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Exploring the Therapeutic Potential of Derris elliptica (Wall.) Benth in Streptozotocin-Induced Diabetic Rats: Phytochemical Characterization and Antidiabetic Evaluation

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Abstract: Derris elliptica (Wall.) Benth, a native medicinal plant, has been used to treat diabetes for centuries; however, comprehensive documentation of its bioactive constituents and therapeutic effectiveness is lacking. This study investigated the phytochemical profile and antidiabetic potential of D. elliptica methanolic leaf extract in diabetic Sprague Dawley rats induced with streptozotocin (STZ). Acute oral toxicity evaluations were conducted in normal rats, and in STZ-induced rats, antidiabetic properties were investigated. Assessed parameters included blood glucose levels, alterations in body weight, biochemical markers, and histological analysis of the pancreas, liver, and kidney. Numerous phytoconstituents were uncovered through qualitative phytochemical assays, 1H NMR, and 1H-13C HSQC screening. Quercetin was identified by HPLC and 1H NMR characterization, and a ceramide analogue compound was isolated and partially characterized by 1H NMR. There were no indications of toxicity or mortality. The treatment with D. elliptica extract significantly (p>0.001) decreased body weight and had a remarkable hypoglycemic effect. Both 200 mg/kg and 400 mg/kg extract concentrations decreased total cholesterol levels significantly (p>0.01 and p>0.05, respectively). In addition, glibenclamide and the 400 mg/kg dose of extract increased serum insulin levels substantially (p > 0.05) and decreased total bilirubin, lactic acid dehydrogenase, aspartate aminotransferase, and alanine aminotransferase levels. In addition to glibenclamide, treatment with D. elliptica extract exhibited cytoprotective effects and increased insulin secretion, exerting an antihyperglycemic potent impact. These results suggest that D. elliptica may have therapeutic potential for managing diabetes mellitus. Keywords: Derris elliptica, streptozotocin, antidiabetic, HPLC, NMR

1. Introduction

Diabetes is a significant public health concern in Malaysia and the prevalence of type 2 diabetes has escalated to 20.8% in adults above 30, affecting 2.8 million individuals (Hussein et al., 2015). The National Health and Morbidity survey states that 3.9 million people aged 18 years and above suffer from diabetes (Institute for Public Health, National Institutes of Health, 2020). Diabetes mellitus can become more costly when complications of the disease occur and dialysis treatment also contributes to long-term burden and health budgets (Crasto, 2021; Kane et al., 2021; J. Singh et al., 2022).

Despite the availability of clinical therapeutic agents, patients may seek an option for alternative remedies (Sharma et al., 2022), such as natural products, to control these complications and improve glycemic control and glucose intolerance (Furman et al., 2020). Medicinal plants with hypoglycemic effects are used worldwide to treat diabetes with minimal side effects, a challenge for improving diabetes care (Aba & Asuzu, 2018).

It's crucial to find an effective, natural and safe oral hypoglycemic agent to prevent, treat, and manage diabetes. Derris elliptica (Wall.) Benth is a leguminous plant from the Fabaceae family and, locally known as akar tuba, has been used traditionally by Malay and Iban communities in Sarawak to treat diabetes since long ago. It also treats several disorders like weakness, menorrhagia, headache, toothache and rheumatism (Chai, 2006). Ceramides isolated from the same plant family may be relevant in the lipotoxicity that causes diabetes, hepatic steatosis, and heart disease (Boon et al., 2013; Chaurasia et al., 2019; Lu & Liang, 2011; Sokolowska & Blachnio-Zabielska, 2019). The diversity of phytochemicals suggests that D. elliptica could serve as a natural source of traditional medicine for the treatment of various diseases or be able to maintain β-cell performance and decrease glucose levels in the blood (Bindu Jacob & Narendhirakannan R.T., 2019; Do et al., 2014; Kooti et al., 2016). Pharmacological studies were carried out to evaluate the D. elliptica methanolic leave extract on streptozotocin (STZ) diabetic-induced rats, including toxicity, biochemical and histopathology on rat model and finally, isolation of phytochemicals from the extract.

2. Materials and methods

2.1. Chemicals and drugs

All chemicals were purchased from local suppliers (Merck, Fisher, Sigma, Chemsolute, Chem Elisa Kit and Pharmaniaga). The chemicals and reagents were n-Hexane (Hex), methanol (MeOH), chloroform ($CHCl_3$) and ethyl acetate (EA), acetonitrile HPLC grade, acetonitrile (CH_3CN) grade deuterated chloroform (CD_3OD), formic acid, standard reference quercetin (Sigma, 95% for HPLC analysis). Streptozotocin was from Sigma Chemicals. Insulin Elisa Kit was obtained from Mercodia Inc., USA.

2.2. Plant material, extraction and fractionation

The fresh leaves of Derris elliptica (D. elliptica) were collected from Tasek Bera (DD Coordinates 3.8166634 102.416665), Kuantan, Pahang Malaysia. The leaves were identified and authenticated by a botanist from Taman Botani, Putrajaya, Malaysia. A voucher specimen (HTBP 5119) was placed at

the herbarium Taman Botani Putrajaya, Malaysia. One (1) kg of leaves was washed, dried at 40°C, and then crushed. The dried powder of D. elliptica was extracted with methanol. The methanol maceration took three days at room temperature with occasional shaking. Filtration and rotary vacuum evaporation removed excess solvent from the extract. The methanolic extract of D. elliptica (DEME)
was then fractionated by silica gel column chromatography packed with silica gel 60 (0.063-0.200 mm,70-230 mesh ASTM, Merck). The crude extract was loaded on a column and eluted with n-hexane, dichloromethane, and methanol gradually to increase polarity. All fractions were dried in a rotatory evaporator at 40°C. 2.3. Phytochemical screening, isolation and characterization
Standard procedures were used to conduct qualitative phytochemical screening utilizing specific reagents to identify the presence groups of compounds such as alkaloids, flavonoids, sugar, phytosterol, and amino acids. Proton (1H) nuclear magnetic resonance (
NMR) and 1H,13C-HSQC spectra were recorded on a Bruker AVANCE III Ascend 600 spectrometer using
a BBO probe with deuterated chloroform (CD3OD) as the solvent and tetramethylsilane (TMS) as an internal reference standard for the screening of extract.
The TLC fingerprint profile was developed following fractionation
using the stationary phase TLC silica gel 60 F254 plates (aluminium sheets, 20 cm × 20 cm, Merck).
Different ratios of n-hexane, chloroform, and ethyl acetate optimized the mobile phase until the best separation was achieved.
For the derivatization procedure, the TLC plates were sprayed with anisaldehyde and ceric sulphate reagent, air-dried at room temperature and heated at 110°C until clear spots appeared on
the TLC plate. The p-anisaldehyde-sulfuric acid reagent was used to derivatize and visualize non-UV-active chemicals on the
TLC plate.
For the HPLC analysis, the sample was prepared by filtering with a 0.45 µm membrane pore size filter into HPLC vials. Chromatographic analyses were performed on Agilent 1200 RP-HPLC and eluted on
the Zorbax C18 column with dimensions 150 mm × 4.6mm and 5 µm pore size. A mobile phase of 0.3 % aqueous formic acid and acetonitrile (CH3CN) was used for optimal chromatographic separation in gradient elution mode. A step-wise gradient elution was utilized, starting at 10% CH3CN and increasing to 90% CH3CN in 40 minutes at 1 ml/min. The chromatogram was recorded on a
diode array detector (DAD) at 254 nm and the data were processed by Chemstation software. The
chromatogram was recorded on a 254 nm diode array detector (DAD) and analyzed by Chemstation software. The targeted chemicals were identified by isocratic elution using 0.3% aqueous formic acid and CH3CN on a C18 column (2.1 x 50 mm, 1.8 (m) at a flow rate of 0.2 ml/min. For the isolation,
the glass preparative TLC silica gel plate (60G F254 Merck, 20 cm x 20 cm) was developed in
a mobile phase containing hexane and ethyl acetate (8:2). Pure compound bands were scraped and rinsed in methanol then filtered. Pure compounds were characterized using 1H-NMR on a Bruker 500 MHz with TMS internal standard and CD3OD as solvent. The raw data were processed with Bruker Software Topspin 2.1 and data was matched to a reference to determine the compound and potential plant functional groups. 2.4. Pharmacological studies 2.4.1. Experimental Animals
A total number of 36 healthy Sprague Dawley (SD) male rats (age 9 to 10 weeks) weighing between 200-250 g were used in the study. The rats were obtained from laboratory animal facility and management (LAFAM),
faculty of pharmacy and transported as per the animal ethics regulation. The rats were acclimatized for one week (7 days) at the
pharmacology laboratory, School of Pharmacy KPJ Healthcare University College (KPJUC), Kota Seriemas, Negeri Sembilan. All experiments adhered to the ethical norms approved by
the Animal Ethics Committee, KPJUC (Approval no: KPJUC /CRI/LEC/EC/2015/09). They were housed in a polypropylene cage lined by corncob bedding with a change interval every 48 hours. Each cage consisted of 6 rats and provided
standard environmental conditions at an ambient temperature of 25 to 27oC with 12 12-hour light-dark cycles. The rats were supplied with standard pellet food (702P Gold Coin, Limited, Malaysia) and water ad libitium. 2.4.2. Acute Toxicity Studies
An acute

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toxicity study followed the Organization for Economic Co-Operation and Development guideline (

OECD) (Section 4 Test No.423).
The study used
six male SD rats (OECD, 2002). The animals were divided into two groups consisting of three animals in each group (n = 3). The rats were fasted for twelve hours before the study and weighed before administration with
the
extract. The acute toxicology dose was calculated in reference to the body weight of the
rats.
The methanolic extract (DEME) was dissolved in distilled water. A single dose of 2000 mg/kg
was
administered orally (oral gavage, stainless steel, 3.00 mm ball diameter (16 G), Havard / USA) attached to 1 ml or 3 ml syringe) to three male rats in the treatment group, whereas control groups received only distilled water. The animals were observed for 30 minutes after dosing
and then monitored hourly until 8 hours. After 8 hours, the animals are monitored once daily for 14 days to observe any changes in toxicological symptoms, including behaviour neurological and autonomic profiles. 2.4.3. Drug treatment and experimental design for antidiabetic activity The pharmacological evaluation was performed in 30 rats. The animals were divided into 5 groups, containing 6 rats in each group (n = 6). The animals were treated with DEME orally at 200 mg/kg and 400 mg/kg for 14 days. The two treatment dsoses were selected from the acute toxicity study as per the OECD guidelines. The drug treatment DAME was started 72 hours after STZ-induced diabetic rats. The treatment design follows as mentioned, Group I: Normal control rats receiving water p.o Group II: Negative control (diabetes induced), treated with STZ, receiving water p.o Group III: Diabetic rats (induced with STZ) and treated with glibenclamide 10 mg/kg Group IV: Diabetic rats (induced with STZ)
and treated
with DEME extract 200 mg/kg Group V: Diabetic rats (induced with STZ)
and treated
with DEME extract 400 mg/kg The food and water intake were monitored daily. The body weights of each rat were measured and recorded with an animal weighing scale (Kent Scientific Scl-101)
on
day 1 and day 14 of the treatment. Weekly blood glucose monitoring was performed on day 7 and day 14 days of treatment for all groups. At the end of the 14-day treatment, blood samples were collected from overnight fasted rats by retro-orbital sinus puncture using a capillary tube under diethyl ether anaesthesia. The serum was separated by centrifuging (Centrifuges, Hettich Zentrifugen, EBA 200) the blood samples at 4000 rpm for 15 minutes and stored at -20°C before biochemical analysis. 2.4.4. Biochemical Analysis Aspartate amino transaminase (AST), Alanine amino transaminase (ALT), Lactate dehydrogenase (LDH), Total cholesterol (TC), Total glucose (TG) and Total bilirubin (T.Bil) were determined (Al-Attar & Alsalmi, 2019) using a semi-automated biochemical analyzer (BioLis 24i Premium) (Biorex Manheim Diagnostics) at Hematology and Clinical Biochemistry Lab, Faculty of Veterinary Medicine, Universiti Putra Malaysia. Serum insulin level was estimated using
the Mercodia Rat Insulin ELISA kit (Ghiasi et al., 2019).
The serum sample was diluted with 50 µl Calibrator 0'at ratio 5 µl: 50 µl. The enzyme conjugate was labelled 1X solution was prepared by gently mixing 1000 µl of enzyme conjugate 11X solution and 10 ml of enzyme conjugate buffer and the enzyme conjugate 1X was kept at 2-8ºC.
The
estimation of insulin in the test sample was determined according to
the manufacturer's direction with a
standard calibrator curve. 2.4.5. Histopathological Study After collection of the blood sample, rats were euthanized by cervical dislocation. Organs such as
the
pancreas, kidneys and livers were removed and rapidly fixed in
a 10%
buffered formalin solution. The tissues were processed for paraffin sectioning by dehydrating in different concentrations of (70% to 100%) ethanol, cleared with xylene and embedded in paraffin wax. Sections cut at 5 µm (Micrometre) thick paraffin were made and stained with haematoxylin and eosin (H & E) staining (Slaoui & Fiette, 2011). Photomicrographs of the stained slides were taken using a light microscope (Olympus Optical) attached to a digital camera (Lumenera, 2.0). 2.4.6. Statistical Analysis Statistical evaluation was done using Graph Pad Prism 7. Analysis of variance (ANOVA)
was
tested when more than 2 groups were involved. Post hoc comparisons were made using

the Turkey test and the
homogeneity test of variances. The data were expressed as mean ± Standard Error Mean (SEM). p-value > 0.05 can be considered statistically significant. 2. Results and discussion 2.1. Phytochemicals screening
and compound characterization Prior to commencing the pharmacological activity study, the phytochemical profile of the D. elliptica methanolic leaves extract was investigated. The results revealed that it contains
alkaloids, reducing sugar, phytosterol, and flavonoids, but not proteins. Table 1 summarizes the results of the phytochemical qualitative screening of D. elliptica methanolic leaves extract. Table 1. Phytochemical qualitative screening of D. elliptica methanolic leaves extract
The high-resolution NMR spectrum (600 MHz, CD3OD) of crude extract
supported the presence of phytosterols, terpenoids, alkaloids, tannins, carbohydrates, and several polar classes of compounds such as polyhydroxy and polyphenols in the extract (Figure 1). The 1H NMR spectrum of
the methanolic extract revealed characteristic resonances of phytosterols, terpenoids at the
upfield region (0.9-1.3) and OH-bearing methine proton resonated at 3.7. 1H NMR data
for the crude methanolic extract showed deshielded protons at 7.2-8.4, indicating a trisubstituted flavonoid. 1H-13C-HSQC correlations confirmed the presence of sugar moieties in the extract. 1H NMR spectra discovered polyphenolic contents in the methanolic extract with deshielded proton resonances. The 1H, 13C-HSQC (Figure 1) technique was used to establish 1H-13C correlations. Correlations of aromatic protons with deshielded carbon atoms and OH-bearing methine proton with methine carbon resonated at 72.6, suggesting the presence of phytosterols (
Figure 1).
Figure 1: 1H NMR spectrum of D. elliptica methanolic leaves extract (left); 1H,13C-HSQC spectrum of D. elliptica leaves methanolic extract (right).
Thirteen silica column chromatography fractions were pooled based on similar spots. F9 had the most spots on its TLC profile, indicating it may contain major compounds. This fraction gave the best separation in CHCl3/n-hexane (7:3) or n-hexane/ethyl acetate mobile phases (8:2). The spot turned violet with an Rf of 0.59 when stained with p-Anisaldehyde-sulfuric acid, suggesting the extract contains
phenolic compounds.
Terpene-like compounds were also detected on the TLC profile
with blue and greyish bands, while steroidal compounds
with a green band had Rf values of 0.82, 0.59, 0.48, and 0.32. Optimization HPLC suggested gradient elution with an acidic mobile phase for separating this sample. Fraction F9's chromatogram shows a major peak at 14.7 minutes and other peaks from 3 to 20 minutes. A compound similar to quercetin was present in the F9 fraction, as indicated by the reference standard quercetin (Figure 2). The two aromatic protons on the benzopyrone of quercetin, at C6 and C8, resonated as a doublet at 6.17 ppm and 6.40 ppm, respectively; The C2' (7.63 ppm) and C6' (7.75 ppm) protons on the catechol substituent resonated as a doublet (J = 8.3 Hz) and singlet, respectively. In contrast, the C5' proton only couples to a single neighbouring proton (C6') and appeared as a doublet at 6.91 ppm. From the 1H NMR spectral data provided, it has been determined that the extract contains quercetin (Figure 2). Figure 2: Above, chromatogram of fraction F9 (left); standard reference quercetin (right); Bottom, 1H NMR characterization quercetin in fraction F9 .
Extensive research indicates that bioflavonoids, with quercetin as an illustrative example, have therapeutic potential for diabetes management. These natural compounds, which are produced by plants via the phenylpropanoid pathway, provide a safer alternative to conventional treatments due to their negligible or non-existent adverse effects. Quercetin's multi-targeted approach, which affects organs such as muscles, the pancreas, the liver, and the small intestine, demonstrates its potential to regulate essential signalling pathways. Furthermore, the ability of quercetin to increase insulin secretion, protect pancreatic beta cells from oxidative stress, and strengthen cellular antioxidant defences demonstrates its capacity to treat not only hyperglycemia but also the macrovascular and microvascular complications of diabetes. Bioflavonoids such as quercetin offer a promising avenue for developing novel and more holistic approaches to diabetes treatment and prevention as research in this field advances (Dhanya, 2022).
Subsequently, phytoconstituents were isolated using preparative TLC, yielding four 1H-NMR-analyzed compounds. Many methylene peaks in 1H-NMR suggest a long aliphatic chain at 0.82 to 2.06 ppm. Multiple signals at 0.84 to 1.311 ppm indicate methyl groups. Broad signals at 3.65 ppm indicated a hydroxyl group, while signals between 4.12 and 4.2 ppm suggested methine protons. A 7.28 ppm doublet signal indicates a secondary amine group (NH). Chemical shifts of major 1H-NMR functional groups were compared to published data, and the ceramide analogue structure was postulated (
Figure 3). Figure 3: 1H-NMR spectra and ceramide structure

Recent research has identified a specific class of lipids, namely ceramides, as a significant factor in the onset and persistence of certain diseases. These ceramides, a subtype of sphingolipids, play a pivotal role in numerous sphingolipid pathways. It has been observed that elevated ceramide levels correlate with compromised cardiovascular and metabolic health. Moreover, it appears that the interaction between ceramides and adipokines, particularly adiponectin and leptin, contributes to the underlying mechanisms of these conditions. It appears that adiponectin mitigates the negative effects of elevated ceramide levels by activating the ceramidase function of its receptors. On the other hand, increased ceramides exacerbate leptin resistance, a crucial pathophysiological phenomenon in obesity and metabolic syndrome (Field et al., 2020; Sokolowska & Blachnio-Zabielska, 2019). 2.2. Pharmacological Studies

2.2.1. Acute toxicity study The drug D. elliptica extract was considered non-toxic, as it does not exhibit any toxic signs or symptoms and no mortality was observed at the dose of 2000 mg/kg (oral) in mice. According to OECD- 423 guidelines, the LD50 of 2000 mg/kg and above is considered unclassified and non-toxic.

2.2.2. Effect of D. elliptica methanolic leaves extract on body weight in STZ-induced diabetic rats. All rats' body weight, blood glucose, and insulin levels were monitored weekly during the experiments. On day 14, normal, negative diabetics and treated diabetics had different body weights. The negative diabetic control group lost 60.9 g, while glibenclamide 10 mg/kg, extract 200 mg/kg, and extract 400 mg/kg lost 82.7 g, 63.6 g, and 35.1 g, respectively. The negative diabetic control group had a mean body weight of 151.3 ± 8.2 mg, while the normal group had 258 8.0 mg. Mean body weight was 297 ± 13.6 mg for glibenclamide, 274 ± 25.4 mg for 200 mg/kg, and 249.3 19.03 mg for 400 mg/kg. The negative diabetic control group lost weight (p> 0.001) compared to the normal group. D. elliptica extract and glibenclamide-treated diabetic rats gained weight (p>0.001) compared to the control group. The results of body weight difference are mentioned in Table 2.

Table 2: Effect of DEME on Body Weight Level of STZ-induced rats

2.2.3. Effect of D. elliptica methanolic leaves extract on biochemical parameters in STZ-induced diabetic rats. The weekly monitoring of blood glucose is regulated after treatment. In the negative control group, glucose levels were significantly higher (p > 0.001) after day 7 but decreased to 459.7 ± 38.95 mg/dl (p > 0.001) after day 14 when compared to the 7th-day level. The STZ-treated group had higher fasting blood glucose. After 14 days of treatment, the rat's total glucose levels were significantly controlled (Table 3). Diabetic control group concentrations were significantly higher (p>0.001) than normal. Glucose levels were lower in glibenclamide-treated diabetic animals (p>0.001). Total glucose in glibenclamide-treated animals reached near normal levels, while 200 mg/kg and 400 mg/kg of extracts reduced glucose and controlled diabetic conditions. After 14 days, diabetic animals administrated with 200 mg/kg and 400 mg/kg extract had better blood glucose control (p> 0.001). Table 4 represents the biochemical parameters. Negative diabetic control group insulin levels were significantly lower (p>0.05) than normal. Diabetic rats treated with 10 mg/kg glibenclamide and 400 mg/kg extract had higher (p>0.05) serum insulin levels. 200 mg/kg reduced insulin, but the diabetic control group did not affect it. Negative diabetic control group ALT levels were significantly higher (p>0.001). Standard drugs and extracts (200 mg/kg and 400 mg/kg) decreased (p>0.05) AST levels and had a protective effect in STZ-induced rats. Serum triglyceride was elevated (p>0.001) in STZ-induced rats and was controlled by 200mg/kg (p>0.05) and 400mg/kg (p>0.001). 200 mg/kg extract lowered total cholesterol significantly (p>0.01), while 400mg/kg had the least effect (p>0.05). Total bilirubin and LDH decreased at 200 mg/kg (p 0.01). 400mg/kg demonstrates a mild reduction.

Table 3: Effect of the DEME on Blood Glucose Level in STZ-Induced Diabetic Rats

Weekly

Table 4: Effect of the DEME on biochemical parameters in STZ-Induced Rats

2.2.4. Histopathological Study

The histological investigation was conducted to assess the effect of extract (200 mg/kg and 400 mg/kg) on kidney, liver, and pancreatic histopathological changes

in normal, diabetes negative control, and glibenclamide. The morphology of organs from the treated animals exhibits a protective effect and is found to reduce cell degeneration. The photomicrographs are shown in Figures 4, 5 and 6. Figure 4: Photomicrographs of Pancreatic
section Figure 5: Photomicrographs of Liver sections Figure 6: Photomicrographs of Kidney sections
Diabetes is considered a metabolic syndrome condition which triggers cardiovascular disease flowed by neuropathy and nephropathy (
Einarson et al., 2018). Treatments for diabetes and other complex metabolic diseases were the key objectives of traditional plant medicines (D. Singh & Singh, 2021). The D. elliptica extract showed promise in controlling glycemia and biochemical regulation in STZ-induced diabetic rats. The D. elliptica leaves extract passed acute toxicity tests. STZ is used to induce diabetes in animal models and to study -cell dysfunction (J. Wu & Yan, 2015). In the STZ-induced diabetes model, many herbal formulations and orient drugs showed promising (Venkatachalam et al., 2021). STZ-induced pancreatic beta cell toxicity and diabetes
activate poly ADP-ribosylation and alkylate DNA. Poly ADP-ribosylation depletes NAD+ and ATP (Eleazu et al., 2013). Oxidative stress in diabetes involves glucose auto-oxidation, protein glycation,
the polyol pathway, and lipid imbalance(Ether & Saif-Ur-Rahman, 2021; Juchli et al., 2021). During these processes, cytokine stimulation produces ROS that damage -cell diabetic rats (Zhang et al., 2016). In this study, the extract controlled diabetic conditions by improving the level of insulin and liver enzymes. D. elliptica

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leaves extract has potential for antidiabetic action in STZ-induced diabetic rats and the effect was found to be more similar to the reference drug glibenclamide.

These findings support the claim that the D. elliptica extract showed antidiabetic activities by improving the body weight in diabetic rats.
The extract at a higher dose (400mg/kg) was more effective than a lower dose (200mg/kg) after 14 days of treatment. As a result, it has been discovered that high-dose extract is more efficient and has a similar therapeutic effect to standard glibenclamide (10 mg/kg). The antidiabetic effect may be due to the increased insulin release from the existing β-cells of the pancreas. The rise in plasma insulin levels that have been observed indicates that the extract stimulates insulin secretion. It is also
effective in increasing body weight and reducing the blood glucose level in
the
chemically induced diabetic in small animal models. D. elliptica extract improved insulin, AST, ALT, TP, TG, LDH, T Bil and TC. Insulin deficiency contributes to derangements of lipid metabolism in DM. Dyslipidemia found in diabetic rats is characterized by elevated levels of TC. These changes in the lipid profile can represent a risk factor
for cardiovascular disease (W.-C. Wu
et al., 2020). It is well established that lipoprotein lipase (LPL) activity plays a central role in serum triglyceride-rich lipoprotein particles and HDL levels. On the other hand, in the diabetic state, this enzyme is poorly activated due to insulin deficiency. As a result, the lack of LPL activity led to hypertriglyceridemia. In addition, this lack of insulin may account for dyslipidemia, as insulin inhibits hydroximethylglutaril coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme for metabolizing cholesterol-rich LDL particles. Furthermore, insulin decreases VLDL formation by regulating the fatty acid levels in plasma and suppresses the VLDL1 production in the liver, independent of the availability of fatty acids (
H. Singh et al., 2020). The extract from D. elliptica leaves may have lipid-lowering effects because it has an insulin-like action, which enhances insulin sensitivity in people with diabetes and contributes to the effects. Moreover,
the administration of STZ induced hepatic damage, which was associated with increased plasmatic levels of AST and ALT. These increased levels were caused by oxidative dysfunction
related to an
imbalance in insulin secretion. The hepatic dysfunction in diabetic conditions as indicated by elevated levels of AST, ALT, TP, TG, LDH, and total bilirubin (
Kotb El-Sayed et al., 2020). The extract-based intervention brought the increased liver enzyme levels back to normal. The results of the histological studies showed that normal pancreatic, liver, and kidney functions are among its antidiabetic mechanisms, along with regeneration and restoration. This might be due to its ability to raise insulin secretion in STZ-induced diabetic rats, which has an anti-hyperglycaemic effect with a high dose of 400 mg/kg extract. The ceramide analogue compound isolated from the plant extract, previously reported in terms of its pharmacological significance, could be important for managing the antidiabetic effect.

Conclusion This investigation has yielded encouraging information regarding its potential therapeutic benefits. While the plant's historical use was well-documented, this study also aims to understand its bioactive constituents and therapeutic efficacy comprehensively. Through a series of meticulous investigations involving acute oral toxicity evaluations in normal rats and antidiabetic evaluations in streptozotocin-induced diabetic rats, this study uncovered several significant findings. Notably, the 14-day oral administration of D. elliptica methanolic leaves extract combined with standard glibenclamide at varying doses resulted in a substantial reduction in body weight and a remarkable hypoglycemic effect, demonstrating its potential as an antidiabetic agent. In addition, our phytochemical analyses, which included qualitative assays, NMR screening, revealed a variety of phytoconstituents within the extract. The identification of quercetin via HPLC and 1H NMR characterization, as well as the isolation and partial characterization of a ceramide analogue compound, sheds light on the complex composition of the extract. There are no indications of toxicity or mortality in relation to the use of D. elliptica extract from this study, which highlights its safety profile. In addition, the extract exhibited positive effects on lipid profiles, notably decreasing total cholesterol levels. In addition, it increased insulin secretion and reduced levels of total bilirubin, lactic acid dehydrogenase, aspartate aminotransferase, and alanine aminotransferase, indicating a potential role in protecting pancreatic function and enhancing metabolic health. The extract's cytoprotective properties and ability to increase insulin secretion, when combined with glibenclamide, highlight its robust antihyperglycemic potential. These findings suggest that D. elliptica may indeed have therapeutic potential of this plant for diabetes management. To fully realize its potential and develop effective treatments for diabetes, additional research and clinical studies are required.

Declaration of interest We declare that we have no conflicts of interest regarding this work.

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During the preparation of this work, the author(s) used ChatGPT 3.5 in order to improve readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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leaves extract has potential for antidiabetic action in STZ-induced diabetic rats and the effect was found to be more similar to the reference drug glibenclamide.

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