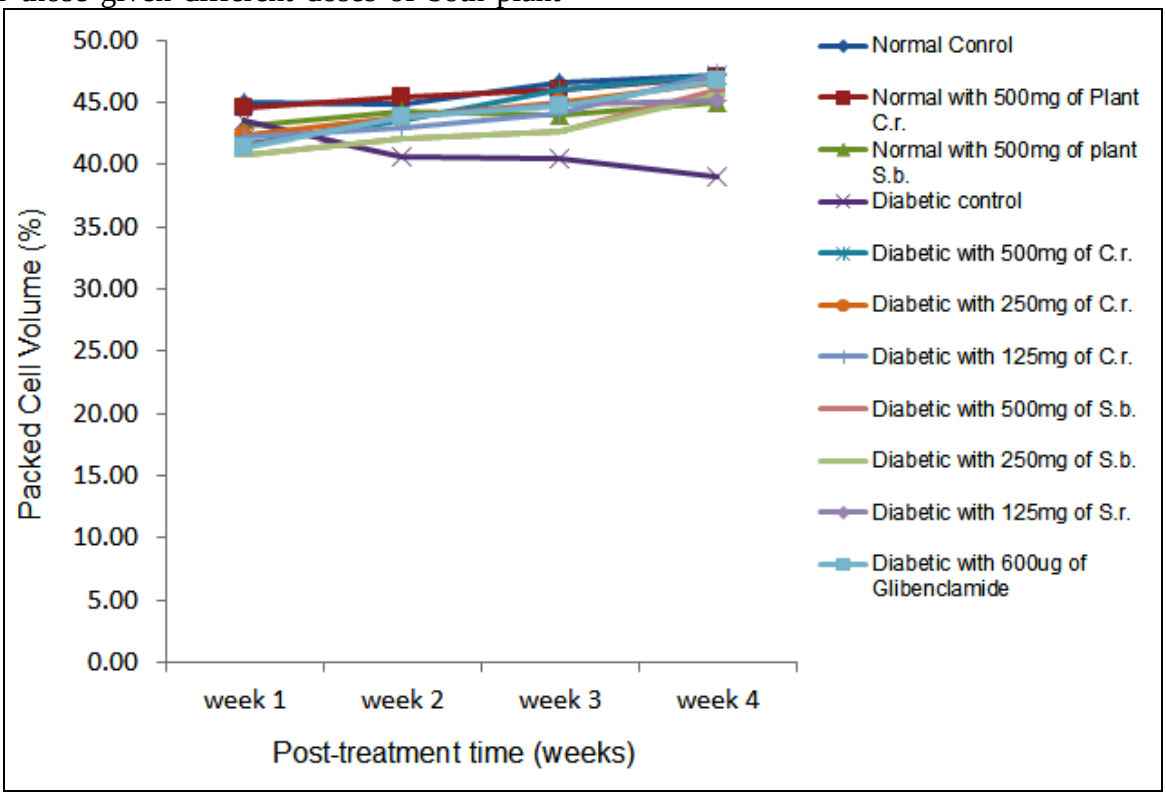

FIGURE 5: WEEKLY PCV OF STZ-INDUCED DIABETIC AND NORMAL RATS TREATED WITH VARIOUS DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* (C.r.) AND *SENECIO BIAFRAE* (S.b.)

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on organ weight in streptozotocin-induced diabetic rats after 28 days. Data on relative organ weight when aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* were orally administrated to the STZ-induced diabetic rats for 28 days are shown in **Table 2**. The relative weights of liver and kidney (but not the heart) were significantly increased in diabetic control rats (p<0.05) when compared with the normal control rats. Significant decreases (p<0.05) were seen in relative weights of liver and kidney for all treated rats when compared with the diabetic control rats.

Although decrease in the relative weight of the heart was observed in all treated groups when compared to the diabetic control group, the decreases were not significant. Thus, administration of the extracts reversed the increase in relative weights of liver and kidney seen in the diabetic state.

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on serum biochemical parameters in streptozotocin-induced diabetic rats after 28 days: The effects of the plant extracts on Biochemical parameters are shown in **Table 3**.

TABLE 2: EFFECT OF ORAL ADMINISTRATION OF DIFFERENT DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* ON RELATIVE ORGAN WEIGHT (G/KG BODY WEIGHT) IN STZ-INDUCED DIABETIC RATS

Group	Heart	Kidney	Liver
A	0.38±0.07	0.56±0.05[a]	2.94±0.29[a]
B	0.34±0.02	0.55±0.04[a]	3.03±0.40[a]
C	0.37±0.07	0.54±0.09[a]	2.81±0.42[a]
D	0.64±0.06	1.90±0.68[c]	5.55±0.88[b]
E	0.37±0.04	0.74±0.06[a]	3.71±0.84[a]
F	0.41±0.08	0.69±0.11[a]	4.06±0.98[a]
G	0.41±0.08	0.75±0.11[a]	4.04±0.72[a]
H	0.36±0.03	0.80±0.10[a]	3.63±0.56[a]
I	0.42±0.12	0.82±0.05[a]	4.08±0.40[a]
J	0.43±0.06	0.80±0.09[a]	4.14±0.31[a]
K	0.42±0.08	0.77±0.09[a]	3.78±0.34[a]

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different ($p<0.05$).

Where Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.,Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

There was significant increase ($p<0.05$) in serum Alanine transaminase (ALT) in diabetic control rats when compared with normal control ones, while a significant decrease ($p<0.05$) was observed in groups E, F and H compared with the diabetic control, but the decrease seen in groups G, I, J and K were not significant when compared with the diabetic control group in serum ALT.

Also in serum Aspartate transaminase (AST), significant decrease ($p<0.05$) was observed in all treated diabetic groups (except group J) when compared with the diabetic control group, while a significant ($p<0.05$) increase was seen in the diabetic group when compared with the normal control group.

The serum Alkaline Phosphatase (ALP) was significantly ($p<0.05$) higher in diabetic control group and lower ($p<0.05$) in the treated diabetic groups.

Significant ($p<0.05$) increases were observed in serum Total Bilirubin (T.BIL) and Direct Bilirubin (D. BIL) for the diabetic control group while a decrease in the two parameters was observed in all diabetic treated groups. However, the serum Total Protein (TP) and Albumin (Alb) were significantly lower ($p<0.05$) in the diabetic control group and higher ($p<0.05$) in all treated diabetic groups.

On the other hand, groups E, F, H and K were significantly ($p<0.05$) lower when compared with the diabetic control group, while groups G, I and J were not significant for serum Creatinine (CREA). Also, an increase ($p<0.05$) in the urea level for diabetic control group was observed and a decrease ($p<0.05$) was seen in treated diabetic groups (except group J).

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on lipid profile in streptozotocin-induced diabetic rats after 28 days: The effect of extracts on serum total cholesterol, total triacylglycerols and low density lipoprotein levels are presented in **Table 4**. The serum triacylglycerols (TRIGS), total cholesterol (CHOL) and low density lipoprotein (LDL)-cholesterol levels were significantly ($P<0.05$) higher in untreated diabetic rats compared with the normal control rats. This dyslipidaemia in the diabetic rats was prevented by administration of both plant extracts and glibenclamide.

Thus, there was significant reduction ($p<0.05$) in the levels of serum triacylglycerols, total cholesterol and low density lipoprotein (LDL)-cholesterol in the groups treated with both plant extracts and the standard drug when compared with the diabetic control group.

On the other hand, the (HDL)-cholesterol level was significantly ($p<0.05$) lower in the diabetic control group compared with the normal rats. An increased (HDL)-cholesterol level was observed in rats treated with both plant extracts and glibenclamide.

TABLE 3: SERUM BIOCHEMICAL CHANGES FOLLOWING ORAL ADMINISTRATION OF DIFFERENT DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* IN STREPTOZOTOCIN-INDUCED DIABETIC RATS AFTER 28 DAYS

GROUP	ALT (U/L)	AST (U/L)	ALP (U/L)	T.BIL (mg/dl)	D.BIL (mg/dl)	TP (mg/dl)	Alb (g/dl)	CREAT (mg/dl)	UREA (mg/dl)
A	22.38±1.05^{a}	15.14±1.81^{a}	89.11±7.92^{a}	0.12±0.02^{a}	0.63±0.06^{a}	10.47±0.98^{a}	3.56±0.34^{a}	2.35±0.72^{a}	29.66±4.90^{a}
B	23.34±1.84^{a}	17.54±1.92^{a}	90.01±3.74^{a}	0.10±0.01^{a}	0.52±0.08^{a}	11.08±0.85^{a}	3.15±0.55^{a}	2.40±0.77^{a}	25.81±5.59^{a}
C	22.27±1.70^{a}	16.09±1.51^{a}	93.46±5.86^{a}	0.12±0.01^{a}	0.58±0.04^{a}	9.92±0.90^{a}	3.11±0.33^{a}	2.81±0.72^{a}	28.40±3.97^{a}
D	31.91±1.47^{b}	27.40±1.69^{b}	156.91±5.85^{b}	0.23±0.02^{b}	0.89±0.03^{b}	5.53±0.73^{b}	1.80±0.20^{b}	5.19±0.61^{b}	50.15±4.76^{b}
E	23.77±2.05^{a}	18.23±2.97^{a}	118.34±7.11^{c}	0.17±0.01^{c}	0.69±0.07^{a}	8.14±0.49^{c}	3.38±0.39^{a}	3.17±0.71^{a}	35.83±3.95^{a}
F	24.61±1.91^{a}	17.81±2.37^{a}	120.76±10.76^{c}	0.15±0.01^{a}	0.70±0.08^{a}	9.07±0.74^{a}	3.17±0.48^{a}	3.11±0.61^{a}	34.95±6.76^{a}
G	27.47±2.71^{b}	21.44±1.72^{c}	125.80±6.79^{c}	0.18±0.02^{d}	0.71±0.06^{a}	8.22±1.78^{c}	2.62±0.36^{b}	3.78±0.79^{ab}	35.50±2.74^{a}
H	23.34±1.10^{a}	20.11±1.99^{a}	110.90±9.33^{c}	0.17±0.01^{d}	0.73±0.05^{a}	8.35±0.66^{c}	3.07±0.12^{a}	3.12±0.94^{a}	31.33±3.19^{a}
I	28.21±1.99^{a}	20.29±5.04^{a}	131.05±10.02^{c}	0.18±0.02^{d}	0.71±0.08^{a}	7.09±0.49^{b}	3.04±0.17^{a}	3.68±0.49^{ab}	34.24±2.57^{a}
J	29.40±3.54^{a}	25.11±1.98^{b}	140.37±10.44^{b}	0.21±0.03^{c}	0.75±0.08^{ab}	7.16±0.77^{b}	2.85±0.55^{a}	3.78±0.51^{ab}	42.66±3.45^{b}
K	28.02±2.15^{a}	21.73±1.69^{d}	125.39±6.86^{c}	0.17±0.03^{d}	0.73±0.07^{a}	8.23±0.30^{c}	3.28±0.78^{a}	3.30±0.79^{a}	37.24±2.82^{a}

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different ($p<0.05$).

Where Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*., Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

TABLE 4: EFFECT OF ORAL ADMINISTRATION OF DIFFERENT DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* ON LIPID PROFILE IN STREPTOZOTOCIN-INDUCED DIABETIC RATS AFTER 28 DAYS

GROUP	CHOL (mg/dl)	C-HDL (mg/dl)	TRIGS (mg/dl)	LDL (mg/dl)
A	76.92±10.34[a]	23.06±1.25[a]	35.71±5.50[a]	46.15±8.10[a]
B	77.99±8.59[a]	23.07±0.92[a]	36.67±6.18[a]	47.58±7.88[a]
C	75.19±6.86[a]	23.79±1.97[a]	34.86±8.03[a]	44.43±5.14[a]
D	162.64±11.30[b]	17.60±0.45[b]	94.00±11.17[b]	126.65±5.46[b]
E	80.53±5.76[a]	23.32±1.07[a]	50.00±7.01[a]	47.61±6.27[a]
F	90.22±5.27[a]	24.00±0.87[a]	52.40±5.85[c]	55.73±6.22[a]
G	95.95±6.45[c]	24.72±1.05[a]	58.00±5.89[c]	59.93±7.14[a]
H	78.84±8.90[a]	23.59±1.68[a]	48.80±6.88[a]	45.09±9.65[a]
I	87.37±8.61[a]	22.27±1.09[a]	53.60±6.37[c]	54.38±4.40[a]
J	85.97±9.96[a]	23.24±0.86[a]	56.00±9.59[c]	51.54±8.75[a]
K	92.21±10.33[a]	22.98±1.77[a]	55.60±8.24[c]	58.47±6.42[a]

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different ($p<0.05$).

Where Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.,Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on oxidative stress markers in streptozotocin-induced diabetic rats after 28 days: A significantly elevated level of thiobarbituric acid reactive substances (TBARS) was observed in diabetic control rats for both liver and kidney when compared with normal control rats (**Table 5 and 6**). However, the TBARS levels in diabetic rats treated with either extracts or glibenclamide were significantly ($p<0.05$) lower than the diabetic control group in both liver and kidney except the glibenclamide group which was not significant in the liver.

The activities of superoxide dismutase (SOD) were significantly higher in diabetic rats treated with both plant extracts or glibenclamide compared to diabetic control rats ($p < 0.05$) in the liver and kidney (Table 5 and 6). There was significant decrease ($p<0.05$) in the diabetic group when compared with the normal control in both organs.

There were non-significant differences in Catalase (CAT) activity in groups G, I and K (in the liver) and groups G, I, J and K (in the kidney) when compared with the diabetic control group.

However, the activities of CAT in diabetic rats treated with both plant extracts and glibenclamide in groups E, F and H (liver) and groups E, F, H and I (kidney) were significantly higher ($p < 0.05$) than the diabetic control rats, while the diabetic control rats were significantly lower in CAT activity when compared with the normal control group.

A significant decrease ($p<0.05$) in the Glutathione S-transferase (GST) activity in the diabetic control group when compared with the normal control was observed for both liver and kidney. Also, the GST activity was significantly higher ($p<0.05$) than the diabetic control group in groups E, F, H and I (liver) and groups E, F, G, H and I (kidney). Although the GST activity in groups G, J and K (liver), J and K (kidney) were higher than the diabetic control rats, but these were not significant.

The Glutathione reductase (GR) activity was significantly ($p < 0.05$) lower in the diabetic control group than the normal control rats. There was significant increase ($p < 0.05$) in GR activity in groups F, H and K when compared with the diabetic control group, while in groups E, G, I and J, though higher values were seen, but the values were not significant.

TABLE 5: EFFECT OF ORAL ADMINISTRATION OF DIFFERENT DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* ON OXIDATIVE STRESS MARKERS IN LIVER OF STREPTOZOTOCIN-INDUCED DIABETIC RATS

GROUP	LIVER TBARS (n moles/g tissue)	LIVER SOD (Units/mg protein)	LIVER CAT (Units/mg protein)	LIVER GST (Units/mg protein)	LIVER GR (Units/mg protein)
A	7.17±0.83^{a}	42.80±2.59^{a}	18.89±2.93^{a}	122.82±8.10^{a}	4.04±0.30^{a}
B	8.94±1.00^{a}	40.69±2.13^{a}	17.57±1.64^{a}	116.01±9.74^{a}	3.34±0.71^{a}
C	8.95±1.05^{a}	42.38±3.88^{a}	16.00±3.58^{a}	120.25±9.29^{a}	3.49±0.49^{a}
D	12.66±1.01^{b}	15.98±1.49^{b}	7.72±0.83^{b}	63.67±5.09^{b}	1.08±0.13^{b}
E	8.08±0.76^{a}	28.39±2.15^{c}	13.39±0.98^{c}	97.77±2.43^{c}	2.07±0.36^{bc}
F	6.00±0.35^{a}	31.05±1.56^{c}	14.94±2.21^{c}	92.72±14.27^{c}	2.66±0.54^{c}
G	9.11±0.89^{a}	28.11±9.02^{c}	12.18±1.94^{b}	78.77±8.29^{bc}	2.06±0.34^{bc}
H	9.36±1.18^{c}	28.09±3.10^{c}	13.53±1.01^{c}	92.03±10.94^{c}	2.36±0.49^{c}
I	7.63±0.84^{a}	29.12±4.20^{c}	12.22±1.65^{b}	89.61±11.85^{c}	2.14±0.38^{bc}
J	7.06±1.19^{a}	20.72±3.88^{b}	13.19±2.52^{c}	74.41±4.60^{bc}	2.01±0.50^{bc}
K	10.78±1.41^{a}	24.85±3.81^{b}	12.70±1.40^{b}	77.39±5.48^{bc}	2.85±0.85^{c}

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different ($p<0.05$).

Where One unit was defined for SOD as: the amount of enzyme giving a 50% inhibition of the reduction of Nitroblue tetrazolium (NBT); CAT as µmol of H_2O_2 consumed per minute; GST as µmol of 1-chloro- 2,4-dinitrobenzene(CDNB) conjugate formed per minute; GR as µmol of CDNB conjugated per minute. Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.,Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

TABLE 6: EFFECT OF ORAL ADMINISTRATION OF DIFFERENT DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* ON OXIDATIVE STRESS MARKERS IN KIDNEY OF STREPTOZOTOCIN-INDUCED DIABETIC RATS

GROUP	KIDNEY TBARS (n moles/g tissue)	KIDNEY SOD (Units/mg protein)	KIDNEY CAT (Units/mg protein)	KIDNEY GST (Units/mg protein)
A	9.64±0.93^{a}	18.00±2.13^{a}	16.00±2.87^{a}	96.67±9.59^{a}
B	7.35±0.86^{b}	16.45±1.84^{a}	15.86±1.74^{a}	95.74±13.02^{a}
C	9.16±1.25^{a}	17.08±1.74^{a}	15.06±2.57^{a}	91.72±11.87^{a}
D	13.59±0.73^{c}	6.25±0.74^{b}	5.37±0.19^{b}	52.55±4.90^{b}
E	9.65±0.62^{a}	12.86±1.10^{c}	10.25±1.53^{c}	80.83±10.86^{a}
F	10.68±0.58^{a}	13.51±0.96^{c}	10.65±1.47^{c}	79.34±6.53^{a}
G	9.95±0.91^{a}	8.80±1.28^{b}	9.15±1.35^{b}	77.16±12.87^{a}
H	10.84±0.52^{a}	13.69±1.60^{c}	10.87±2.58^{c}	103.19±6.32^{a}
I	10.22±0.92^{a}	11.30±1.51^{c}	9.20±1.85^{b}	91.24±11.96^{a}
J	9.14±1.30^{a}	8.79±0.87^{b}	8.56±1.38^{b}	74.46±13.84^{b}
K	8.88±0.61^{a}	9.27±0.78^{b}	8.77±1.66^{b}	77.00±5.09^{a}

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different ($p<0.05$).

Where One unit was defined for SOD as: the amount of enzyme giving a 50% inhibition of the reduction of Nitroblue tetrazolium (NBT); CAT- µmol of H_2O_2 consumed per minute; GST as µmol of 1-chloro- 2,4-dinitrobenzene(CDNB) conjugate formed per minute. Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.,Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

Effect of aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* on carbohydrate metabolizing enzymes in streptozotocin-induced diabetic rats after 28 days: The effect of *Cleome rutidosperma* and *Senecio biafrae* extracts on carbohydrate metabolizing enzymes in streptozotocin-induced diabetic rats is shown in **Table 7**: Glucose 6 phospatase (G6Pase) activity was significantly lower ($p<0.05$) in diabetic group when compared with normal control group, while G6Pase activity was significantly increased in all treated diabetic groups (except group J) compared with the diabetic control group.

The diabetic rats showed low activity of glucokinase (GCK).Treatment with the plant extracts and glibenclamide significantly ($P < 0.05$) increased the glucokinase activity when compared with the control group in a dose-dependent manner in groups E, F, G, H and K (Table 7). However, the activity of GCK was significantly higher than the diabetic control in groups I and J.

TABLE 7: EFFECT OF ORAL ADMINISTRATION OF DIFFERENT DOSES OF AQUEOUS EXTRACTS OF *CLEOME RUTIDOSPERMA* AND *SENECIO BIAFRAE* ON CARBOHYDRATE METABOLIZING ENZYMES (GLUCOSE 6- PHOSPHATASE AND GLUCOKINASE) IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

GROUP	Liver G6Ptase (Units/mg protein)	Liver Glucokinase (Units/mg protein)
A	0.18 ± 0.05^{a}	177.33 ± 13.27^{a}
B	0.20 ± 0.07^{a}	178.24 ± 17.66^{a}
C	0.21 ± 0.05^{a}	173.34 ± 11.75^{a}
D	0.50 ± 0.07^{b}	115.89 ± 11.62^{b}
E	0.27 ± 0.05^{a}	151.15 ± 13.47^{a}
F	0.26 ± 0.08^{a}	163.67 ± 22.86^{a}
G	0.27 ± 0.05^{a}	160.25 ± 11.06^{a}
H	0.31 ± 0.07^{c}	150.20 ± 14.16^{a}
I	0.33 ± 0.06^{c}	140.17 ± 13.13^{a}
J	0.40 ± 0.05^{b}	135.60 ± 14.07^{b}
K	0.31 ± 0.03^{c}	153.80 ± 8.77^{a}

Values are mean of seven determination ± SD; Values with different superscripts along a column are statistically different ($p<0.05$).

Where one unit was defined for G6Ptase as µmol of Pi liberated per minute and Glucokinase as µmol of glucose-6-phosphate formed per minute. Group A: Normal untreated rats ,Group B: Normal rats given 500mg/kg body weight of *Cleome rutidosperma* extract, Group C: Normal rats given 500mg/kg body weight of *Senecio biafrae* extract, Group D: Diabetic control rats, Group E, F & G: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Cleome rutidosperma*.,Group H, I & J: Diabetic rats given 500, 250 and 125 mg/kg body weight respectively of aqueous extracts of *Senecio biafrae* and Group K: Diabetic rats given reference drug, glibenclamide (600 µg/kg of body weight).

DISCUSSION: Use of herbal medicine is a common practice in many countries, particularly in Asia and Africa. The currently available drug regimens for management of diabetes mellitus have certain drawbacks and therefore, there is a need to find safer and more effective antidiabetic drugs [28].

Diabetes mellitus of long duration is associated with several complications such as atherosclerosis, myocardial infarction, nephropathy etc. These complications have long been assumed to be related to chronically elevated glucose level in blood.

Hyperglycemia leads to hyperosmolarity and reduction of intracellular water [29]. It also causes a negative energy balance and enhanced hunger in diabetic patients. The enhanced blood glucose level spills over into the kidney as well as increasing an osmotic diuresis leading to polyuria.

STZ-induced diabetes is characterized by a severe loss of body weight. Glibenclamide is often used as a standard antidiabetic drug in STZ-induced moderate diabetes to be compared with a variety of hypoglycemic compounds and its effectiveness is known [30, 31].

However, in this study, the above drugs did not normalize the body weight completely as it remained less than that of control rats.

A significant decrease in the body weights of diabetic animals as seen from the results after induction of diabetes with streptozotocin, agrees with the finding of Oyedemi *et al*., [32] who observed similar effect on diabetic animals induced with streptozotocin. This reduction has been linked to degradation of structural proteins and muscle wasting.

Oral administration of both plant extracts and glibenclamide administration was able to improve the body weight of the animals. The result indicated that both extracts possess the ability of managing glucose level as well as controlling muscle wasting and induced adipogenesis [33].

The feed and water intake of the diabetic rats were significantly increased as compared with the normal rats, while a decrease was seen in the treated groups. These symptoms are well known markers of diabetes in both human and animal models which are direct consequence of insulin deficiency. Increased water consumption of the diabetic rats as shown could be explained by the fact that the higher sugar level in the blood causes an increase in osmotic diuresis, resulting in large quantities of urine to be passed. Thirst and hunger are compensatory responses to the loss of fluid and the inability to utilize nutrients [34]. The feed and water intake were significantly reduced after administration of *Cleome rutidosperma* and *Senecio biafrae* extracts.

In this study, continuous treatment with the leaf extract of *Cleome rutidosperma* and root extract of *Senecio biafrae* for a period of 4 weeks caused significant decrease($p<0.05$) in blood glucose level of treated rats compared to untreated diabetic rats in a dose dependent manner (figure 4). The antihyperglycemic activities of the plants were comparable with glibenclamide, a standard hypoglycemic drug.

Comparatively, *Cleome rutidosperma* produced the most significant reductions of blood glucose levels in treated diabetic rats. Some plants extracts are reported to exert hypoglycemic action by potentiating the insulin effect, either by stimulating the pancreatic secretion of insulin from the cells of islets of Langerhans [35] or its release from bound insulin, while others act through extra pancreatic mechanisms by inhibition of hepatic glucose production or corrections of insulin resistance [36]. The plants extracts may have acted through one of the above mechanisms. Phytochemical compounds like phenols, tannins, alkaloids, steroids, cardiac glycosides and terpenes which have been demonstrated to be present in extracts of the plant in our previous work may be responsible for their antidiabetic activities [37]. The plausible mechanism of action of these herbs are still unclear but may be elucidated in ongoing research on these plants**.**

The significant decrease ($P<0.05$) in the level of packed cell volume (PCV) in diabetic control rats (figure 5) compared with the control group may be as a result of the cellular damage on the erythrocyte membrane as a result of oxidative stress imposed by diabetes [38].

The increased liver weight in STZ-induced diabetic rats as seen reflected liver hypertrophied due to abnormal glycogen metabolism, accumulated acetyl-CoA, increased fat synthesis and accumulation of fat in the liver due to inhibition of insulin secretion [39].

When diabetes mellitus (DM) occurs, the free fatty acid produced by decomposition of body fat due to lack of insulin is transferred into the liver. Triacylglycerols are synthesized and accumulates in the liver and eventually make the weight of liver to increase. It is known that the reason why the weight of kidney is increased is that when diabetes mellitus occurs, the size and volume of kidney are increased together with increase of glomerular filtration rate as the burden of kidney is getting bigger due to increase of urine excretion. In diabetic rats, the kidneys can become hypertrophic due to the metabolism of glucose to UDP-glucose or glycogen that accumulates in the medangial cells in the glomerulus or discharge of glucose and increase of RNA and DNA synthesis that promotes cell division of the kidney. Diabetic glomerular hypertrophy constitutes an early event in the progression of glomerular pathology which occurs in the absence of mesengial expansion[40].

The elevation of liver biomarker enzymes, such as AST, ALT and ALP in diabetic control rats (Table 3) indicates that diabetes may induce hepatic dysfunction [41].

It has been found by Larcan *et al*., [42] that liver was necrotized in diabetic patients. Therefore, the increment of the activities of AST, ALT and ALP in serum may be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream [43], which gives an indication that diabetes causes hepatic damage. On the other hand, treatment of the diabetic rats with either extract of *Cleome rutidosperma* or *Senecio biafrae* or glibenclamide caused reduction in the activity of these enzymes in serum (Table 3) when compared to the mean values of diabetic control group.

Although there was an increase in serum bilirubin ($p < 0.05$) in diabetic control rats when compared with the normal control rats, *Cleome rutidosperma* and *Senecio biafrae* administration caused significant ($p < 0.05$) decrease in serum bilirubin of STZ-diabetic rats compared to the diabetic control rats.

Rana *et al*., [44] reported that the increase in plasma bilirubin (hyper-bilirubenimia) may result from the decrease of liver uptake, conjugation or increase bilirubin production from hemolysis. Also, the elevation in serum bilirubin indicates liver damage as confirmed by the changes in the activities of serum and liver enzymes.

Serum albumin and total protein are some of the markers of liver dysfunction. Albumin is known for transportation of bilirubin and other substances in blood [45]. Significant increase in the level of albumin may indicate that the synthetic function of the liver has not been significantly affected yet and also suggest that free albumin is elevated due to the decreased level of bilirubin in tested animals. Bilirubin formed from breakdown of red blood cells in the reticulo endothelial cells are transported in plasma bound to albumin [45], thus the decrease in bilirubin level is as a result of reduction in the natural oxidative break down of red blood cells and may account for the observed increase in albumin, as less albumin was bound in the treated rats.

It therefore seems that the plant extracts (*Cleome rutidosperma* and *Senecio biafrae*) might provide resistance to oxidative break down of red blood cells membranes and may be considered safe.

Hyperglycemia increases the generation of free radicals by glucose auto-oxidation and the increment of free radicals may lead to kidney cells damage [46].

The main function of the kidneys is to excrete the waste products of metabolism and to regulate the body concentration of water and salt. Diabetic hyperglycemia has been shown to induce elevation of plasma levels of urea and creatinine which are considered as significant markers of renal dysfunction. The significant ($p < 0.05$) increase in the level of serum urea and creatinine in the diabetic control group when compared with normal control group as shown in Table 3, indicates that diabetes could lead to renal dysfunction [47]. While after treatment of STZ-diabetic rats with aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* or glibenclamide, the level of urea was significantly ($p < 0.05$) decreased in serum compared to the mean value of diabetic control group.

The serum triacylglycerols, total cholesterol and low density lipoprotein (LDL)-cholesterol concentrations were seen to be significantly ($P<0.05$) higher in untreated diabetic rats and HDL-cholesterol was lower compared with the normal control (Table 4). These effects were prevented in *Cleome rutidosperma* and *Senecio biafrae* treated rats. Diabetic dyslipidaemia is marked in diabetic rats by elevated triacylglycerols, cholesterol, low density lipoprotein (LDL) and decreased high density lipoprotein (HDL), which constitutes an important cardiovascular risk factors [48]. Lipids play a vital role in the pathogenesis of diabetes mellitus and the most common lipid abnormalities in diabetes are hypercholesterolemia. The reductions in serum triacylglycerols, total cholesterol and low density lipoprotein (LDL)-cholesterol concentrations and increase in HDL observed in the treated groups could be beneficial in preventing diabetic complications as well as improving lipid metabolism in diabetics [49].

There was a significant increase in TBARS in diabetic rats as compared to normal rats. Oral administration of *Cleome rutidosperma* and *Senecio biafrae* extracts for 28 days exhibited a significant reduction on this parameter.

Rajasekaran *et al*., [50] have also reported increased lipid peroxide levels in diabetic rats. Lipid peroxidation of unsaturated fatty acids is a frequently used indicator of increased oxidative stress and subsequent oxidative damage. The observed increase in antioxidant status and decline in TBARS concentration in *Cleome rutidosperma* and *Senecio biafrae* extract treated diabetic rats suggests their potent antilipidperoxidative and antioxidative effects.

Like many chronic diseases, diabetes is widely believed to increase oxidative stress. In diabetes an increase in oxidative stress arises due to compromise in natural antioxidant mechanisms and an increase in oxygen free radical production. Oxidative stress is the shift in balance between cellular oxidation-reduction reactions in favour of oxidation, leading to cellular damage and is indicated by accumulation of oxidized products of lipids, proteins and nucleic acids. Decreased activities of enzymatic antioxidants such as SOD have been well documented in STZ induced diabetic rats [51]. Individuals with reduced CAT activity suffer a heightened risk of developing diabetes [50]. In this study, oral administration of *Cleome rutidosperma* and *Senecio biafrae* extracts for 28 days significantly increased the SOD and CAT activities in STZ-induced diabetic rats.

Glutathione S-transferases (GSTs) are a family of enzymes that catalyze the addition of the tripeptide glutathione to endogenous and xenobiotic substrates which have electrophilic functional groups. They play an important role in the detoxification and metabolism of many xenobiotic and endobiotic compounds [52].

The significant decrease in the GST activity in diabetic control group when compared with the normal control for both liver and kidney (Tables 5 & 6) was prevented by the administration of the aqueous extracts of *Cleome rutidosperma* and *Senecio biafrae* for 28 days in the diabetic rats. The effect was shown to be dose-dependent. These observations are in tandem with the reports of previous researchers who have noted a marked decrease in the activity of antioxidant enzymes such as catalase and GST activity, in liver, kidney and pancreatic tissues from diabetic rats [53].

Increased GST activity might be one of the defense mechanism in these animals to detoxify or neutralize the toxic metabolites generated in liver by the diabetes. The effects of this antioxidant may be useful in delaying the complicated effects of diabetes as retinopathy, nephropathy and neuropathy due to imbalance between free radicals and antioxidant systems.

Treatment with extracts of *Cleome rutidosperma* and *Senecio biafrae* resulted in significant increase in glutathione reductase (GR) activity in diabetic rats when compared with the diabetic control group with observed decrease GR activity (Table 5). GR is a family of homologous proteins whose members are dimeric, NADPH dependent and FAD containing enzymes. GR maintains the cellular levels of GSH (by the reduction of oxidized glutathione), which protects the cellular membranes from peroxides [54]. The increase in GR activity in the treated diabetic rats implies that the extracts protect the tissues from oxidative damage. Comparatively, the mean values of the liver and Kidney antioxidant enzymes activities were significantly higher in the *Cleome rutidosperma* treated groups (E, F and G) than those of groups H, I and J (*Senecio biafrae* treated).

Blood glucose levels are regulated by the pathways utilizing and generating glucose. Hence the activities of some of the key enzymes of carbohydrate metabolism were estimated in liver of control and diabetic rats (Table 7).

The activity of hepatic glucokinase was decreased while the activity of hepatic Glucose 6-phosphatase was increased in diabetic rats as compared to the normal rats. Oral administration of *Cleome rutidosperma* and *Senecio biafrae* for 28 days caused a significant ($p < 0.05$) improvement in the enzyme activities in diabetic rats. Thus, administration of both extracts enhanced the prevention of high G6Pase activity in diabetic rats. Glucose 6 phosphatase (G6Pase), a key enzyme in gluconeogenesis or glycogenolysis, in which it catalyzes the hydrolysis of glucose 6 phosphate (G6P) to glucose and phosphate, plays an important role in glucose homeostasis in the liver and, as such, is a potential target for treatment strategies of diabetes.

Also, Zhang *et al*., [55] reported that glucokinase enzyme activity was decreased by more than 90% in the liver of diabetic rats. Glucose is transported out of the liver to increase blood glucose concentration. Diabetes increases the expression of G6Pase activity [56].

The reduction in G6Pase as seen in the treated groups can lead to a decrease in gluconeogenesis and blood glucose concentration [57]. Increased glucose-6- phosphatase activity in diabetic rats provides H^+, which binds with $NADP^+$ in the form of NADPH and enhances the synthesis of fats from carbohydrates (i.e. lipogenesis) [58] and finally, contributes to increased levels of glucose in the blood.

CONCLUSION: The results of the present study confirm the antidiabetic activities of aqueous extracts of *Cleome rutidosperma* (leaves) and *Senecio biafrae* (roots) when administered to STZ - induced diabetic animals. This confirmation justifies the uses of these plants in ethnomedicine for the treatment of diabetes. The results suggest the presence of biologically active components which may be worth further investigation and elucidation. Further studies are in fact currently under way to isolate and characterize the active principle (s) of the crude extracts.

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