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Hypoglycaemic effects of *Salvia officinalis* extracts on alloxan-induced diabetic Swiss albino mice

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Diabetes mellitus is the fourth killer disease globally. The available management strategies are quite expensive and sometimes unsafe. This necessitates the need for bio-active drugs from medicinal plants. Although *Salvia officinalis* (sage) is used in herbal medicine, the scientific validation for anti-diabetic effects of various extracts has been elusive. The present study aimed to determine and compare the anti-hyperglycaemic efficacy of methanolic, hexane, ethyl acetate, and aqueous leaf extracts of *Salvia officinalis* in alloxan-induced diabetic mice. Phytochemical screening of the extracts revealed presence of flavanone, sterols, saponins, tannins, alkaloids, and triterpenes. The extracts were subjected to preliminary *in vivo* bio-assays at dosage levels of 400 mg/kg for 7 days through oral administration. The aqueous extract demonstrated significant hypoglycaemic effect, $p<0.05$ hence subjected to further hypoglycaemic studies for 15 days. There was a significant decrease in blood sugar levels of groups treated with aqueous extract at 400 mg/kg and 600 mg/kg doses from 452.00 ± 11.13 mg/dL and 431.00 ± 10.65 mg/dL to 256.33 ± 5.12 mg/dL and 256.67 ± 8.74 mg/dL. Weight gain improved significantly from 28.05 ± 0.39 g and 27.38 ± 0.52 g to 29.32 ± 0.42 g and 28.55 ± 0.38 g respectively compared to controls, $p<0.05$. Histopathological studies revealed no significant changes in liver and kidney tissues. Besides, no significant cytotoxic effect was reported. Results from this study indicate that aqueous extract of *Salvia officinalis* is a potential anti-hyperglycaemic and can be used in modulating blood glucose levels.

Key words: Diabetes mellitus, *Salvia officinalis,* aqueous extract, hypoglycaemic effect, phytochemicals.

INTRODUCTION

Diabetes mellitus is a global non-communicable disease with rapidly increasing prevalence in the world (Mendenhall et al., 2017). It is a major healthcare problem experienced by many people due to defect of the endocrine system as well as a complex metabolic disorder that leads to syndromes such as stroke, heart

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attack, and peripheral vascular disease (Patel et al., 2011). High glucose levels in the blood (hyperglycemia) which is an indicator of diabetes is as a result of reduced/lack of insulin secretion by the pancreas, decreased sensitivity of the target tissues to the hormone insulin, or due to a combination of these two factors (International Diabetes Federation, 2013).

Diabetes can lead to numerous complications that are classified into acute, sub-acute or chronic. Complications associated with the acute form of diabetes mellitus include hypoglycemia, hyperosmolarite, hyperglycemia, diabetic ketoacidosis, and non-ketotic syndrome (Kitabchi et al., 2009). Sub-acute complications are polyuria, polydipsia, visual blurriness, weight loss, and lack of energy (Kuchake and Upasani, 2013). Chronic complications are associated with long-term damages like nephropathy, neuropathy, hypertension, hepatopathy, cardiomyopathy, diabetic foot ulcers, retinopathy, and reproductive damage (Lotfy et al., 2017). Chronic hyperglycemia leads to increase in production of oxygen free radicals due to autoxidation of glucose and glycation of the body proteins (Yaribeygi et al., 2019). This, generates oxidative stress resulting to secondary complications affecting various body organs such as the kidneys, eyes, arteries, and nerves (Henriksen et al., 2011).

Although diabetes was a rare disease in the past, it has become a big problem in recent years. In 2013, diabetes caused 5.1 million deaths, an increase of 0.5 million compared to 2011. It is anticipated that over 592 million people with diabetes by the year 2035 may die. In the year 2000, about 177 million people suffered from diabetes globally and by 2015 the number had risen to 415 million which is predicted to increase to about 642 million by the year 2040. In Africa, 14.2 million people are diabetic, and they are estimated to rise to 34.2 million by 2040 (International Diabetes Federation, 2015). Due to the increasing mortality incidence, search for newer, affordable, and safer bioactive anti-hyperglycaemic agents from medicinal plants has become an area of interest to scientists.

Salvia officinalis commonly known as sage, is an evergreen, perennial shrub in the *Lamiaceae* family (Sharma and Schaefer, 2019). It has grayish-green leaves, woody stems and blue to purplish flowers. It is native to the Mediterranean region but has naturalized in many parts of the world. Sage has been used in herbal medicine for a long time in the treatment of various illnesses. It is reported to have anti-inflammatory, antibacterial, and anti-fungal properties (Ghorbani and Esmaeilizadeh, 2017). It is also known for lipid profiling and antioxidant properties responsible for hypoglycaemic effects (Bommer et al., 2009; Schapowal et al., 2009). The aim of this study was to determine and compare the anti-hyperglycaemic efficacy of methanolic, hexane, ethyl acetate, and aqueous extracts of *S. officinalis* in alloxan-induced diabetic mice.

MATERIALS AND METHODS

Study area

Fresh leaves were collected from Egerton University's Botanic Garden which is at an altitude of 2127 m and 1° 37″ south of Equator. The plant was authenticated by a qualified taxonomist, Prof Samuel Kariuki at Egerton University and the voucher specimen deposited at the Department of Biological Sciences, Egerton University with an assigned voucher specimen number (NB 238).

Extraction

The collected leaves were dried under shade to constant weight and ground to a fine powder using a blending machine (Thomas-Wiley Laboratory Mill Model 4). The powdered material (500 g) was soaked in 1.5 L of distilled methanol for 72 h at room temperature with intermittent shaking. The extract was decanted and filtered using Whatman No. 1 filter paper. The obtained filtrate was concentrated to dryness using a rotary Evaporator machine (BUCHI-R 205) under reduced pressure. The concentrated methanolic crude extract was divided into two parts with one portion stored in a vial at 4ºC awaiting bio-assays. The remaining portion was suspended in distilled water, extracted with hexane and thereafter ethyl acetate to give hexane, ethyl acetate, and aqueous crude fractions respectively (Kosgei et al., 2014).

Phytochemical screening

Phytonutrients present in various extracts were determined according to standard procedures by Harborne (1998). Tests were performed for alkaloids, saponins, triterpenes, steroid glycosides, sterols, anthracene aglycone, flavonone aglycones, flavonols, flavanone, and tannins.

Experimental animals

Two-month old healthy male Swiss albino mice weighing (25-30 g) were procured from Kenya Medical Research Institute (KEMRI), Nairobi, Kenya. The animals were housed in polypropylene cages, six mice in each with wood shaving as beddings. They were fed with standard mice pellets obtained from Unga Ltd, Nairobi, Kenya (crude protein 18.1%, crude fibre 7%, calcium 0.8%, phosphorous 0.8%, and fat 8%). The feed and water were available *ad libitum* except during the day of blood sampling when animals were fasted overnight with access to water only. The mice were acclimatized to standard laboratory environmental conditions, temperature (23 ± 2°C) dark and light cycles (12:12 h) for 2 weeks. The studies were performed with the approval of Institute of Primate Research (IPR) Animal Care and Ethics Committee [Ref: ISERC/10/2017].

Experimental design

Preliminary screening of the extracts was carried out using six mice per extract. The extracts were fed orally by use of an intra-gastric gavage for a period of 7 days. Each animal received 0.3 mL of the prepared extract (400 mg/kg). The aqueous extract was selected for extensive study as it lowered blood sugar levels significantly compared to other extracts. The mice were randomized into 5 groups of 6 mice each.

Group I: (Control- Non-diabetic- Untreated mice)
Group II: (Diabetic control- Diabetic treated group)

Group III: (Diabetic mice treated with 400 mg/kg of the aqueous extract)
Group IV: (Diabetic mice treated with 600 mg/kg of the aqueous extract) and
Group V: (Control-Diabetic mice treated with 2 mg/kg glibenclamide drug).

Induction of diabetes in mice

The animals were marked with wet picric acid for ease of identification. They were fasted overnight before injection of the alloxan® monohydrate chemical intraperitoneally as a single dose of 200 mg/kg bwt. After five (5) days (with access to food and water), the experimental animals were screened for hyperglycemia by determining their fasting blood sugar level using the glucose oxidase kit (SoftStyle Glucometer and SoftStyle Blood Glucose Test Strips from Chem-labs Limited, Nairobi Kenya). Blood glucose levels above 200 mg/dL was considered diabetic and used in the study.

Blood sugar and body weight determination

The animal's tails were first sterilized with 10% alcohol. Blood was withdrawn by tail snipping from each animal for blood sugar analysis. Baseline blood sugar levels of all the animals were taken before extract administration and fasting blood sugar determined at intervals of 72 h (3 days) for 360 h (15 days). Baseline body weights of the various treatment groups were measured before and during the study period at intervals of 72 h using an electronic beam balance (model type: BL-220H).

Histopathology tests

Kidney and liver tissues were examined for histopathology using standard procedures according to Scott (1999). The organs were fixed and preserved in 10% (v/v) formalin and then processed for paraffin embedding. Paraffin embedded sections (7 µm thick) were stained with haematoxylin and eosin dye (H&E), and then examined under light microscopy (HumaScope Advanced^{LED} Binocular digital microscope) for pathology. Comparison of the various tissues was made between different treatment groups.

Data analysis

The obtained data was expressed as mean ± standard error of the mean (mean ± S.E.M). Data was subjected to one-way analysis of variance (ANOVA) followed by Turkey post hoc test using Statistical Package for Social Sciences (SPSS) software [version 23]. $P<0.05$ was considered statistically significant.

RESULTS

Phytochemical tests

S. officinalis leaves showed presence of various phytochemicals as shown in Table 1. Flavanones, saponins, and alkaloids were abundant in aqueous fraction.

Preliminary screening of the crude extracts

The effect of *S. officinalis* extracts on Fasting Blood Sugar (FBS) is indicated in Table 2. The aqueous extract lowered fasting blood sugar levels significantly from 487.67 ± 2.58 to 426.33 ± 2.95 mg/dL ($p<0.05$). Hexane and methanolic extracts as well indicated a significant decrease in blood sugar levels from 490.67 ± 3.01 and 497.00 ± 2.78 mg/dL to 473.00 ± 2.73 and 488.00 ± 2.82 mg/dL, respectively. The ethyl acetate extract, on the other hand, indicated an increase in blood sugar levels from 482.33 ± 0.42 to 519.00 ± 10.30 mg/dL.

Hypoglycaemic activity of aqueous extract

Oral administration of aqueous extract at doses of 400 and 600 mg/kg respectively indicated a significant decrease ($p<0.05$) in fasting blood sugar levels compared to the controls (Table 3). Groups administered with aqueous extract indicated a greater decrease in blood sugar levels compared to glibenclamide treated group.

Body weight

Aqueous extract at 400 and 600 mg/kg indicated a significant ($p<0.05$) improvement in body weight compared to the controls. Nevertheless, weight gained by Group V (administered with glibenclamide drug) was not significantly different ($p<0.05$) from the diabetic control (Table 4). Group III treated with 400 mg/kg recorded the highest weight gain from 27.57 ± 0.50 to 28.55 ± 0.38 g. On the other hand, Group V treated with glibenclamide drug recorded the least weight gain from 26.77 ± 0.19 to 27.55 ± 0.36 g.

Histopathological tests

Liver histopathology

Liver cells of healthy mice showed normal cellular architecture characterized by normal hepatic cells with distinct nuclei and hepatic cords. Severe cellular degenerative changes were observed in diabetic control group. The general architectural structure of the liver cell was lost with severe necrosis and fibrosis noted. Tissues treated with the aqueous extract and glibenclamide drug also showed similar degenerative changes. Several necrotic areas were observed and normal cellular architecture destroyed (Figure 1).

Kidney histopathology

The kidney sections of Group I showed normal renal architecture with distinct glomeruli, Bowman's capsule and tubules. The kidney sections of Group II indicated tubular cellular necrosis and fibrosis. Tissues treated with the aqueous extract showed tubular cellular necrosis with intratubular fibrosis, renal hemorrhage, and erythrocytic infiltration. Similarly, group treated with glibenclamide

Table 1. Phytochemicals present in *Salvia officinalis* fractions**.**

Phytochemicals tested	Methanolic fraction	Ethyl acetate fraction	Hexane fraction	Aqueous fraction
Flavanone aglycones	++	++	-	++
Flavonols	++	+++	-	-
Flavanones	+++	-	-	+++
Saponins	-	-	-	+++
Condensed tannins	++	-	+	++
Hydrolyzed tannis	-	++	+	-
Atheracene aglycones	-	+	-	++
Sterols	++	+	++	+
Triterpenes	++	++	++	+
Alkaloids	+++	-	-	+++

The sign (+) indicates presence of trace amounts of phytonutrients, (++) moderate presence of phytonutrients, (+++) abundant presence of phytonutrients, and (-) absence of phytonutrients.

Table 2. Effects of *S. officinalis* crude extracts on blood sugar levels after administration to alloxan-induced diabetic mice.

Extract	Mean blood sugar levels (mg/dL)		
	FBS levels at -5 days	FBS levels at 0 days	FBS levels at 7 days
Methanolic	90.00 ± 1.59	497.00 ± 2.78	488.00 ± 2.82*
Ethyl acetate	84.33 ± 2.76	482.33 ± 0.42	519.00 ± 10.30*
Hexane	89.67 ± 0.56	490.67 ± 3.01	473.00 ± 2.73*
Aqueous	88.33 ± 1.52	487.67 ± 2.58	426.33 ± 2.95*
Diabetic Control	82.67 ± 3.27	488.00 ± 2.82	563.00 ± 2.98
Non-diabetic Control	86.33 ± 1.69	85.00 ± 0.73*	83.00 ± 0.73*

Results are expressed as Mean ± S.E.M (n=6). Means within respective columns followed by asterisk are significantly different compared to diabetic control at p<0.05. Analyzed by One-way ANOVA followed by Tukey post hoc test.

Table 3. Effects of aqueous extract on blood sugar levels of various treatment groups after administration to alloxan-induced diabetic mice.

Day/Treatment	Fasting Blood Sugar (FBS) Levels (mg/dL)				
	Group I	Group II	Group III	Group IV	Group V
-5 days	85.17 ± 1.66	85.67 ± 2.42	81.83 ± 1.38	85.50 ± 2.68	86.33 ± 1.91
0 days	84.33 ± 1.45*	444.67 ± 14.07	452.00 ± 11.13	431.00 ± 10.65	451.83 ± 5.88
3 days	83.83 ± 1.83*	454.67 ± 12.62	412.83 ± 9.39	377.33 ± 17.22*	452.67 ± 8.07
Day 6	86.67 ± 1.67*	446.67 ± 10.47	374.83 ± 4.11*	371.67 ± 14.24*	395.83 ± 9.70*
Day 9	82.67 ± 1.09*	457.33 ± 4.29	340.67 ± 8.30*	327.67 ± 12.02*	361.33 ± 15.11*
Day 12	85.00 ± 1.93*	473.00 ± 5.74	287.17 ± 6.64*	290.33 ± 9.58*	337.00 ± 13.74*
Day 15	86.50 ± 2.83*	480.67 ± 4.65	256.33 ± 5.12*	256.67 ± 8.74*	300.00 ± 7.17*

Results are expressed as Mean ± S.E.M (n=6). Means within respective rows followed by asterisk are significantly different compared to diabetic control at p<0.05. Analyzed by One-way ANOVA followed by Tukey post hoc test. Group I: Non-diabetic control; Group II: Diabetic control; Group III: Treatment group (400 mg/kg aqueous extract); Group IV: Treatment group (600 mg/kg aqueous extract); Group V: Treatment group (2 mg/kg glibenclamide drug).

drug indicated tubular and glomerulus atrophy, fibrosis and necrosis (Figure 2).

DISCUSSION

Alloxan is a diabetogenic agent that causes destruction of the pancreatic β-cells of the islets of Langerhans, thereby affecting insulin production (King, 2012). Insulin deficiency leads to increased glucose levels in the blood. Results from this study showed that oral administration of methanolic, hexane, and aqueous extracts at a dose of 400 mg/kg decreased fasting blood sugar of alloxan-induced diabetic mice significantly for a period of 7 days.

Table 4. Body weights of different treatment groups.

Day/Treatment	Body weight (g)				
	Group I	Group II	Group III	Group IV	Group V
-5 days	27.77 ± 0.21	27.92 ±0.55	28.25 ±0.36	27.57 ± 0.50	26.77 ± 0.19
0 days	27.85 ± 0.22	27.60 ± 0.58	28.05 ± 0.39	27.38 ± 0.52	26.45 ± 0.22
Day 3	27.92 ± 0.21	27.23 ± 0.55	27.73 ± 0.41	27.07 ±0.61	25.87 ± 0.19
Day 6	27.80 ± 0.22	26.78 ± 0.78	28.62 ± 0.41	27.60 ± 0.49	26.55 ± 0.32
Day 9	27.93 ± 0.22	26.48 ± 0.82	29.1 ± 0.38*	28.17 ± 0.48	27.08 ± 0.38
Day 12	27.90 ± 0.20	25.97 ± 0.86	28.82 ± 0.42*	28.22 ± 0.41*	27.27 ± 0.36
Day 15	27.87 ± 0.24*	25.72 ± 0.86	29.32 ± 0.42*	28.55 ± 0.38*	27.55 ± 0.36

Results are expressed as Mean ± S.E.M (n=6). Means within respective rows followed by asterisk are significantly different compared to diabetic control at p<0.05. Analyzed by One-way ANOVA followed by Tukey post hoc test. Group I: Non-diabetic control; Group II: Diabetic control; Group III: Treatment group (400 mg/kg aqueous extract); Group IV: Treatment group (600 mg/kg aqueous extract); Group V: Treatment group (2 mg/kg glibenclamide drug).

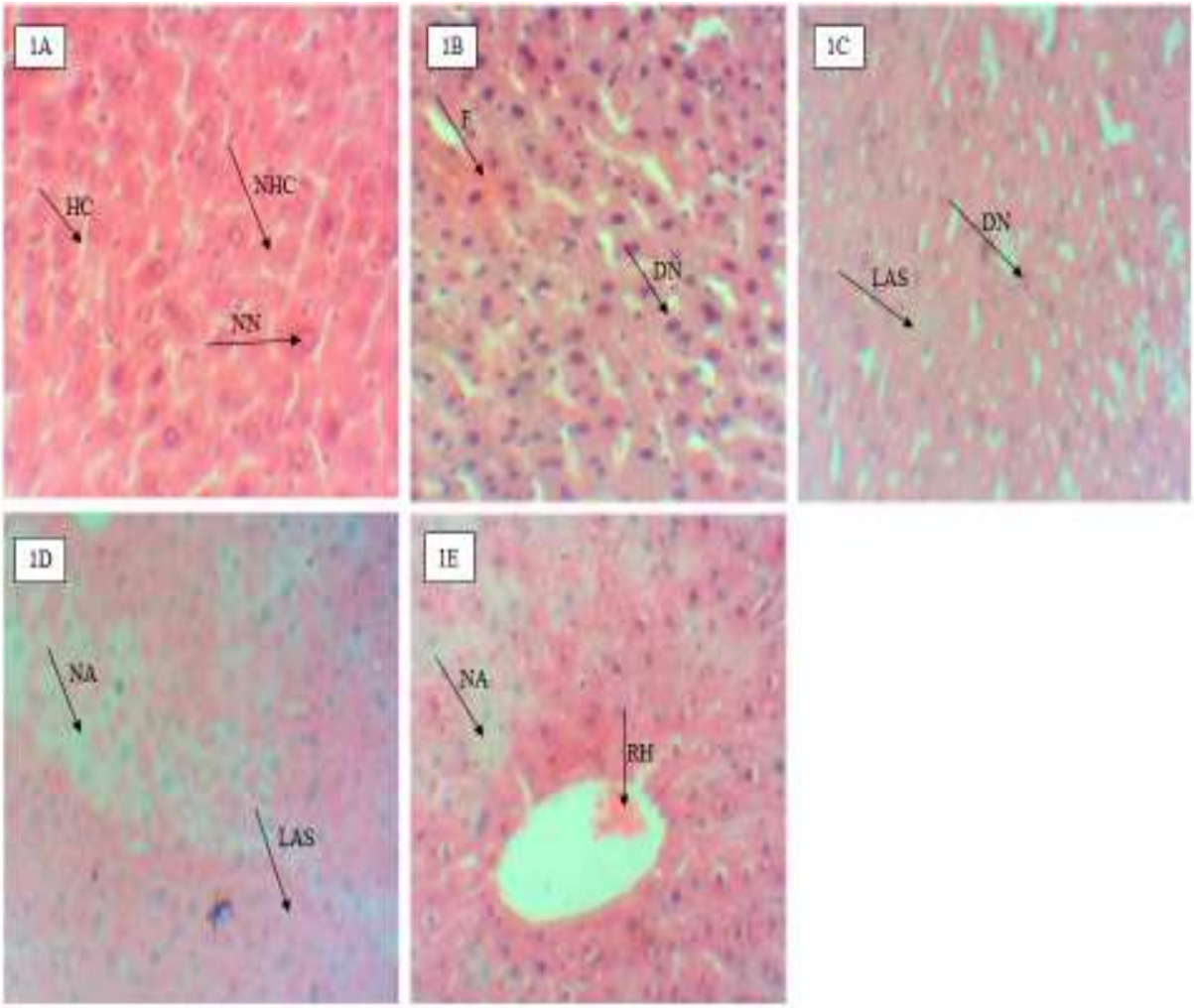

Figure 1. Histological plates of liver sections (Magnification: ×40): Group I (1A) showed normal hepatic cells (NHC), hepatic cords (HC), and normal nucleus (NN). Group II (1B) exhibited fibrosis (F) and dense nucleus (DN). Group III (1C) showed dense nucleus (DN) and lack of architectural structure (LAS). Group IV (1D) showed necrotic areas (NA) and lack of architectural structure (LAS). Group V (1E) showed necrotic areas (NA) and renal hemorrhage (RH). Group I: Non-diabetic control; Group II: Diabetic control; Group III: Treatment group (400 mg/kg aqueous extract); Group IV: Treatment group (600 mg/kg aqueous extract); Group V: Treatment group (2 mg/kg glibenclamide drug).

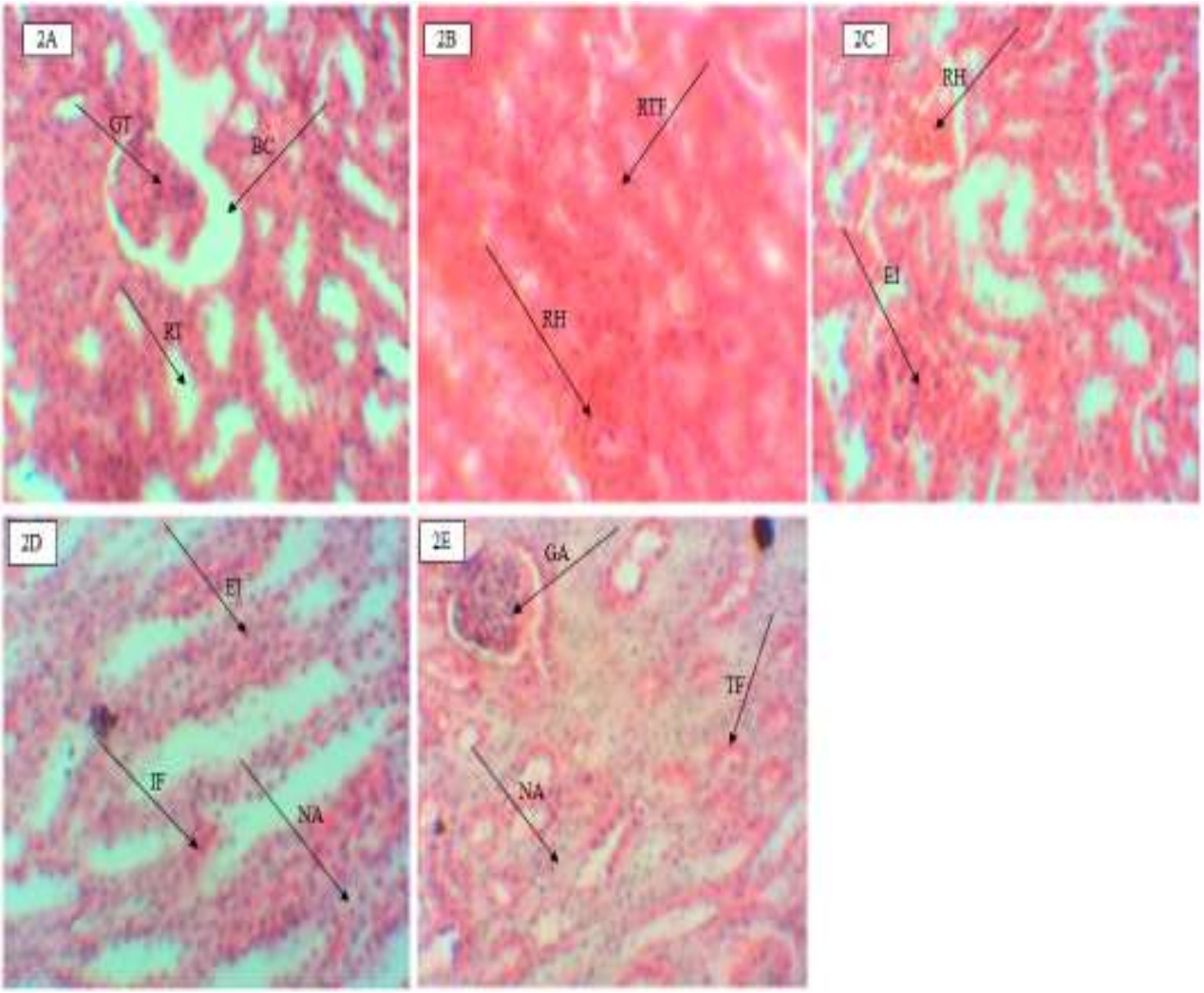

Figure 2. Histological plates of kidney sections (Magnification: ×40): Group I (2A) showed normal Bowman's capsule (BC), glomerulus tuft (GT), and renal tubules (RT). Group II (2B) showed renal tubular fibrosis (RTF) and renal hemorrhage (RH). Group III (2C) showed renal hemorrhage (RH) and ethrocytic infiltration (EI). Group IV (2D) showed ethrocytic infiltration (EI), intratubular fibrosis (IF), and necrotic areas (NA). Group V (2E) showed glomerulus atrophy (GA), tubular fibrosis (TF), and necrotic areas (NA). Group I: Non-diabetic control; Group II: Diabetic control; Group III: Treatment group (400 mg/kg aqueous extract); Group IV: Treatment group (600 mg/kg aqueous extract); Group V: Treatment group (2 mg/kg glibenclamide drug).

The glucose lowering effects of these extracts might be linked to presence of flavanones, flavonols, tannins, triterpenes, alkaloids, saponins, and sterols (Aghajanyan and Trchounian, 2018). Flavonoids and terpenes have been documented to possess anti-diabetic effect through insulin like-effect (Balasubashini et al., 2004). Ferulic acid and quercertin are flavonoids which have an effect on pancreatic β-cells of alloxan-induced diabetic rats. They cause cell proliferation hence secretion of more insulin (Mahesh and Menon, 2004). Flavonols and flavanones are classes of flavonoids identified in methanolic, ethyl acetate, and aqueous crude extracts. They possess anti-oxidant activity which scavenges free radicals generated during the progression of diabetes mellitus, thereby offering protection against possible damage to various tissues (Kawser et al., 2016).

Nevertheless, other classes of phytochemicals identified could also be responsible for hypoglycaemic effect. For instance, the hexane extract did not reveal any presence of flavanones and flavonols, but lowered blood sugar levels of diabetic mice significantly. Phenolic acids and tannins are polyphenols known to possess antioxidant activities hence it is responsible for free radical scavenging effect (de Almeida et al., 2005). Studies by Pan et al. (2003) and Rao and Gurfinkel (2000) have also demonstrated the hypoglycaemic activity exhibited by tannins. Since tannins were detected in the hexane extract in this study, they could have contributed to its

hypoglycaemic effect.

A hyperglycaemic effect was noted in ethyl acetate extract where it demonstrated an increase in blood sugar levels. It showed presence of flavanone aglycones, flavonols, hydrolyzed tannis, atheracene aglycones, sterols, and triterpenes. These metabolites could be working in an antagonistic manner, thereby inhibiting the activity of each other (Njeru et al., 2015). This could probably be linked to the reason why ethyl acetate extract demonstrated lack of hypoglycaemic effect.

Administration of the aqueous extract at doses of 400 and 600 mg/kg for 15 days caused a significant drop in blood sugar levels and a gradual increase in weight gain ($p<0.05$). The results obtained were consistent with those recorded by Eidi and Eidi (2009) who demonstrated the hypoglycaemic and weight improvement effect of *S. officinalis* aqueous extract. Similar results were reported by Salah et al. (2016) who documented the hypoglycaemic character of *S. officinalis* aqueous extract. Weight gain for the group administered with glibenclamide drug, however, was not statistically significant compared to the diabetic control. This demonstrates the potency of *S. officinalis* aqueous extract as compared to the glibenclamide drug. Diabetic control group also showed signs of polyphagia, polydipsia, and polyuria. Weight loss observed in a diabetic state is usually as a result of muscle wasting due to poor carbohydrate utilization. Consequently, it stimulates protein breakdown in order to provide amino acids necessary for gluconeogenesis to occur (Barazzoni et al., 2017).

Although the exact mode of action through which these extracts lower blood sugar levels has not yet been elucidated, it is thought to act through various mechanisms. Lima et al. (2006) reported that plant extracts cause regeneration of the destroyed pancreatic β-cells, protect the intact functional beta cells from further damage, increase plasma membrane permeability, and stimulate insulin secretion. Another study by Bnouham et al. (2006) also noted that plant extracts could possess insulin-like activity, increase peripheral utilization of glucose, decrease the rate of glycogenesis, increase synthesis of hepatic glycogen, or inhibit intestinal glucose absorption (Mahdizadeh et al., 2018).

Garcia-Compean et al. (2009) demonstrated that mitochondria oxidative stress generated due to diabetes leads to generation of free radicals that induces inflammation, necrosis, and fibrosis to the cells. Administration of aqueous extract on the diabetic mice at the dosage levels of 400 and 600 mg/kg did not indicate any significant histopathological changes compared to controls. In contrast, Essawy et al. (2018) documented protective effects of the aqueous extract of *S. officinalis* on damaged liver cells of mice. However, in this study, the hepatoprotective and nephroprotective effect of the aqueous extract is implicated. This could be attributed to the fact that the cells were already destroyed beyond repair or the treatment period was too short to give an effect. Nevertheless, the extract was not cytotoxic to the liver and kidney cells as no further damage was observed and no deaths of the animals was recorded during the study period. The extract could have, therefore, played a huge role in causing attenuation of the oxidative stress and also enhancing the antioxidant defense system (Ashour et al., 2017).

Conclusion

The study indicates that methanolic, hexane, and aqueous extracts of *S. officinalis* possess anti-diabetic potential at a dose of 400 mg/kg. At the same concentration, however, ethyl acetate extract proved to be hyperglycaemic. The aqueous extract at 400 and 600 mg/kg produced better effects compared to glibenclamide. Thus, it can be further explored for the development of phytomedicines for the management of diabetes mellitus. The histopathological studies and tissue examination of kidney and liver organs proved that aqueous extract is not toxic. Future research should involve active compounds identification, determination of the mode/mechanism of action, and possible synergistic interactions with other extracts.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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