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Hydro-alcoholic Root Extracts of *Ziziphus abyssinica* is Effective in Diabetes Nephropathy and Diabetic Wound

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Abstract

Background: This study evaluated the potential of *Ziziphus abysinnica* root extract in managing type 2 diabetes mellitus (T2DM) and its associated complication, diabetic nephropathy, and impaired wound healing.

Methodology: Blood glucose concentrations were measured daily for 14 days after daily administrations of *Ziziphus abysinnica* (30, 100, and 300 mg/kg, p.o), metformin (300 mg/kg, p.o) as a positive control, and normal saline as negative control before diabetes induction using a single dose of streptozotocin (60 mg/kg, i.p) and nicotinamide (120 mg/kg, i.p).

Results: Generally, the percentage of blood glucose levels were analysed following administration of drugs was found to be dose-dependent. The highest dose of *Z. abysinnica* (300 mg/kg) had a higher percentage reduction in blood glucose concentration when compared to metformin (300 mg/kg). Histopathological analysis was performed on the kidneys following administration with *Ziziphus abysinnica* in diabetic rats. The lowest dose group administered with (30 mg/kg) demonstrated minimal to moderate pathological changes to the kidney architecture. In contrast, the 100 mg/kg and 300 mg/kg dose groups displayed maximal toxic pathologic changes to the kidney nephrons.

Conclusion: Overall, our study has demonstrated the antidiabetic potential of *Ziziphus abysinnica*, suggesting its possible therapeutic benefit in diabetic nephropathy.

Keywords: *Diabetic nephropathy; Diabetic wound; Type 2 Diabetes mellitus; Ziziphus abysinnica*

Introduction

Diabetes Mellitus (DM) is a metabolic disease characterised by a relative or absolute lack of insulin, resulting in hyperglycaemia. Persistent DM can lead to chronic hyperglycaemia, which leads to a variety of multiorgan complications such as neuropathy, nephropathy, retinopathy, increased risk of cardiovascular diseases, and impaired wound healing. The wound healing impairment observed in diabetic could be caused by numerous factors such as inadequate blood supply, reduced proliferation of fibroblast, and decreased inflammatory changes [1]. The International Diabetes Federation (IDF) estimates that currently, 463 million adults worldwide are affected by DM, and this figure is expected to reach a staggering 578 million by 2030 [2], of which Type 2 Diabetes (T2D) accounts for more than 90%. T2D is a complex, heterogeneous and polygenic disease characterised mainly by insulin resistance and pancreatic β-cell dysfunction [3], which leads to chronic hyperglycemia. Diabetes is considered one of the five leading causes of mortality worldwide [4]. In modern medicine, no satisfactory effective therapy is available to cure diabetes [5]. Currently, T2D is predominantly managed with oral antidiabetic drugs such as sulfonylureas, biguanides, and α-glucosidase inhibitors [6]. Unfortunately, these synthetic antidiabetic agents are beset with some side effects such as diarrhea, nausea, and liver failure [7].

The kidneys are one of the primary targets, which are affected by diabetes mellitus (DM). Diabetic nephropathy (DN) is the leading cause of chronic kidney failure, and consequently, a significant cause of renal morbidity and mortality. It is estimated that about 40% of all people with DM develop clinical evidence of nephropathy, but a considerably smaller fraction of type II diabetic patient's progress to end-stage renal disease (ESRD). Advanced or end-stage kidney disease occurs in as many as 40% of both type I and type II diabetics [8,9].

Ziziphus abyssinica is a semi-deciduous flowering shrub or tree which belongs to the family Rhamnaceae. The plant has a widespread distribution almost throughout Africa and is commonly known as catch thorn. A decoction of the plant is traditionally used to treat diabetes mellitus [10] among the rural inhabitants of northern Nigeria and some parts of Ghana. The roots are boiled, and the liquid is drunk as a treatment for early postpartum pains, stomach aches, snake bites, and an abortifacient. The leaves are also boiled and used as a steam bath to treat pneumonia [10]. The extract from the plant's edible fruit has been reported to possess the antioxidant property and antibacterial activity against *Pseudomonas*

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aeruginosa, *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* [11]. The root extract of the plant is known to possess anti-plasmodial, anti-ulcerative, analgesic, and anti-diarrhoeal properties [12-14]. Additionally, the plant's root bark extract has been reported to possess an inhibitory effect against acute inflammation [15].

Despite the widespread use of the plant in folklore medicine across many African countries, no scientific data is backing this plant's roots in managing diabetes and its associated complications such as diabetic nephropathy. This study hypothesized that *Ziziphus abyssinica* has a blood glucose-reducing effect and heals wounds in diabetic rats.

Methods

Plant material

The roots of *Ziziphus abyssinica* were collected from Ejura, in the Ashanti region of Ghana, in June and authenticated at the Herbarium unit of the School of Biological Sciences, Kwame Nkrumah University of Science and Technology. The roots were shade-dried for one month, with a voucher specimen KNUST/HM/2016/L003 kept in the School of Biological Sciences' herbarium.

Plant extraction

The dried roots were pulverized into powder with an electric mill. A one kg of the powdered material was soaked with 3 L of 70% ethanol and maintained on a mechanical shaker for 72 h. The extract obtained was filtered and labeled ZAE and the filtrate concentrated using a rotary evaporator (Rotavapor R-215 model, BÜCHI Labortechnik AG, Flawil, Switzerland) under reduced pressure (50°C) and temperature (40°C). The filtrate was then placed in a desiccator containing activated silica gel to dry, and the dried mass was refrigerated at 4°C until ready to be used.

Preparation of ointment

Formulation of ointment was done using a review of earlier stated methods [16]. The ointment was prepared by taking 0.3% preservatives (methylparaben, propylparaben), 30% humectants (petroleum jelly), and 19.5% emulsifying wax in 500 ml of distilled water and 1.5% emulsifying agent (acetyl alcohol), and 15% glycerin in 45% liquid paraffin. Both oily and aqueous phases were mixed at 700°C, and three graded fractions of the cooled extract were added separately. The resultant ointment was homogenized by Soxhlet, a homogenizer at 3000 rpm, into a creamy form and stored in tight plastic containers.

Animals

Male Sprague-Dawley (SD) rats (250-300 g) were purchased from the Noguchi Memorial Institute for Medical Research, University of Ghana, Ghana. The animals were housed in stainless steel cages (34 × 47 × 18) cm3 in groups of six rats at the animal house facility of the Department of Biomedical Sciences, University of Cape Coast, Ghana. The male SD rats were maintained under standard laboratory conditions, 12-hour light/dark cycle, standard food and water ad libitum, 25°C, and free movement in their cages. The experimental animals were approved by the Ethics Review Committee of the Department of Biomedical Sciences, UCC. Experimental animals were handled per the Animal Welfare Regulation and the Public Health Service Policy on Humane Care and Use of Laboratory animals.

Drugs and chemicals

Streptozotocin (STZ) and nicotinamide (Sigma-Aldrich Inc, St. Louis, MO, USA), as well as metformin hydrochloride (Ernest Chemist, Accra, Ghana), were administered to the SD rats.

Experimental design

Induction of diabetes

Diabetes was induced in overnight fasted rats. Sprague-Dawley rats (250-300 g) were randomized into seven groups (n=5) and given one of the following treatments for 14 days post-induction:

Group I (naïve control): normal saline 10 ml/kg, p.o.

Group II (positive control): metformin 300 mg/kg, p.o +becaplemin ointment

Group III (disease control): normal saline 10 ml/kg, i.p.

Groups IV, V, and VI (test groups): *Ziziphus abysinnica* (ZAE) 30, 100, and 300 mg/kg p.o. respectively.

Test rats (except group I) received a single intraperitoneal injection of 60 mg/kg streptozotocin dissolved in 2 ml/kg citrate buffer (pH=4.5). A 20-minute post-intraperitoneal administration of nicotinamide 120 mg/kg i.p. was performed.

Confirmation of type 2 diabetes mellitus

Fasting blood glucose (FBG) concentration was measured using samples from the lateral tail vein with the help of a glucometer (OneTouch® Ultra, USA). Experimental animals with fasting blood glucose levels of 10 mmol/L or greater were considered diabetic and were used for the study.

Blood glucose monitoring

Blood glucose concentrations were measured after an overnight fast using a glucometer. Small incisions were made on the lateral part of the tail of each animal, and blood was obtained for measuring blood glucose levels. Twelve hours after the last treatment, the fasting blood sugar (FBS) levels were measured again.

Excision wound model

The rats were anaesthetized with slight vapor inhalation of diethyl ether. The hair at the vertebral area of the rats was shaved prior to wound creation, and the application field for the ointment was outlined with a marking pen. An excision wound of 1.5cm in diameter and 2mm depth was created on the

dorsum of the rats using sterile toothed forceps and surgical blades.

Wound induction

Animals in Group II received topical application of Penicillin ointment. Groups IV, V, and VI were treated topically with the extract ointment (15% w/w) of *Ziziphus abyssinica* roots. Group I received no treatment, thus serving as the negative control group in diabetic animals.

The wound healing evaluation

Screening for the wound healing activity of the ointment was performed by the excision wound model described by Ozay Y, Kasim MC, Guzel-Ozay S, Cimbiz A, Gurlek-Olgun E & Ozyurt MS. The diabetic animals were divided into 5 sub-groups, each containing 5 animals. The control group was treated topically with sterile normal saline. Groups IV, V, and VI were treated topically with ZAE ointment (15%w/w), whereas group II received topical application of Becaplemin gel 0.01% (Regranex) for 14 days. The progressive changes in wound area were measured in mm2 by tracing the wound boundaries around it on transparent polythene paper daily for 14 days of treatment. The polythene paper was then placed on the graph paper and traced out. The healed area was calculated by subtracting from the total wound area.

Histology of kidney tissue

Experimental animals were euthanised through chloroform anaesthesia, and their kidneys were carefully harvested and preserved in 10% formalin at room temperature for microscopic evaluations. The harvested kidney tissues were fixed in 10% formalin, dehydrated in ethanol solutions of increasing concentrations (50-100%), cleared in xylene, and embedded in paraffin wax. Transverse sections of 5-6µm were obtained using a microtome (Bright 5040, Bright Instrument Company Ltd., England) and stained with hematoxylin and eosin (H&E) for microscopic evaluation of tissue integrity. Microscopic examinations were done using a binocular clinical light microscope with a digital camera (Olympus CX1, Japan) connected to a computer. Photomicrographs of the tissues were generated using the ×100 objective lens for further analysis of pathological abnormalities such as leukocyte infiltration, haemorrhage, fatty changes, necrosis, and congestion.

Statistical analysis

GraphPad Prism for Windows Version 7.0 (GraphPad Software, San Diego, CA, USA) was used for all statistical analysis. Data were expressed as a mean ± standard error of the mean (SEM). Differences among treatment group means were assessed using a one-way analysis of variance (ANOVA) followed with the Dunnett posthoc test. $P<0.05$ was considered statistically significant for all tests.

Results

Effect of *Ziziphus abysinnica* on the blood glucose levels

The blood glucose concentrations were measured in normal and experimental rats on days 2, 4, 6, 8, 10, 12, and 14 of treatment **(Figure 1).**

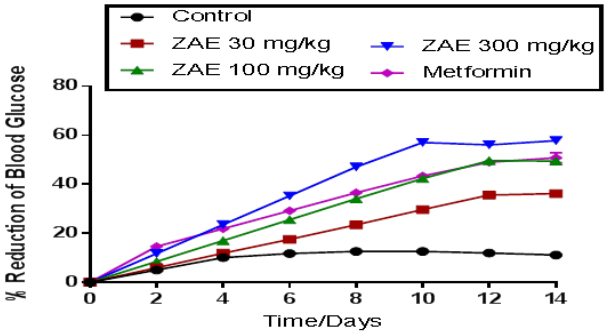

Figure 1: Effect of Ziziphus abyssinica on percentage reduction of blood glucose level in STZ-induced diabetic rats. Sprague-Dawley rats received either saline 10 ml/kg, metformin 300 mg/kg, or Ziziphus abysinnica 30, 100, and 300 mg/kg p.o., and challenged with streptozotocin (60 mg/kg, i.p.) 20 min post-administration of nicotinamide (120 mg/kg i.p.). Fasting blood glucose concentration was measured before and 12 h after treatments.

The percentage reduction of blood glucose in the treatment groups increased steadily from day 2, with the 300 mg/kg ZAE treatment group having the highest value (% reduction) by day 14. ZAE treatment groups showed a dose-dependent hypoglycaemic effect compared to the naïve control. Metformin (300 mg/kg) showed a higher percentage reduction when compared to ZAE (30 mg/kg, 100mg/kg) respectively **(Figure 2)**.

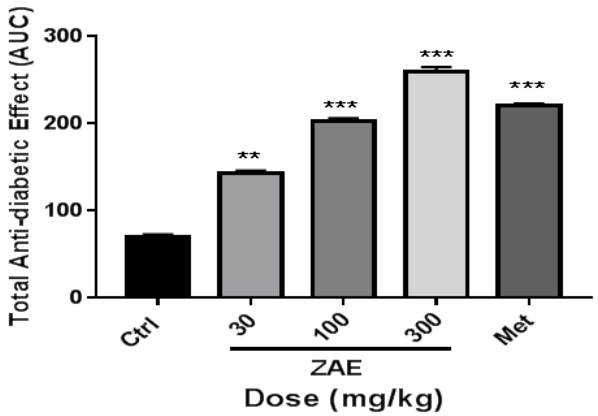

Figure 2: Effect of *Ziziphus abyssinica* on the mean fasting blood glucose concentration in STZ-induced diabetic rats. Sprague-Dawley rats received either saline 10 ml/kg, metformin 300 mg, or Ziziphus abysinnica 30, 100, and 300 mg/kg p.o. Test SD rats were challenged with streptozotocin (60 mg/kg, i.p.) 20 min post-administration of nicotinamide (120 mg/kg i.p.). Fasting blood glucose concentration was measured before and 12 h after treatments.

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Wound healing effect of *Ziziphus abyssinica* extract ointment in streptozotocin-induced diabetes

ZAE ointment at doses 2.5%, 5%, and 10% showed a significant increase in wound contraction rate compared to the negative control beginning from the 8th day through to the 14th day ($p<0.005$). Also, 2.5%, 5%, and 10% ZAE ointment demonstrated a significant total wound healing effect with a mean coverage of 705.0 ± 6.163, 679.7 ± 37.62, and 690 ± 32.69 rate of wound contraction compared to the negative control (515.9 ± 52.63). The penicillin ointment had total mean coverage of 684.2 ± 26.62 at a significance of $p<0.05$ against the negative control **(Figure 3)**.

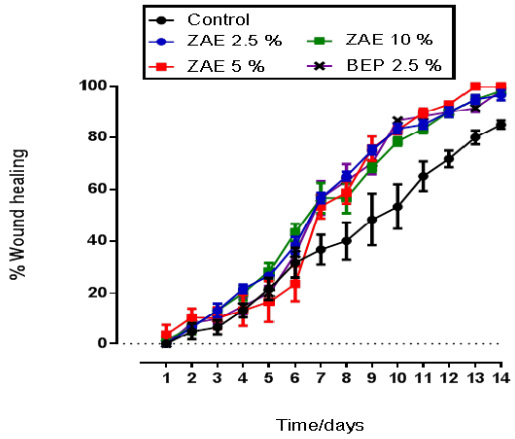

Figure 3: Assessment of *Ziziphus abyssinica* ointment on wound healing (% reduction in wound diameter) in STZ-induced diabetic rats treated topically with 2.5% becaplemin ointment or 2.5%, 5.0%, and 10% *Ziziphus abyssinica*.

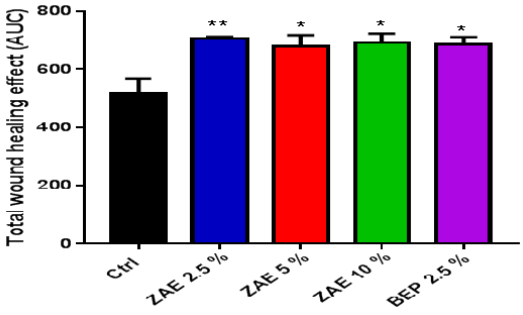

Figure 4: Assessment of *Ziziphus abyssinica* ointment on total wound healing in STZ-induced diabetic rats treated topically with 2.5% becaplemin ointment, or 2.5%, 5.0%, and 10% of *Ziziphus abyssinica* ointment for 14 days. ** $p< 0.005$ and *$p<0.01$.

Effect *Ziziphus abysinnica* on kidney histology

Figure 5 presents kidney micrographs of naïve control rats, diabetic rats with no treatments, and rats that received metformin, the various doses of the plant extracts. No morphological changes were observed in saline control rats. Diabetic rats without treatment showed severe forms of increased capsular space, vasodilatations, tubular hypertrophy, and moderate thickening of the basement membrane of glomeruli. Treated SD rats with metformin show severe thickening of the basement membrane of glomeruli alongside moderate changes, including congestion and shrinkage of glomerular. Diabetic rats treated with the least dose of extract show mild pathological changes except for shrinkage of glomerular, which is low. Meanwhile, 100 mg/kg and 300mg/kg show severe pathological changes **(Figure 5)**.

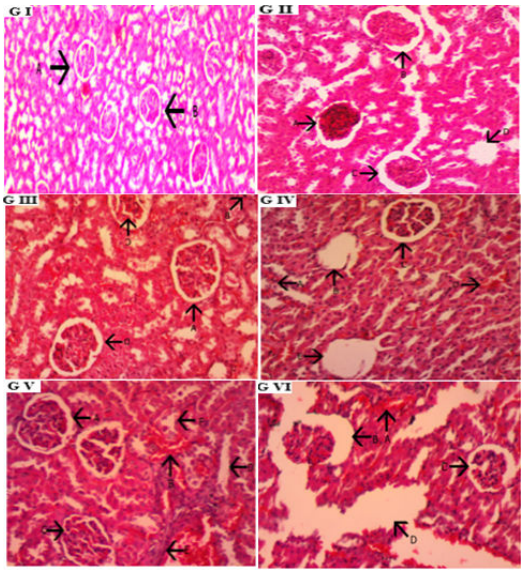

Figure 5: Effect Ziziphus abysinnica on kidney damage in STZ-induced diabetes.

Sprague-Dawley rats received either saline 10 ml/kg, metformin 300 mg/kg, or Ziziphus abysinnica 30, 100, and 300 mg/kg p.o. Test SD rats were challenged with streptozotocin (60 mg/kg, i.p.) 20 min post-administration of nicotinamide (120 mg/kg i.p.). Rats were sacrificed; kidneys removed and fixed on 10% formalin, and embedded in paraffin. About 5-6µm sections were stained with H&E for histopathological examination. Kidney micrographs for G IV, G V, and G VI=diabetes treated with 30, 100, and 300 mg/kg (p.o) ZA extracts respectively. G II=positive control group (metformin 300 mg/kg (p.o). G III= negative control group. G I=normal control group. A, B, and C are sections of the kidney showing the renal corpuscles and renal tubules. A shows a normal architecture of the tubules and renal corpuscles whiles B and C show pathologic changes such as an increase in capsular space, tubular hypertrophy, thickening of the basement membrane of the glomeruli, vasodilatations, congestion, and shrinkage of the glomeruli in varying degrees.

Discussion

Results obtained after the 14-day intervention showed that the *Ziziphus abyssinica* extract effectively lowered blood glucose concentration at all doses in a dose-dependent manner. The highest dose of the extract (300 mg/kg) had the most profound antidiabetic effect, reducing blood glucose concentration by nearly 60%. This was followed by the diabetic rats in G V and G IV, which received 100 mg/kg (30%) and 30 mg/kg (28%) of the plant extract respectively. From the results, it can be seen that the higher the dose(s) of the plant extract, the higher the percentage reduction and vice versa. Thus, the anti-hyperglycemic activity of the plant extract exhibits a dose-

dependent effect. Again, from the results, the comparison of the mean fasting blood glucose concentration values of graded doses of the plant extract with that of the diabetic control group all gave a p-value which was less than 0.05. This means that the mean fasting blood glucose concentration was significantly less in treated SD rats when compared to the diabetic control group.

The anti-hyperglycemic activity exhibited by the plant extract in this experiment can be attributed to the bioactive compounds present in the plant. Previous studies on the phytochemical analysis of *Ziziphus abyssinica* showed that the plant contains alkaloids, tannins, flavonoids, saponins, and steroids [11]. These active constituents (alkaloids, tannins, flavonoids, and steroids) are all families of compounds that have been documented to possess anti-hyperglycemic effect [17]. Thus, one or a combination of some or all of the compounds mentioned above could have been responsible for the anti-hyperglycemic effect of the extract. Highlighting the exact mechanism of action of some of these compounds,[18] reported that saponins act as the anti-hyperglycemic agent by lowering glucagon levels which were evidenced by a decrease in glucose-6-phosphatase and fructose 1, 6-diphosphatase activities in their study.

Both glucose-6-phosphatase and fructose 1, 6-diphosphatase are essential enzymes that catalyse gluconeogenic reactions in the liver. The phosphorylation and activation of these enzymes are dependent on circulating levels of glucagon. In diabetes mellitus, there is uncontrolled hepatic gluconeogenesis, which contributes to the hyperglycemia [19]. Thus, it could be possible that in diabetic animals, the lowering of glucagon levels by saponin inhibited gluconeogenesis in the liver, which consequently resulted in a decrease in the uncontrolled hepatic output of glucose into the plasma. Furthermore, tannins have also been reported to inhibit insulin degradation and improve glucose utilization [20,21].

Another mechanism by which the plant extract can cause its anti-hyperglycemic action may be through the stimulation of insulin secretion from the remaining intact pancreatic beta cells. This mechanism is postulated on the basis that the activity of the streptozotocin may have destroyed many pancreatic beta cells. Consequently, it is expected that the remaining pancreatic beta cells have to be stimulated to secrete a sufficient amount of insulin capable of causing a significant fall in the blood glucose level. As stated previously, the phytochemical screening of *Ziziphus abyssinica* revealed the presence of saponins [11]. Saponins have been shown to stimulate insulin release from the pancreas [22]. Thus, saponins in the plant extract make the above-postulated mechanism more likely to be true.

In previous studies, their results showed a significant increase in serum level of insulin in diabetic animals that were treated with *Ziziphus* extract [23,24]. This observation indicates that *Ziziphus* extracts may enhance insulin release from pancreatic beta cells, either by regenerating the partially destroyed pancreatic beta cells or releasing insulin stored in the granules. Furthermore, saponins have also been reported to inhibit the absorption of glucose from the intestine [25]. This saponin ability could be one of the alternative mechanisms through which the plant extract reduced the serum glucose concentrations in diabetic animals.

The normal control group showed regular cellular glomerular tufts in a tubules background with cuboidal cell epithelial lining with no pathological changes. In 'G III,' which was diabetes without treatment, the polyuria in the diabetic rats induced stress on the kidney cells, which caused congestion as a result of rupture of renal vessels and other pathological problems `such as tubular hypertrophy as a result of engorgement of tubules with fluids due to imbalance in osmolality caused by the damage to the nephrons [26]. Also, hyperglycemia by itself is an independent risk factor for acute tubular injury due to the activation of free radicals and oxidative stress in tubular cells. In 'G II,' where the condition was treated with a standard drug (300 mg/kg of metformin), the kidney exhibited some moderate pathologic changes such as thickening of the basement membrane of glomeruli which was because of loss of functionality of the epithelial cells and connective tissue cells to synthesise collagen fibres and reticular fibres. This consequently results in renal damage through renal hypoperfusion or endothelial injury through the release of various circulating substances.

In 'G IV', the animals received the lowest dose (30mg/kg) of the extract, and this produced minimal or moderate pathological changes to the kidney architecture, whereas groups 'G V' and' G VI' received 100mg/kg and 300mg/kg doses of the extract respectively which were very toxic as compared to the control and contributed to maximal toxic pathologic changes to the kidney nephrons. These maximal pathologic changes, such as severe thickening of the basement membrane, tubular hypertrophy was as a result of the loss of functionality of the epithelial cells and connective tissue cells to synthesise collagen fibres and reticular fibres and engorgement of tubules with fluids due to an imbalance in osmolality caused by the damage to the nephrons [26]. Congestion of the tubules was because of damage to the renal veins caused by the toxic doses of the plant extract. This consequently led to the rapture of renal veins and engorgement of glomerular vessels with blood.

The study showed that topical application of *Ziziphus abyssinica* extract (ZAE) ointment to diabetic wounds exhibited significant improvement in wound contraction and epithelialization on day eight and beyond compared to the control group. Wound contraction helps the edges of the wound pull together, and epithelization causes new covering over the wound. ZAE ointment treated wounds were dry and uninflamed, indicating that ZA roots contain abundant astringent and anti-inflammatory properties. The effects observed could be attributed to the presence of tannins, flavonoids, and alkaloids [11]. Tannins possess astringent property. Alkaloids and flavonoids have also been shown to have anti-inflammatory activity. Flavonoids also demonstrated high antioxidant and free radical-scavenging properties, enhancing the level of antioxidant enzymes in granuloma tissue [27].

Wound exudates usually provide a conducive environment for microbial growth. Bacteria such as *P. aeruginosa* and *S. aureus* isolated from wounds have been resistant to some antibacterial agents. The study observed that ZAE ointment could have promoted wound healing by inhibiting the growth of bacteria, resulting in possible wound healing. The antimicrobial activity

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may be due to the presence of flavonoids [28] in ZAE. Sterols and polyphenols have been reported to be responsible for wound healing due to their free radical-scavenging and antioxidant activity. These phytochemicals are also known to possess lipid peroxidation reduction abilities, which prevents cell necrosis and improves vascularity (angiogenesis), thus increasing circulation (oxygen and essential nutrients) to the injured site [29]. The resultant effect is enhanced epithelial cell proliferation [30].

Conclusion

Conclusively, the anti-hyperglycaemic effect of the root extract of *Ziziphus abyssinica* was exhibited by the various doses, with the highest dose showing the highest percentage reduction in glucose concentration. Even though the percentage glucose concentration reduction was much higher than metformin, there were moderate pathological changes to the kidneys. Topical application of ZA ointment showed efficacy for treating diabetic wounds. Put together, the present study has demonstrated the potential of *Ziziphus abyssinica* in managing diabetes and diabetic nephropathy in murine models.

Conflict of interest

The authors declare that they have no conflict of interest.

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