Med & Health Jun 2023; 18(1): 117-135 https://doi.org/10.17576/MH.2023.1801.12

ORIGINAL ARTICLE

Antidiabetic Effect of *Actinodaphne angustifolia* and Profiling of Bioactive Metabolites using UPLC-QToF/ESI-MS Method

MD. SHAEKH F[1], WAN MAZNAH WI[1], MOHD FADHLIZIL FASIHI MA[3,4], SHIHAB UDDIN A[5], KAMRUL R[2], SAIFUL NIZAM T[3], AKM MOYEENUL H[3,5]

[1]Faculty of Chemical and Process Engineering Technology, Universiti Malaysia Pahang, Lebuh Persiaran Tun Khalil Yaakob, 26300, Gambang, Kuantan, Pahang, Malaysia.
[2]Quality Assurance Department, Incepta Pharmaceuticals Limited, Zirabo Unit, Zirabo, Savar, Dhaka 1340, Bangladesh.
[3]Bio Aromatic Research Centre, Universiti Malaysia Pahang, Lebuh Persiaran Tun Khalil Yaakob, 26300, Gambang, Kuantan, Pahang, Malaysia.
[4]Faculty of Industrial Science and Technology, Universiti Malaysia Pahang, Lebuh Persiaran Tun Khalil Yaakob, 26300, Gambang, Kuantan, Pahang, Malaysia.
[5]Department of Pharmacy, School of Medicine, University of Asia Pacific, 74/A, Green Road, Farmgate, Dhaka-1205, Bangladesh.

ABSTRAK

Diabetes mellitus adalah gangguan kronik yang menyebabkan paras glukosa darah meningkat akibat kekurangan insulin, sama ada sepenuhnya atau sebahagian. Kami menyiasat sifat antidiabetik Actinodaphne angustifolia dalam model tikus dan mengenal pasti fitokimia bioaktif dengan menggunakan kaedah UPLC-QTOF/ESI-MS. Struktur pankreas tikus, profil lipid dan glukosa darah dinilai selepas intervensi selama satu minggu. Analisis UPLC-QTOF/ESI-MS telah dijalankan untuk mengenal pasti flavonoid dan terpenoid dalam ekstrak daun. Ekstrak Actinodaphne angustifolia dengan ketara meningkatkan lipoprotein berketumpatan tinggi (HDL) ($p<0.05$) sambil mengurangkan jumlah kolesterol (TC), lipoprotein berketumpatan rendah (LDL) dan glukosa darah. Tambahan pula, struktur seni tisu pulau pankreas juga pulih dengan baik berbanding kumpulan kawalan. Sebanyak 45 flavonoid dan 109 sebatian terpenoid telah dikenal pasti menggunakan analisis berasaskan UPLC-QTOF/ESI-MS dan kajian tambahan perlu dijalankan untuk mengenal pasti agen antidiabetik yang berpotensi.

Kata kunci: aktiviti antidiabetik, Actinodaphne angustifolia, fitokimia, UPLC-QTOF/ESI-MS

Address for correspondence and reprint requests: AKM Moyeenul Huq. Bio Aromatic Research Centre, Universiti Malaysia Pahang, Lebuhraya Tun Razak, 26300, Gambang, Kuantan, Pahang, Malaysia. Tel: +6018-2620051 Email: moyeenul@ump.edu.my; moyeenul.rph@uap-bd.edu/ Wan Maznah Wan Ishak. Faculty of Chemical and Process Engineering Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak, 26300, Gambang, Kuantan, Pahang, Malaysia. Tel: +6017-7142780 E-mail: wanmaznah@ump.edu.my

ABSTRACT

Diabetes mellitus is a chronic disorder that causes elevated blood glucose levels due to a lack of insulin, either completely or partially. We investigated the antidiabetic property of *Actinodaphne angustifolia* in a rat model and identified the bioactive phytochemicals by using the UPLC-QTOF/ESI-MS method. The rats' pancreatic structures, lipid profile and blood glucose were assessed after a one-week intervention. UPLC-QTOF/ESI-MS analysis was conducted to identify flavonoids and terpenoids in the leaf extract. *Actinodaphne angustifolia* extract markedly increased the high-density lipoprotein (HDL) ($p<0.05$) while reducing total cholesterol (TC), low-density lipoprotein (LDL) and blood glucose. Furthermore, the tissue architecture of pancreatic islets was also well recovered as compared to the control group. A total of 45 flavonoids and 109 terpenoid compounds were identified using UPLC-QTOF/ESI-MS-based analysis and additional studies should be undertaken to identify the potential antidiabetic agents.

Keywords: antidiabetic activity, *Actinodaphne angustifolia*, phytochemical, UPLC-QTOF/ESI-MS

INTRODUCTION

Almost 6% of the global population is affected by diabetes mellitus. This is a multifaceted and chronic metabolic disease that is also becoming prevalent in low to middle-income countries (Forid et al. 2021; Deore et al. 2022). It is reported that 422 million of the global population are diabetic and 1.5 million patients died due to diabetes (Nazir et al. 2018). However, according to the International Diabetes Federation (IDF) in 2021, 537 million people diagnosed with diabetics and projected to reach 643 and 784 million by 2030 and 2045, respectively. The IDF also reported that diabeties was responsible for 6.7 million deaths in 2021 (International Diabetes Federation 2021).

One of the main ways that diabetes causes damage to tissues is through the reactive oxygen species (ROS) generated by hyperglycemia (Dewanjee et al. 2009). Moreover, chronic hyperglycemia can lead to damage to the kidneys, eyes, arteries and nerves due to the glycation of proteins (Foretz et al. 2019). To defend and repair against such damage, researchers have been investigating many natural products that contain antioxidants, which are substances that can scavenge ROS and reactive nitrogen species (RNS), thus reducing the risk of diabetes complications and enhancing the immune defense (Deore et al. 2011).

At present, several drugs are available in market, such as hormone replacement (insulin) and glucose-lowering agents such as thiazolidinediones, biguanides,

sulfonylureas and alpha-glucosidase inhibitors, but most of them have side effects like vomiting, anorexia, skin rashes, heartburn and gastrointestinal discomforts (Mawa et al. 2019; Forid et al. 2021). Thus, many researchers are investigating the use of herbal remedies in treating a wide varieties of diseases, including diabetes, that have less or no side effects and toxicity while still being efficient and cost-effective.

Actinodaphne angustifolia (*A. angustifolia)* Nees is an Asian plant (Family- Lauraceae) (Uddin et al. 2020). The *Actinodaphne* is an important genus both pharmaceutically and medicinally. The trees are usually 3 to 25 m in height. The leaves are clustered or nearly verticillate, rarely alternate or opposite, unlobed, pinninerved and rarely triplinerved. They have small, greenish star-shaped flowers. It is widely distributed in the forests of Bangladesh, India, Malaysia and Indonesia (Purkayastha 1985). Traditionally, a decoction of *A. angustifolia* leaf is used in kidney trouble due to stone (Lokendrajit et al. 2011). The leaf is also used as a folk medicine to treat diabetes and urinary disorders in the Khagrachari district of Chittagong (Uddin et al. 2020). It is very little available information on the pharmacological activities which only include antidiarrheal, antioxidant and thrombolytic activities (Uddin et al. 2020). Several phytochemical studies of the leaves showed the presence of hydrocarbons, friedelin, vitexin, quercetin-3-O-rhamnoside and β-sitosterol (Rastogi & Mehrotra 1992; Asolkar et al. 1992). Despite of the traditional antidiabetic application of *A. aungustifolia* leaf, there has been no study conducted to verify its folklore use. Therefore, the current study was carried out to evaluate the antidiabetic activity of *A. angustifolia* in rat model.

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals and reagents were analytical grade except stated otherwise. Ethanol and alloxan were from Sigma-Aldrich Chemicals, CA, USA. The standard drug glibenclamide was purchased from Chadwell Heath Essex, England.

Plant Collection and Identification

The fresh leaves of *A. angustifolia* were obtained from the Chattogram district in March 2018. An expert taxonomist from the Bangladesh National Herbarium Dhaka, Bangladesh was consulted to identify the plant. For future reference, a voucher specimen (accession No. 46052) was submitted to the Bangladesh National Herbarium, Mirpur and Dhaka.

Preparation of Crude Extract

Distilled water was used to wash the fresh *A. angustifolia* leaves. Then, shade-drying was used to dry the leaves for 10 days at room temperature (25 ± 1°C) to avoid damaging by heat-sensitive phytochemicals. After drying, a mechanical grinder (Miyako, Model No: DL-718 Jiaxing China) was used to grind the leaves into 500 g of powder which was then stored in an

airtight container. A simple maceration technique was used for extraction in 2.5 L of ethanol (96%) at room temperature (25 ± 1°C) using 400 g of the powder. The extraction was continued for 7 days with occasional stirring, filtered and concentrated under reduced pressure in a rotary evaporator (Barloworld, Berkshire, UK) at 50°C. The resultant concentrated extract was then air-dried to completely remove any remaining solvents and stored at 4°C for test.

Experimental Animals and Their Husbandary

A total of 24 male and female Long-Evans rats (5-6 weeks old; average body weight 92-9 g) were purchased from the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR, B), located in Mohakhali, Dhaka, Bangladesh. A typical rat pellet diet obtained from the ICDDR,B was given along with access to fresh drinking water during the experiment. The rats were kept in plastic cages with bedding made of soft wood shavings in an adequately ventilated chamber at a constant temperature of 25°C, a relative humidity of 55-65% and a 12 hours cycle of day and night. Animals were handled in accordance with ethical guideline of Southeast University animal ethics committee (Approval. No.: SEU/Pharm/CECR/102/2019).

Acute Toxicity of *A. angustifolia*

A modified protocol has been adopted based on OECD guideline to evaluate the preliminary toxicity profile of the *A. angustifolia* (OECD 2000). Long-Evans rats were distributed into two groups (two rats in each group) and fasted overnight (water only). Group-I was given a single oral dose of 500 mg/kg body weight of *A. angustifolia* extract, and Group-II received a single oral dose of *A. angustifolia* (1000 mg/kg body weight). For a total of 10 days, each animal was checked following oral administration of *A. angustifolia*, at the first 30 minutes and periodically throughout the first 24 hours, with extra care given during the first 4 hours and every day after that. The rats were closely monitored and individual records of each rat were kept for obvious behavioral, neurological, and autonomic alterations, and each animal's unique records were kept. Additional records on tremor, convulsion, salivation, diarrhea, lethargy, sleep, coma, and death were also noted if any.

Diabetes Induction and Design of the Experiment

For the diabetes induction, 16 Long-Evans rats of both sexes with the average body weights of 92 ± 9 g were used. Alloxan monohydrate (150 mg/kg) was administered intraperitoneally (IP) once to overnight-fasted rats. Rats with consistent fasting serum glucose levels of >7.5 mmol/L for 3 days after alloxan injection were considered as diabetic as measured by a portable glucometer (Accu-Chek, Japan). After 72 hours of alloxan injection, *A. angustifolia* treatment was begun. Feeding cannulas were used to deliver the plant extract, standard

drug glibenclamide and saline. Fasting blood glucose level was estimated on the 3rd, 5th and 7th day of the study. The following groups were divided for the animals: (i) Normal control (I): Only saline water was given; (ii) Diabetic control (II): Diabetic rats with no treatment (alloxan; 150 mg/kg; IP); (iii) Positive control (III): Diabetic rats treated with standard drug (alloxan;150 mg/kg; IP) + glibenclamide (5 mg/kg; PO); (iv) Treatment group (IV): Alloxan induced (150 mg/kg; IP) + *A. angustifolia* (250 mg/kg; PO); and (v) Treatment group (V): Alloxan induced (150 mg/kg; IP) + *A. angustifolia* (500 mg/kg; PO).

Biochemical Analysis

After receiving treatment for 7 days, the animals' fasting serum glucose levels were assessed. Diethyl ether was used to anesthetise the rats before they were decapitated. In accordance with the heart puncture procedure of Kärber et al. (1931), blood was drawn into a dry test tube by cardiac puncture with the help of a disposable syringe and then centrifuged at 112 g for 15 minutes. The plasma was kept at 4°C until further biochemical evaluations. Wet reagent diagnostic kits together with a biochemical analyser (BAS 100TS, Spectronics Corporation, LA, U.S.A) were used in accordance with the manufacturer's instructions to measure the total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) (Hodge et al. 2020; Parthasarathy et al. 2009; Mueller et al. 1977).

Histopathological Studies

Histopathological studies were carried out following the method described by Forid et al. 2021. The comparative effect of the leaf extract of *A. angustifolia* and standard glibenclamide on the pancreatic tissue architecture was observed. The pancreas of treated rats was collected from each group when sacrificed and cleaned with saline water and preserved in formalin solution (10%). After washing, the pancreas was washed and dehydrated with alcohol followed by cleaning with xylene and paraffin blocks. The blocks were subsequently sliced into serial sections (4-5 µm thickness) using a semi-automated microtome (Biobase BK-MT390S, Jinan, Shandong, China). After that, the sections were hydrated with lowering concentrations of alcohol and deparaffinised with xylene. The slides were then rinsed with water after being dyed with hematoxylene for 10 minutes. These were inspected, stained with eosin once again, washed with xylene, dehydrated with increasing alcohol concentrations and then mounted. An Optica DP20 system was used to view the histopathological pictures, pancreatic tissue shape and cellular state.

Phytochemical Profiling of Bioactive Extract

UPLC-MS was used to determine the phytoconstituents of the *A. angustifolia* extract. Waters ACQUITY UPLC IClass/Xevo and a Waters Xevo G2 Q-TOF mass spectrometer were coupled and integrated with positive electrospray

ionisation mode for the UPLCMS analysis (Milford, MA, USA). About 100 mg of the extract was dissolved in 1 mL of ethanol to create extract samples. A Zorbax Eclipse plus Acquity UPLC BEH C18 column (1.7 m particle size) 2.1 mm x 50 mm in diameter was used for separation. From m/z 50 to 1000, a complete scan mode was run while maintaining a 120°C source temperature. A gradient elution system was created using solvents A and B, solvent A was water with 0.1% formic acid and solvent B was acetonitrile with 0.1% formic acid. For the first 15 minutes, the elution conditions were 99% solvent A and 1% solvent B, then 65% solvent A and 35% solvent B for 1 minute, then a progressive increase in solvent A to 100% over 2 minutes, and lastly a gradual increase in solvent B to 99% and solvent A 1% over 2 minutes. For nebulising and collision gases, ultra-high-pure nitrogen (N2) and helium (He), respectively, were employed. A 2.0 kV capillary voltage in positive electrospray mode was used. Other inferred instrument settings were a 100 V source offset, 550°C desolvation temperature, 50 L/h cone gas flow with 120°C temperature desolvation gas flow and 800 L/h.

Statistical Analysis

All experimental data obtained were expressed as mean standard error of mean (SEM) where n=4. Data were normalised by One way-ANOVA statistical tool was used and Tukey's post hoc test was done to analyse the difference, using GraphPad Prism ,version 6 (GraphPad Software, USA). The *p*-value less than 0.05 was considered as significant value.

RESULTS AND DISCUSSIONS

Acute Oral Toxicity and Dose Selection

Animals are used in acute oral toxicity studies to determine the safety of products based on plants and other formulations for humans. The oral treatment of *A. angustifolia* to rats did not affect any changes in their behavioral characteristics in the acute toxicity investigation. Even at the greater dose of 1000 mg/kg body weight of *A. angustifolia* ethanol leaves extract, no detrimental and abnormal effects of the experimental animals were seen. As very little pharmacological studies had been conducted on this plant species and its potential acute toxicity at higher doses was needed to be carried out along with sub-acute and chronic toxicity profile.

Effect of *A. angustifolia* on Blood Glucose Levels

Figure 1 illustrated how the *A. angustifolia* leaf extract affected the blood sugar level. The administration of alloxan raised blood glucose levels significantly which remained stable over the course of the study in comparison to the normal control group (4.45 ± 0.03 mmol/L). When comparing with the diabetic group, the *A. angustifolia* extract at 250 and 500 mg/kg body weight doses were able to substantially lower the increased blood glucose level (11.8 ± 0.5 mmol/L,

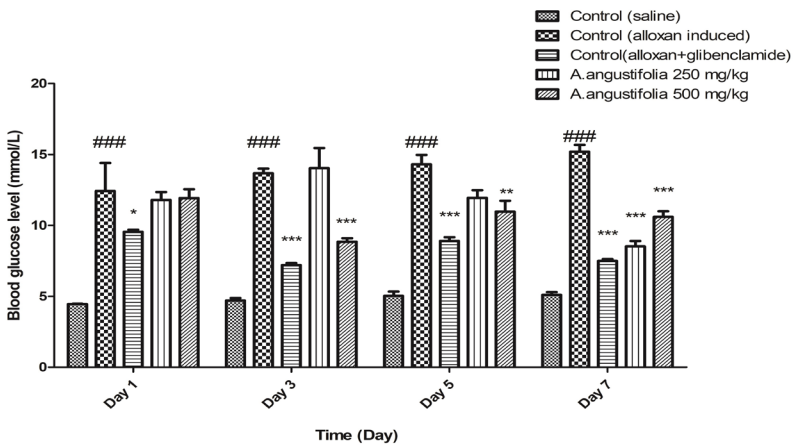

Figure 1: Effect of A. angustifolia ethanol leaf extract on blood glucose level. Glibenclamide was used as a positive control. The values were represented as mean ± SEM; n = 4. One-way ANOVA with Tukey post-hoc analysis was done where (*) represented p<0.05 from the alloxan induced control and (#) represented significant from the control (saline) groups.

p<0.001 and (11.92 ± 0.62 mmol/L, p<0.001 respectively) over the duration of the treatment after each. Throughout the course of the 7-days intervention, a progressive reduction in blood glucose was seen (Figure 1). In this study, only fasting glucose level was measured. Therefore, acute oral glucose tolerance test and insulin level measurement needed to be done to determine how quickly glucose is cleared from the blood and to diagnose insulin resistance.

Effect of *A. angustifolia* extract on Lipid Profiles

Serum lipid profiles were measured as depicted in Figure 2. In comparison to the diabetic control group, both dosages of *A. angustifolia* extract (250 and 500 mg/kg body weight) reduced LDL levels (5.69 ± 0.14 mmol/L, p<0.001) while continued to enhance the HDL levels (9.41 ± 0.53 and 7.76 ± 0.66 mmol/L, respectively, p<0.001). Reduced levels of total blood cholesterol of 8.58 ± 1.07 mmol/L (p<0.001) by 250 mg/kg and 7.76 ± 0.66 mmol/L (p<0.001) by 500 mg/kg were also seen. In comparison to the diabetic control group (4.78 ± 0.05 mmol/L), the triglyceride level was considerably reduced (p<0.01 only at the dosage of 500 mg/kg body, or 2.9 ± 0.32 mmol/L).

Dyslipidemia is the major consequence of diabetes mellitus which is characterised by abnormal HDL, LDL, TG or TC blood level in patients and increases the risk of cardiovascular disease (CVD) and mortality. Current therapies for this condition include the use of statins. However, statins possess adverse effects, including paralysis, cataracts, memory loss, myositis, myalgias, hepatotoxicity, polyneuropathy, myopathy and tendinopathy (Muhammad et al. 2019; Abbaszadeh et al. 2018). These problems could be minimised by using alternative remedies such as

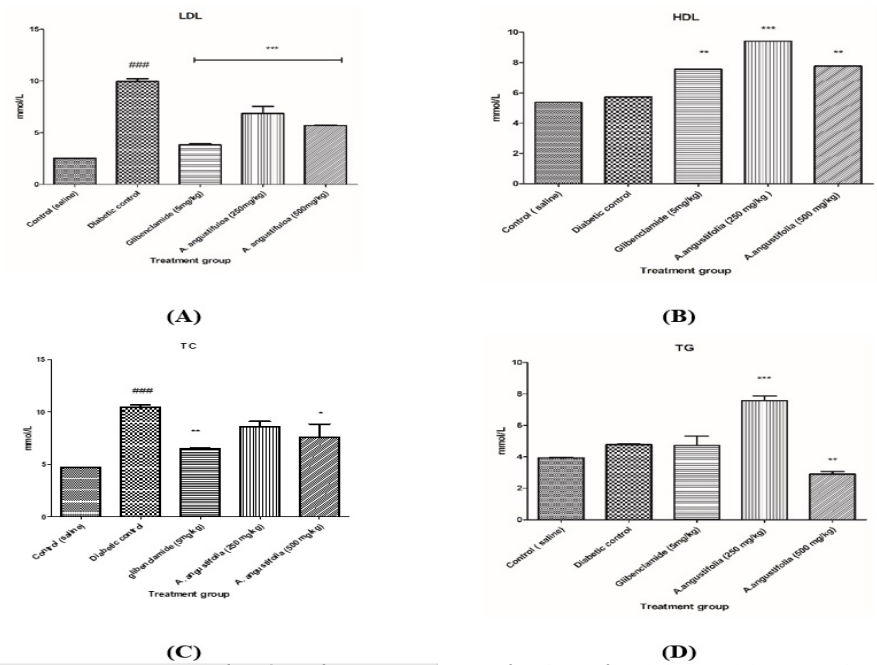

Figure 2: Effect of *A. angustifolia* ethanol extract on serum lipid profiles: (A) LDL, (B) HDL, (C) TC and (D) TG levels of different treatment groups. Glibenclamide at 5 mg/kg body weight dose was used as positive control. Data represented here as mean ± SEM of four animals and were analyzed via One-way ANOVA using Dunnet multiple range post hoc test. The sign (*) over the bar denoted significant different from diabetic control, and (#) indicated significant difference from control (saline).

herbal medicines to treat dyslipidemia without the potential negative effects of pharmaceutical medicines (Amani et al. 2018). Herbs are rich in many bioactive components such fibers, antioxidants, flavonoids, glycosides, plant sterols, saponins, catechins, stanols and triterpenoids, and can be used as functional foods (Amani et al. 2018; Enkhmaa et al. 2015; Alipour et al. 2018). In hyperlipidemia, there is less glucose transport into the cells. Therefore, lipids are more available in the form of LDL fat and deposited to the arterial wall as fatty plaques. These fatty plaques are transported to the liver by HDL for elimination (Virmani et al. 2006). Therefore, the level of HDL and LDL in blood in an inversely proportional manner which is expected to be the therapeutic application of *A. angustifolia* extract.

Effect of *A. angustifolia* Extract on Pancreatic Tissue Architecture

The hematoxylin and eosin staining method was used to examine the morphology of the pancreatic tissues of the different experimental groups. The histopathology of the pancreatic islets were shown in Figure 3. Figure 3A showed a normal tissue morphology of the pancreas and islet cells in normal rats (group I). However, the size and number of the β islet cells were found to be reduced in the diabetic-induced (150 mg/kg) group

II rats, that resulted in shrinkage. On the other hand, the morphology of pancreatic islets was restored and improved in the animals with diabetes in groups IV and V that were treated with *A. angustifolia* extract (250 mg/kg and 500 mg/kg body weight, respectively). This outcome was also similar to those given glibenclamide (5 mg/kg). The pancreas helps to control metabolism. Changes in the production, sensitivity, and control of insulin during metabolic activities are reflected in the structural changes in the pancreas. The characteristics of pancreatic destruction include islet atrophy, a decline in number of β-cells, and cellular damage (Jaiswal et al. 2017). Alloxan-injected rats might have recovered from the effects of the drug mostly due to the regeneration of β islet cells after they were destroyed by the alloxan. The increased number of β-cells in the pancreas in Figure 3 D, E might be an indication of the recovery effect of *A. angustifolia* leaf extracts. This possible mechanism could be the survival of a greater number of β-cells upon *A. angustifolia* treatment to release more insulin.

Identification of Flavonoids and Triterpenoids from *A. angustifolia* Leaf Extract by UPLC-QTOF/ESI-MS

Due to the potential antidiabetic

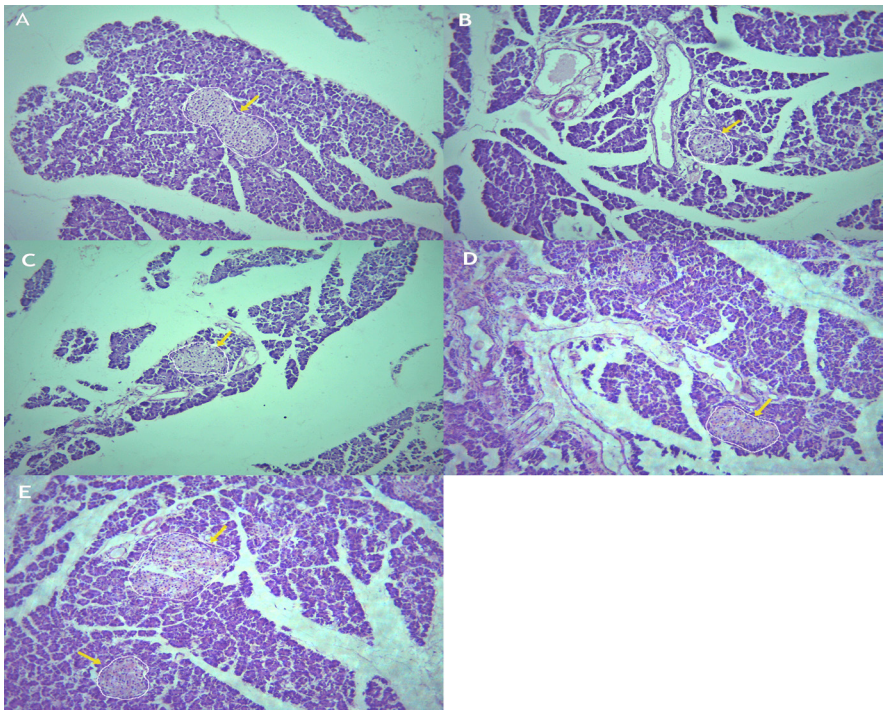

Figure 3: Histopathological slides of rat pancreas cells after 7 days of treatment: (A) normal control (presence of normal islet cells), (B) diabetic control (shrinkage of the islet cells), (C) diabetic + glibenclamide 5 mg/kg (increased number and size of islet cells), (D) diabetic + *A. angustifolia* extract 250 mg/kg (improved size and shape of islet cells), and (E) diabetic + *A. angustifolia* extract 500 mg/kg (restored number and size of islets).

activity, the bioactive extract was then further subjected to phytochemical profiling by using UPLC-QTOF/ESI-MS that can separate and analyse the compounds. This technique can provide the inclusive mass of different ions and accurate chemical formulae (Yousefi et al. 2013). In our study, the positive mode ((+) ESI-MS) and negative mode ((-) ESI-MS) managed to identify the presence of flavonoids based on the pattern of mass fragments, and ion response that were automatically elucidated and verified. The identified compounds were classified either as good match with an error of ± 5 mDa or as poor match with an error of ± 10 mDa by the UNIFY software.

A total of 45 flavonoids and 109 triterpenoid compounds were identified from the ethanolic extract of *A. angustifolia* as presented in Table 1. The biological activity of plant extracts is due to the presence of different chemical constituents in it. The numerous bioactive compounds could be presented as a mixture which plays a synergistic role for the activity. Some of the identified flavonoids and terpenoids in *A. angusifolia* extract have been reported to show various biological activities and might be responsible for its antidiabetic activity. Flavonoids have a wide range of beneficial effects on metabolic illnesses including diabetes (Middleton et al. 2000). Flavonoids' can regulate insulin signaling and production, carbohydrate digestion glucose absorption and adipose deposition (Vinayagam & Xu 2015) by targeting pathways, related to cell proliferation, stimulating insulin secretion, decreasing apoptosis, and alleviating hyperglycemia through regulating glucose metabolism in the liver (Graf et al. 2005).

Among the identified flavonoids in this study, 3,4-dihydroxyphenothyl-3-O-β-D-glucopyranoside has been reported to exhibit antioxidant activity (Ukaegbu et al. 2018). Another compound, episappanol, has an anti-inflammatory effect (Mueller et al. 2016). Meanwhile, cyclomorusin is an extended flavonoid, and it is a moderate inhibitor of acetylcholinesterase and a strong inhibitor of platelet-activating factor induced platelet aggregation and has a potential role as an anti-hypoglycemic agent (Abd-EL-Mawla et al. 2011; Fernández-Rojas et al. 2022). Jaceosidin has a role as an anti-inflammatory agent (Kim et al. 2008), an apoptosis inducer (Lv et al. 2008), an anti-allergic, antineoplastic (Nam et al. 2013) and antidiabetic agent (Kang et al. 2007). Apocynin B has been reported for its hepato and neuro protective activities (Petrônio et al. 2013; Simonyi et al. 2012) and neuroprotective activity. Irisflorentin can suppress allergic inflammation (Li & Meng et al. 2019). Bowdichione is a hydroxyisoflavone and it exhibits antineoplastic and anti-inflammatory activities (Umehara et al. 2009).

The antioxidant flavonoid molecule kaempferol, also known as kaempferol 3 or kaempferide, lowers oxidative stress, possesses antibacterial and geroprotective properties. Rat studies have also shown that kaempferol has a hypoglycemic and hypolipidemic effects (Devi et al. 2015; Imran et al. 2019; Ren et al. 2019; Chandramohan et al. 2014). It

Table 1: Tentative identified flavonoid compounds using UPLC-QTOF/ESI-MS-Based analysis from *A. angustifolia*.

SL. No.	Observed RT (min)	Compound name	Chemical Formula	Observed neutral mass (Da)	Observed m/z	Mass error (ppm)	Adducts
			Flavonoids				
1	0.41	Carthamidin	$C_{15}H_{12}O_6$	288.0608	288.0602	-9.1	-e
2	0.47	Sanggenon H	$C_{20}H_{18}O_6$	354.1068	354.1063	-9.9	-e
3	0.59	Kuwanon L	$C_{35}H_{30}O_1$	626.1823	626.1817	5.5	-e
4	0.8	3,4-Dihydroxy phenothyl-3-O-β-D-glucopyranoside		288.0822	289.0895	-7.9	+H
5	1.81	Episappanol	$C_{16}H_{16}O_6$	304.0945	311.11	-0.6	+Li
6	2.37	Cyclomorusin	$C_{25}H_{22}O_6$	418.1446	419.1519	7	+H
7	3.05	Kuwanon A	$C_{25}H_{24}O_6$	420.1601	421.1673	6.6	+H
8	3.84	3,4-Dihydroverbenalin	$C_{15}H_{10}O_5$	390.1502	391.1575	-6	+H, +Na
9	3.9	Jaceosidin	$C_{17}H_{14}O_7$	330.074	337.0894	0.1	+Li
10	4.54	2′-Hydroxynaringenin	$C_{15}H_{12}O_6$	288.0633	289.0706	-0.3	+H
11	5.03	Apocynin B	$C_{24}H_{20}O_{10}$	468.1061	475.1216	1	+Li
12	5.06	Quercetagetin-3,4′-dimethyl ether	$C_{17}H_{14}O_7$	346.0689	353.0843	0	+Li
13	5.17	Kushenol T	$C_{25}H_{30}O_6$	426.2023	426.2018	-4.6	-e
14	5.36	7-Hydroxy-3,5,6,8,3′,4′-hexamethoxyflavone		418.1265	425.142	0.3	+Li
15	5.42	Gardenin E	$C_{19}H_{18}O_9$	390.0954	397.1108	0.7	+Li
16	5.78	Irisflorentin	$C_{20}H_{18}O_8$	386.1031	409.0924	7.3	+Na
17	5.79	Arecatannin A1	$C_{45}H_{38}O_{18}$	866.2073	867.2146	1.8	+H, +K, +Na
18	6.49	Sanggenon A	$C_{25}H_{24}O_7$	436.1494	436.1489	-6.3	-e
19	7.39	Natsudaidain	$C_{21}H_{22}O_9$	418.1265	419.1338	0.4	+H
20	7.96	Ulmoside		508.1824	515.1979	6.3	+Li
21	8.46	Viscidulin I	$C_{15}H_{10}O_7$	302.0426	303.0499	-0.2	+H
22	8.5	Bowdichione	$C_{16}H_{10}O_6$	298.0502	305.0656	7.9	+Li
23	8.5	Kaempferol	$C_{15}H_{10}O_6$	286.0475	287.0548	-0.7	+H
24	8.61	Macrophylloside D	$C_{41}H_{44}O_{20}$	558.1952	558.1947	0.6	-e
25	8.75	Isocryptomerin	$C_{31}H_{20}O_{10}$	552.1088	559.1243	5.7	+Li
26	9.34	Kushenol P	$C_{26}H_{32}O_7$	456.212	495.1752	-5.6	+K
27	9.45	Pedalitin	$C_{16}H_{12}O_7$	316.0578	317.0651	-1.6	+H
28	9.46	Quercetin-3-methyl ether	$C_{16}H_{12}O_7$	316.0578	317.0651	-1.6	+H
29	9.58	Retusine	$C_{19}H_{18}O_7$	358.1053	397.0685	0.2	+K
30	9.82	Resokaempferol	$C_{21}H_{20}O_{10}$	270.0527	271.06	-0.3	+H

31	9.83	Kushecarpins C	$C_{17}H_{16}O_7$	332.0918	355.081	6.2	+Na
32	10.82	Galangin (Norizalpinin)	$C_{15}H_{10}O_5$	270.0525	271.0597	-1.4	+H
33	10.83	5,7,2′,5′-Tetrahydroxy-flavone	$C_{15}H_{12}O_6$	286.0477	287.055	-0.1	+H
34	10.83	Fisetin	$C_{15}H_{10}O_6$	286.0477	287.055	-0.1	+H
35	11.02	Mulberrofuran P	$C_{34}H_{22}O_9$	574.1285	575.1358	3.7	+H
36	12.11	Isoirigenin	$C_{18}H_{16}O_8$	360.0842	361.0914	-1	+H
37	13.09	Casticin	$C_{19}H_{18}O_8$	374.1	375.1073	-0.5	+H
38	13.49	Kushenol S	$C_{20}H_{20}O_5$	340.1309	347.1464	-0.4	+Li
39	14.98	Leucodelphinidin	$C_{15}H_{14}O_8$	322.0706	345.0598	4.9	+Na
40	15.51	5-Hydroxyauranetin	$C_{20}H_{20}O_8$	388.1158	389.1231	0	+H
41	16.58	3′-Deoxysappanol	$C_{16}H_{16}O_5$	288.0992	289.1065	-1.9	+H
42	16.58	Irisolidone	$C_{17}H_{14}O_6$	314.0792	315.0865	0.6	+H
43	16.6	Quercetagetin-6,7,3′,4′-tetramethyl ether	$C_{19}H_{18}O_8$	374.1001	375.1074	-0.2	+H, -e
44	16.66	Asebotin	$C_{22}H_{26}O_1$	450.1536	457.1691	2.2	+Li
45	16.71	Dichotomitin	$C_{18}H_{14}O_8$	358.0679	359.0751	-2.8	+H
		Triterpenoids					
1	0.35	Turpinionosides B	$C_{19}H_{34}O_8$	390.2232	413.2124	-2.2	+Na
2	0.47	Oxybenzoyl paeoniflorin	$C_{30}H_{32}O_{14}$	600.1874	601.1947	3.1	+H, -e
3	1.66	Reptoside	$C_{17}H_{26}O_{40}$	392.1291	393.1364	-2.8	+H
4	1.94	Agnuside	$C_{22}H_{26}O_{11}$	466.1473	473.1628	-0.2	+Li
5	2.55	Divaricatol	$C_{17}H_{18}O_7$	334.105	341.1204	-0.3	+Li
6	2.68	Monotropein	$C_{16}H_{22}O_{11}$	390.1134	391.1207	-2.8	+H, +Na
7	3.27	Loganin_1	$C_{17}H_{26}O_{10}$	390.1524	413.1416	-0.2	+Na
8	3.32	7-O-Methylmorroniside	$C_{18}H_{28}O_{11}$	420.1605	421.1678	-2.6	+H
9	3.47	Aucubin	$C_{15}H_{22}O_9$	346.1265	369.1157	0.1	+Na, +H
10	3.5	Ginkgolide C	$C_{20}H_{24}O_{11}$	440.1323	447.1477	0.4	+Li
11	4.07	Mudanpioside G	$C_{16}H_{24}O_8$	344.1447	345.152	-2.4	+H
12	4.87	Bruceine B	$C_{23}H_{28}O_{11}$	480.1609	481.1682	-2.3	+H, +Li
13	5.08	Lactucopicrin	$C_{23}H_{22}O_7$	410.137	417.1524	0.4	+Li
14	5.29	Cichorioside C	$C_{21}H_{32}O_9$	428.2027	429.21	-1.9	+H
15	5.34	Curcolone	$C_{15}H_{18}O_3$	246.128	269.1172	2.4	+Na
16	5.42	Dehydrobruceine B	$C_{23}H_{26}O_{11}$	478.1475	485.1629	0	+Li
17	5.54	Schizonepetoside E	$C_{16}H_{28}O_8$	348.1785	371.1677	0	+Na
18	5.89	Ginkgolide J	$C_{20}H_{24}O_{10}$	424.1347	425.142	-2.3	+H
19	6.14	Taraxacin	$C_{15}H_{14}O_3$	242.0966	265.0858	2.3	+Na
20	6.23	Bruceine E	$C_{20}H_{28}O_9$	412.1716	419.1871	-1.7	+Li
21	6.24	Nigakilactone H	$C_{22}H_{32}O_8$	424.2128	463.176	3.1	+K
22	6.26	Rehmannioside D	$C_{27}H_{42}O_{20}$	686.2238	709.213	-3.2	+Na

23	6.72	Bruceine A	$C_{26}H_{34}O_{11}$	522.2101	545.1993	0	+Na
24	6.94	1,6-O,O-Diacetylbritannilactone	$C_{19}H_{26}O_6$	350.1732	357.1887	0.3	+Li
25	7.09	Brusatol	$C_{26}H_{32}O_{11}$	520.1941	527.2096	-0.3	+Li
26	7.38	Bruceoside B	$C_{32}H_{42}O_{16}$	682.2487	705.2379	1.4	+Na
27	7.75	Icariside B4	$C_{19}H_{32}O_8$	388.2097	411.1989	-0.1	+Na
28	7.81	Genkwadaphnin	$C_{34}H_{34}O_{10}$	602.2142	602.2136	-1	-e
29	7.95	Picrasin F	$C_{22}H_{30}O_8$	422.1966	422.196	2.5	-e
30	8.05	Kansuiphorin A	$C_{54}H_{90}O_9$	882.6599	883.6672	1.4	+H, -e
31	8.2	Nomilin	$C_{28}H_{34}O_9$	514.2178	514.2173	-2.5	-e
32	8.2	Turpinionosides E	$C_{19}H_{32}O_8$	388.2095	411.1987	-0.3	+Na
33	8.62	Picrasin G	$C_{21}H_{28}O_7$	392.1816	393.1889	-1.9	+H
34	8.69	Ambrosin	$C_{15}H_{18}O_3$	246.1248	247.1321	-0.8	+H
35	8.7	(-)-Istanbulin A	$C_{15}H_{20}O_4$	264.1355	287.1248	-0.6	+Na, +H
36	8.75	7-Hydroxy-1-methoxy-2-methoxyxanthone	$C_{14}H_{10}O_4$	286.0475	287.0548	-0.2	+H
37	8.84	Magnaldehyde B	$C_{18}H_{16}O_3$	280.1094	280.1088	-0.6	-e
38	8.95	Esculentagenin	$C_{31}H_{46}O_8$	546.3219	585.2851	2.6	+K
39	8.95	Ganoderic acid α	$C_{32}H_{46}O_9$	574.3116	581.327	-2.6	+Li
40	9.16	Yadanzioside C	$C_{34}H_{46}O_{17}$	726.2731	749.2623	-0.4	+Na
41	9.18	Scutellone C		530.2518	537.2672	0.2	+Li
42	9.32	Nigakilactone E	$C_{24}H_{34}O_8$	450.2256	457.2411	0.2	+Li
43	9.38	Pseudolaric acid A O-β-D-glucopyranoside	$C_{29}H_{38}O_{13}$	550.2409	557.2564	-0.5	+Li
44	9.41	Melianol	$C_{30}H_{48}O_4$	612.3337	613.341	3.9	+H
45	9.48	Stilbostemin D	$C_{16}H_{18}O_3$	258.1262	265.1416	0.6	+Li
46	9.55	Picrasinol B	$C_{22}H_{32}O_6$	392.2192	399.2347	-0.7	+Li
47	9.82	Nobilone	$C_{14}H_{10}O_4$	242.0578	243.0651	-0.1	+H, -e
48	9.88	Taraxacolide-1-O-β-D-glucopyranoside	$C_{21}H_{32}O_9$	430.2204	453.2096	0.1	+Na
49	10.04	Oxyphyllenone B	$C_{12}H_{18}O_3$	210.1256	233.1149	0	+Na
50	10.75	Nomilinic acid	$C_{28}H_{36}O_{10}$	532.2304	539.2458	-0.5	+Li
51	11.48	Perillylaldehyde	$C_{10}H_{14}O$	164.1218	187.111	1.7	+Na
52	11.48	Lucidenic acid D2 methyl ester	$C_{29}H_{38}O_8$	528.2719	551.2611	-0.4	+Na
53	11.58	Blestrianol B	$C_{30}H_{30}O_6$	588.218	589.2252	3.2	+H
54	11.6	Crocetin	$C_{20}H_{24}O_4$	328.1668	335.1823	-0.7	+Li
55	11.96	Simalikalactone D	$C_{25}H_{34}O_9$	478.22	485.2355	-0.3	+Li
56	11.97	Nimbolidin D	$C_{36}H_{44}O_9$	726.3663	749.3555	4.8	+Na
57	12.18	Yadanzioside A	$C_{32}H_{44}O_{16}$	684.2608	685.2681	-2.1	+H
58	12.18	Platycodigenin	$C_{30}H_{48}O_7$	520.3449	559.308	4.9	+K
59	12.27	Ilicic acid	$C_{15}H_{24}O_3$	252.1718	275.161	-0.8	+Na

60	12.31	Yadanzioside P	$C_{34}H_{46}O_{16}$	710.28	733.2692	1.4	+Na
61	13.99	Picrasinoside G	$C_{28}H_{44}O_{12}$	572.2819	573.2891	-1.4	+H
62	14.12	Neotussilagolactone	$C_{21}H_{28}O_4$	344.1984	351.2139	-0.4	+Li
63	14.33	(E)-Aldosecologanin	$C_{34}H_{46}O_{19}$	742.2728	743.28	4.4	+H
64	14.36	Eclalbasaponin IX	$C_{36}H_{62}O_8$	702.404	725.3933	2.8	+Na
65	14.63	Dihydroactinidiolide	$C_{11}H_{16}O_2$	180.1148	181.1221	-0.3	+H, +Na
66	16.02	Curcumenone	$C_{15}H_{22}O_2$	234.1615	257.1507	-0.5	+Na
67	16.12	Eclalbasaponin V		714.3679	753.3311	3	+K
68	16.15	Isolinderalactone	$C_{15}H_{16}O_3$	244.1075	267.0967	-2.5	+Na
69	16.31	Palbinone	$C_{22}H_{30}O_4$	358.2139	365.2293	-0.5	+Li
70	16.37	Picrasinoside H	$C_{30}H_{44}O_{13}$	612.2773	651.2405	-0.9	+K
71	16.52	Poricoic acid C	$C_{31}H_{46}O_4$	482.3446	505.3338	5	+Na, +Li
72	16.52	Asperulosidic acid	$C_{18}H_{24}O_{12}$	432.1229	439.1384	-3.9	+Li
73	16.53	Tenuifolin	$C_{36}H_{56}O_{12}$	680.3802	680.3797	3	-e, +H, +Na
74	16.53	Gedunin	$C_{28}H_{34}O_7$	482.2342	483.2415	3.8	+H
75	16.53	Lucidenic acid O	$C_{27}H_{40}O_7$	476.2771	477.2844	-0.3	+H, +Na
76	16.53	Olibanumols J	$C_{30}H_{52}O_3$	460.3928	461.4001	1.1	+H
77	16.54	Cucurbitacin B	$C_{32}H_{46}O_8$	558.3236	597.2867	4.3	+K, +H, +Li, +Na
78	16.55	Dehydrosoyasaponin I	$C_{48}H_{76}O_{18}$	940.5026	940.502	-0.6	-e
79	16.56	Crocetin dimethyl ester	$C_{22}H_{28}O_4$	356.2	363.2154	1.2	+Li
80	16.58	Arnicolide D	$C_{19}H_{24}O_5$	332.1595	333.1668	-2.9	+H
81	16.6	Raddeanoside R13		896.515	896.5144	1.7	-e
82	16.61	14-Deoxyandrographolide	$C_{20}H_{30}O_4$	334.2129	335.2201	-1.6	+H
83	16.62	Onitin	$C_{15}H_{20}O_3$	248.1432	271.1324	1.9	+Na, +H
84	16.63	Agroastragaloside II	$C_{43}H_{72}O_{15}$	828.4915	828.491	4.4	-e
85	16.64	Oxyphyllol B	$C_{15}H_{22}O_2$	234.1632	257.1524	1.2	+Na
86	16.65	Ganoderenic acid C	$C_{30}H_{46}O_7$	516.3059	517.3132	-2.8	+H, +Na
87	16.65	Sericic acid	$C_{30}H_{48}O_6$	504.3429	504.3424	-2.2	-e
88	16.68	Curzerene	$C_{15}H_{20}O$	216.1511	217.1583	-0.3	+H
89	16.71	Lindestrene	$C_{15}H_{18}O$	214.1357	215.1429	-0.1	+H
90	16.72	Oleanonic acid	$C_{30}H_{48}O_3$	454.3408	454.3403	-3.9	-e
91	16.76	Nigakilactone I	$C_{21}H_{28}O_6$	376.1884	383.2039	-0.2	+Li
92	16.77	Dehydrofukinone	$C_{15}H_{22}O$	218.1668	219.1741	-0.3	+H
93	16.79	Prosapogenin 2	$C_{32}H_{48}O_8$	560.3369	567.3524	2	+Li, +H
94	16.79	Methyl ganoderate B	$C_{31}H_{46}O_7$	530.3233	537.3388	-1	+Li
95	16.87	Ginsenoside F3	$C_{41}H_{70}O_{13}$	770.4791	771.4864	-2.5	+H, +Li
96	16.87	Deglucose chikusetsusaponin IVa		632.3926	639.408	0.1	+Li, +Na

97	16.87	Quinatoside A	$C_{53}H_{86}O_{23}$	588.3662	595.3816	0	+Li, +Na
98	16.88	Poricoic acid AM	$C_{31}H_{46}O_5$	512.3471	513.3544	-3.1	+H
99	16.88	Zizyberanalic acid	$C_{30}H_{46}O_4$	470.3404	493.3297	0.8	+Na, +Li
100	16.9	Koryoginsenoside R1	$C_{46}H_{76}O_{15}$	868.5192	869.5265	0.8	+H
101	17.03	Ganoderic acid V	$C_{32}H_{48}O_6$	528.3436	529.3508	-1.5	+H
102	17.03	Andrograpanin	$C_{20}H_{30}O_3$	318.2193	325.2348	-0.2	+Li
103	17.04	Azedarachin C	$C_{32}H_{42}O_{10}$	586.2826	609.2718	4.8	+Na
104	17.05	Hyptadienic acid	$C_{30}H_{46}O_4$	470.3417	493.331	2.1	+Na
105	17.23	Curculigo saponin B	$C_{35}H_{58}O_8$	606.4132	613.4286	0	+Li
106	17.55	Picrasinoside E	$C_{30}H_{46}O_{13}$	614.2917	621.3071	-2.2	+Li
107	17.8	Curculigo saponin L	$C_{42}H_{72}O_{13}$	784.4951	791.5106	-2.2	+Li
108	17.91	Verticiol	$C_{20}H_{34}O$	290.2613	291.2686	0.3	+H
109	18.46	Caryophyllene oxide	$C_{15}H_{24}O$	220.1826	221.1899	-0.1	+H

can be used to treat a range of acute and chronic inflammatory diseases because of its anti-inflammatory characteristics. Resokaempferol also has anti-inflammatory activity (Yu et al. 2016). Quercetin 3,4′-dimethyl ether is a dimethoxyflavone that is a 3,4′-dimethyl ether derivative of quercetin which is isolated from *Combretum quadrangulare* and it has roles as an antioxidant and antineoplastic agents (Azeem et al. 2022; Di Petrillo et al. 2022). Meanwhile, quercetin-3-methyl ether shows neuroprotective and antidiabetic activities with promising chemopreventive potential against esophageal carcinogenesis (Dok-Go et al. 2003; Zhao et al. 2018). Another study showed that it can inhibit breast cancer cell growth by inducing G2/M arrest and apoptosis (Li et al. 2013). Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4Hchromen4-one), a common active ingredient in Chinese traditional medicine, is a polyhydroxy flavonoid usually found in fruits, leaves and flowers of various plants (Boots et al. 2008). It is claimed to have anti-inflammation, anticancer, anti-fibrosis, anti-oxidation effects (Fu et al. 2020; Shi et al. 2008), antidiabetic effects and prevention of neurodegeneration in diabetic retinopathy (Vessal et al. 2003; Ola et al. 2017; Gomes et al. 2015). Due to the biological activities, these flavonoids may prevent cardiovascular and other lifestyle-related diseases (Kobori et al. 2009).

Triterpenes appear to have different pharmacological properties. Previous studies have shown that these substances exhibit anti-diabetic actions. They have the ability to regulate plasma glucose and insulin levels, inhibit the onset of insulin resistance and block glucose metabolism enzymes. Triterpenes also have potential to be used for the prevention of diabetic complications. Triterpenes have a high antioxidant activity and prevent the production of advanced glycation end products, which have been linked to the pathophysiology of poor wound healing, diabetic neuropathy, embryopathy and

nephropathy (Nazaruk & Borzym-Kluczyk 2015).

Loganin is a plant metabolite that has demonstrated pharmacological efficacy as an antioxidant, neuroprotective agent and as treatment for diabetic neuropathy. Loganin also protects against hepatic damage and other diabetes problems induced by oxidative stress and the production of advanced glycation end products (Jiang et al. 2012; Lee et al. 2009; Yamabe et al. 2010). Ginkgolide C, an active constituent of *Gingko biloba* has been reported to increase both adipose triglyceride and hormone-sensitive lipase enzymes for increased lipolysis with suppression of lipid accumulation in differentiated adipocytes (Liou et al. 2015). Gedunin is a limonoid which is found mostly in the seeds of many Meliaceae genera. Anti-inflammatory, antiallergic, anticancer, antimalarial, insecticidal, antibacterial and neuroprotective properties have been attributed to gedunin. It also has potential for the antidiabetic activity reported by Ponnusamy et al. (2015). Moreover, other species of the *Actinidaphne* genus have been studied for anti-diabetic activity. Bhaskaran et al. (2019) studied the antidiabetic activity of *Actinodaphne hookeri* and found a strong hypoglycemic effect with improved lipid profile and restoration of damaged pancreatic β-cells.

CONCLUSION

Our study suggested that *A. angustifolia* leaf ethanolic extract may be useful in the management of diabetes and its consequences, as they protected the pancreas by restoring the damaged beta islets and improving the lipid profiles. The presence of a number of bioactive flavonoids and triterpenoids might suggest its potential role for bioactivity. More investigations are required to completely comprehend its mechanism and isolate the bioactive components for further development as an antidiabetic natural product.

REFERENCES

Abbaszadeh, A., Darabi, S., Hasanvand, A., Amini-Khoei, H., Abbasnezhad, A., Choghakhori, R., Aaliehpour, A. 2018. Minocycline through attenuation of oxidative stress and inflammatory response reduces the neuropathic pain in a rat model of chronic constriction injury. *Iran J Basic Med Sci* **21**(2): 138.

Abd-el-Mawla, A., Mohamed, K.M., Mostafa, A.M. 2011. Induction of biologically active flavonoids in cell cultures of Morus nigra and testing their hypoglycemic efficacy. *Sci Pharm* **79**(4): 951-62.

Alipour, M., Malihi, R., Hosseini, S.A., Abbasnezhad, A., Ghavami, A., Shahmohammadi, H.A., Ghanavati, M. 2018. The effects of catechins on related risk factors with type 2 diabetes: a review. *Prog Nutr* **20**(1): 12-20.

Amani, R., Abbasnezhad, A., Hajiani, E., Cheraghian, B., Abdoli, Z., Choghakhori, R. 2018. Vitamin D3 induced decrease in IL-17 and malondialdehyde and increase in IL-10 and total antioxidant capacity levels in patients with irritable bowel syndrome. *Iran J Immunol* **15**(3): 186-96.

Asolkar, L.V., Kakkar, K.K., Chakre, O.J. 1992. Glossary of Indian medicinal plants with active principles, Part 1. *New Delhi: National Institute of Science Communication and Information Resources (CSIR)*: 230-1.

Azeem, M., Hanif, M., Mahmood, K., Ameer, N., Chughtai, F.R.S., Abid, U. 2022. An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review. *Polym Bull* **:** 1-22.

Boots, A.W., Haenen, G.R., Bast, A. 2008. Health effects of quercetin: from antioxidant to nutraceutical. *Eur J Pharmacol* **585**(2-3): 325-37.

Bhaskaran, M., Mruthunjaya, K., Manjula, S.N., Rajan, D. 2019. Evaluation of anti-diabetic activity of leaves of Actinodaphne hookeri Meissn. *Int J Pharm Sci Res* **10**(1): 83-96.

Chandramohan, G., Al-Numair, K.S., Alsaif, M.A., Veeramani, C. 2014. Antidiabetic effect of kaempferol a flavonoid compound, on streptozotocin-induced diabetic rats with special reference to glycoprotein components. *Prog Nutr* **17**(1): 50-7.

Deore, A.B., Sapakal, V.D., & Naikwade, N.S. 2011. Role of oxidative stress in pathogenesis of diabetes and its complications. *Pharmacologyonline* **2**: 603-21.

Dewanjee, S., Das, A.K., Sahu, R., Gangopadhyay, M. 2009. Antidiabetic activity of Diospyros peregrina fruit: effect on hyperglycemia, hyperlipidemia and augmented oxidative stress in experimental type 2 diabetes. *Food Chem Toxicol* **47**(10): 2679-85.

Di Petrillo, A., Orrù, G., Fais, A., Fantini, M.C. 2022. Quercetin and its derivates as antiviral potentials: A comprehensive review. *Phytother Res* **36**(1): **26**6-78.

Devi, K.P., Malar, D.S., Nabavi, S.F., Sureda, A., Xiao, J., Nabavi, S.M., Daglia, M. 2015. Kaempferol and inflammation: From chemistry to medicine. *Pharmacol Res* **99**: 1-10.

Dok-Go, H., Lee, K.H., Kim, H.J., Lee, E.H., Lee, J., Song, Y.S., Cho, J. 2003. Neuroprotective effects of antioxidative flavonoids, quercetin, (+)-dihydroquercetin and quercetin 3-methyl ether, isolated from Opuntia ficus-indica var. saboten. *Brain* Res **965**(1-2): 130-6.

Enkhmaa, B., Surampudi, P., Anuurad, E., Berglund, L. 2018. Lifestyle changes: effect of diet, exercise, functional food, and obesity treatment on lipids and lipoproteins. [Updated 2018 Sep 11]. South Dartmouth (MA): MDText.com, Inc..

Fernández-Rojas, M., Rodríguez, L., Trostchansky, A., Fuentes, E. 2022. Regulation of platelet function by natural bioactive compounds. *Food Biosci* **48:** 101742.

Foretz, M., Guigas, B., Viollet, B. 2019. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. *Nat Rev Endocrinol* **15**(10): 569-89.

Forid, M.S., Rahman, M.A., Aluwi, M.F.F.M., Uddin, M.N., Roy, T.G., Mohanta, M.C., Amiruddin Zakaria, Z. 2021. Pharmacoinformatics and UPLC-QTOF/ESI-MS-Based phytochemical screening of *Combretum Indicum* against oxidative stress and alloxan-induced diabetes in long–evans rats. *Molecules* **26**(15): 4634.

Fu, J., Huang, J., Lin, M., Xie, T., You, T. 2020. Quercetin promotes diabetic wound healing via switching macrophages from M1 to M2 polarization. *J Surg Res* **246** :213-23.

Gomes, I.B., Porto, M.L., Santos, M.C., Campagnaro, B.P., Gava, A.L., Meyrelles, S.S., Vasquez, E.C. 2015. The protective effects of oral low-dose quercetin on diabetic nephropathy in hypercholesterolemic mice. *Front Physiol* **6***:* 247.

Graf, B.A., Milbury, P.E., Blumberg, J.B. 2005. Flavonols, flavones, flavanones, and human health: epidemiological evidence. *J Med Food* **8**(3): 281-90.

Hodge, A., Sterner, B. 2020. Toxicity classes; canadian centre for occupational health safety: Hamilton, ON, Canada, 2005. Available online: http://www.ccohs.ca/oshanswers/chemicals/id50.htm [3 August 2020].

International Diabetes Federation. 2021. *IDF diabetes Atlas*, Brussels.

Imran, M., Salehi, B., Sharifi-Rad, J., Aslam Gondal, T., Saeed, F., Imran, A., Estevinho, L. M. 2019. Kaempferol: A key emphasis to its anticancer potential. *Molecules* **24**(12): 2277.

Jaiswal, Y.S., Tatke, P.A., Gabhe, S.Y., Vaidya, A.B. 2017. Antidiabetic activity of extracts of Anacardium occidentale Linn. leaves on n-streptozotocin diabetic rats. *J Tradit Complement Med* **7**(4): 421-7.

Jiang, W.L., Zhang, S.P., Hou, J., Zhu, H.B. 2012. Effect of loganin on experimental diabetic nephropathy. *Phytomedicine* **19**(3-4): 217-22.

Kärber, G. 1931. Beitrag zur kollektiven Behandlung pharmakologischer Reihenversuche. *Naunyn-Schmiedebergs Archiv für experimentelle pathologie und pharmakologie* **162**(4): 480-3.

Kang, Y.J., Jung, U.J., Jeon, S.M., Yeo, J.Y., Kim, H.J., Kim, D. J., Choi, M.S. 2007. Antihyperglycemic and antioxidant properties of jaceosidin, a flavonoid isolated from artemisia princeps, in type 2 diabetic mice. *Diabetes* **56**.

Kim, M.J., Han, J.M., Jin, Y.Y., Baek, N.I., Bang, M.H., Chung, H.G., Jeong, T.S. 2008. In vitro antioxidant and anti-inflammatory activities of Jaceosidin from *Artemisia princeps Pampanini* cv. Sajabal. *Arch Pharm Res* **31**(4): 429-37.

Kobori, M., Masumoto, S., Akimoto, Y., Takahashi, Y. 2009. Dietary quercetin alleviates diabetic symptoms and reduces streptozotocin-induced disturbance of hepatic gene expression in mice. *Mol Nutr Food Res* **53**(7): 859-68.

Lee, K.Y., Sung, S.H., Kim, S.H., Jang, Y.P., Oh, T.H., Kim, Y.C. 2009. Cognitive-enhancing activity of loganin isolated from *Cornus officinalis* in scopolamine-induced amnesic mice. *Arch Pharm Res* **32**(5): 677-83.

Li, Y., Meng, F. 2019. Irisflorentin suppresses allergic inflammation in mast cells via reducing histamine release and production of pro-inflammatory cytokines. *Acta Pol Pharm* **76**(4): 725-33.

Li, J., Zhu, F., Lubet, R.A., De Luca, A., Grubbs, C., Ericson, M.E., and Bode, A.M. 2013. Quercetin-3-methyl ether inhibits lapatinib-sensitive and resistant breast cancer cell growth by inducing G2/M arrest and apoptosis. *Mol Carcinog* **52**(2): 134-43.

Liou, C.J., Lai, X.Y., Chen, Y.L., Wang, C.L., Wei, C.H., Huang, W.C. 2015. Ginkgolide C suppresses adipogenesis in 3T3-L1 adipocytes via the AMPK signaling pathway. *Evid Based Complement Alternat Med* **2015**: 298635.

Lokendrajit, N., Swapana, N., Singh, C.D., Singh, C.B. 2011. Herbal folk medicines used for urinary and calculi/stone cases complaints in Manipur. *NeBIO* **2**(3): 1-5

Lv, W., Sheng, X., Chen, T., Xu, Q., Xie, X. 2008. Jaceosidin induces apoptosis in human ovary cancer cells through mitochondrial pathway. *J Biomed Biotechnol* **2008**: 394802.

Mawa, J., Rahman, M.A., Hashem, M.A., Hosen, M.J. 2019. *Leea macrophylla* root extract upregulates the mRNA expression for antioxidative enzymes and repairs the necrosis of pancreatic β-cell and kidney tissues in fructose-fed Type 2 diabetic rats. *Biomed Pharmacother* **110***:* 74-84.

Middleton, E., Kandaswami, C., Theoharides, T.C. 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev* **52**(4): 673-751.

Mueller, P.H., Schmuelling, R.M., Liebich, H.M., Eggstein, M. 1977. A fully enzymatic triglyceride determination (author's transl). *J Clin Chem Clin Biochem* **15**(9): 457-64.

Mueller, M., Weinmann, D., Toegel, S., Holzer, W., Unger, F.M., Viernstein, H. 2016. Compounds from Caesalpinia sappan with anti-inflammatory properties in macrophages and chondrocytes. *Food Funct* **7**(3): 1671-9.

Muhammad, Z.A., Ahmad, T., Baloch, N. 2019. Can alternate-day statin regimen minimize its adverse effects on muscle and tendon?: A systematic review. *J Pak Med Assoc* **69**(7): 1006.

Nam, Y., Choi, M., Hwang, H., Lee, M.G., Kwon, B.M., Lee, W.H., Suk, K. 2013. Natural flavone jaceosidin is a neuroinflammation inhibitor. *Phytother Res* **27**(3): 404-11.

Nazaruk, J., Borzym-Kluczyk, M. 2015. The role of triterpenes in the management of diabetes mellitus and its complications. *Phytochem Rev* **14**(4): 675-90.

Nazir, M.A., AlGhamdi, L., AlKadi, M., AlBeajan, N., AlRashoudi, L., AlHussan, M. 2018. The burden of diabetes, its oral complications and their prevention and management. Open access Maced J Med Sci 6(8), 1545-53.

OECD/OCDE. Guideline for the Testing of Chemicals. Revised Draft Guideline 423: Acute Oral Toxicity; OECD: Paris, France, 2000.

Ola, M.S., Ahmed, M.M., Shams, S., Al-Rejaie, S.S. 2017. Neuroprotective effects of quercetin in diabetic rat retina. *Saudi J Biol Sci* **24**(6): 1186-94.

Parthasarathy, R., Ilavarasan, R., Karrunakaran, C.M. 2009. Antidiabetic activity of *Thespesia populnea* bark and leaf extract against streptozotocin induced diabetic rats. *Int J Pharmtech Res* **1**(4): 1069-72.

Petrônio, M.S., Zeraik, M.L., Da Fonseca, L.M., Ximenes, V.F. 2013. Apocynin: chemical and biophysical properties of a NADPH oxidase inhibitor. *Molecules* **18**(3): 2821-39.

Ponnusamy, S., Haldar, S., Mulani, F., Zinjarde, S., Thulasiram, H., RaviKumar, A. 2015. Gedunin and azadiradione: human pancreatic alpha-amylase inhibiting limonoids from neem (*Azadirachta indica*) as anti-diabetic agents. *PloS One* **10**(10): e0140113.

Purkayastha, S.K. 1985. Indian woods. Their identification, properties and uses. Vol. V. Oleaceae to Santalaceae.

Rastogi, R.P., Mehrotra, B. 1993. Compendium of Indian Medicinal Plants. 6V. Publications & Information Directorate.

Ren, J.I.E., Lu, Y., Qian, Y., Chen, B., Wu, T.A.O., Ji, G. 2019. Recent progress regarding kaempferol for the treatment of various diseases. *Exp Ther Med* **18**(4): 2759-76.

Simonyi, A., Serfozo, P., Lehmidi, T.M., Cui, J., Gu, Z., Lubahn, D.B., Sun, G.Y. 2012. The neuroprotective effects of apocynin. *Front Biosci (Elite edition)* **4**: 2183.

Shi, G.J., Li, Y., Cao, Q.H., Wu, H.X., Tang, X.Y., Gao, X.H., Yang, Y. 2019. In vitro and in vivo evidence that quercetin protects against diabetes and its complications: A systematic review of the literature. *Biomed Pharmacother* **109***:* 1085-99.

Uddin, M.N., Alam, T., Islam, M.A., Khan, T.A., Zaman, R.U., Azam, S., Jakaria, M. 2020. Evaluation of carbon tetrachloride fraction of *Actinodaphne angustifolia Nees* (Lauraceae) leaf extract for antioxidant, cytotoxic, thrombolytic and antidiarrheal properties. *Biosci Rep* **40**(6): BSR20201110.

Ukaegbu, C.I., Shah, S.R., Hazrulrizawati, A. H., Alara, O.R. 2018. Acetone extract of *Flammulina velutipes caps*: A promising source of antioxidant and anticancer agents. *Beni-Suef Univ J Basic Appl Sci* **7**(4): 675-82.

Umehara, K., Nemoto, K., Matsushita, A., Terada, E., Monthakantirat, O., De-Eknamkul, W., Noguchi, H. 2009. Flavonoids from the heartwood of the Thai medicinal plant *Dalbergia parviflora* and their effects on estrogenic-responsive human breast cancer cells. *J Nat Prod* **72**(12): 2163-8.

Vessal, M., Hemmati, M., Vasei, M. 2003. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Compa Biochem Physiol C Toxicol Pharmacol* **135**(3): 357-64.

Vinayagam, R., Xu, B. 2015. Antidiabetic properties of dietary flavonoids: a cellular mechanism review. *Nutr Metab* **12**: 60.

Virmani, R., Burke, A.P., Kolodgie, F. 2006. Morphological characteristics of coronary

atherosclerosis in diabetes mellitus. *Can J Cardiol* **22**: 81B-84B.

Yu, Q., Zeng, K., Ma, X., Song, F., Jiang, Y., Tu, P., Wang, X. 2016. Resokaempferol-mediated anti-inflammatory effects on activated macrophages via the inhibition of JAK2/STAT3, NF-κB and JNK/p38 MAPK signaling pathways. *Int Immunopharmacol* **38**: 104-14.

Yamabe, N., Noh, J.S., Park, C.H., Kang, K.S., Shibahara, N., Tanaka, T., Yokozawa, T. 2010. Evaluation of loganin, iridoid glycoside from Corni Fructus, on hepatic and renal glucolipotoxicity and inflammation in type 2 diabetic db/db mice. *Eur J Pharmacol* **648**(1-3): 179-87.

Yousefi, F., Mahjoub, S., Pouramir, M., Khadir, F. 2013. Hypoglycemic activity of *Pyrus biossieriana Buhse* leaf extract and arbutin: Inhibitory effects on alpha amylase and alpha glucosidase. *Caspian J Intern Med* **4**(4): 763.

Zhao, S., Jiang, Y., Zhao, J., Li, H., Yin, X., Wang, Y, Liu, K. 2018. Quercetin-3-methyl ether inhibits esophageal carcinogenesis by targeting the AKT/mTOR/p70S6K and MAPK pathways. *Mol Carcinog* **57**(11): 1540-52.

Received: 09 Aug 2022
Accepted: 15 Sept 2022