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Antidiabetic and antioxidant potential of *Durio zibethinus* Murr. leaves ethanolic extract

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Durio zibethinus Murr., commonly called Durian, though well known for its rich medicinal uses, only fewer studies are available on the leaves of this plant. In this study, we investigated the antioxidant and antidiabetic potential of ethanol extract of *D. zibethinus* leaves (DZL) from Malaysian geographical origin. DZL was subjected to the preliminary phytochemical screening along with the quantitative analysis of phenols and flavonoids. The *in vitro* antioxidant properties were evaluated by DPPH and ABTS methods and *in vitro* antidiabetic properties were evaluated by α-amylase and α-glucosidase enzyme inhibition studies. The results of the above biological activities were expressed as inhibitory concentration 50% for DZL and standard drugs (acarbose and ascorbic acid). Based on the acute oral toxicity test, two test doses (100 and 200 mg/kg) of DZL were compared with glibenclamide (5 mg/kg) for their effect on fasting blood glucose at various time intervals (0 to12 h) in glucose-loaded normoglycemic rats. DZL (200 mg/kg) showed a better response in streptozotocin (STZ) induced diabetic rats. The antioxidant assay of DZL showed an appreciable extract inhibitory concentration 50% against the free radicals generated by DPPH (1.61±0.07 µg/ mL) and ABTS (1.47±0.07 µg/mL) assays. Similarly, the *in vitro* antidiabetic assay results demonstrated a dose-dependent inhibition of α-amylase (2.58±0.08 µg/mL) and α-glucosidase enzymes (2.41±0.08 µg/ mL) by DZL. Both glucose-loaded normoglycemic rats and STZ-induced diabetic rats treated with DZL (200 mg/kg) exhibited a significant post-dose reduction in blood glucose levels (P <0.01, 8 h and P <0.001, 12 h) when compared to normal and diabetic control rats, respectively. These findings suggest that the presence of polyphenols in DZL might be responsible for antioxidant and antidiabetic properties and DZL could be a natural source as an herbal remedy for diabetes.

Keywords: α-Amylase, Durian, α-Glucosidase, Polyphenols, Streptozotocin

Diabetes mellitus (DM) is a degenerative illness regularly found throughout the globe, and the prevalence number shows increasing patterns every year. The International Diabetes Federation and World Health Organization (WHO) predicts the pervasiveness of diabetes increase by 2 to 3 times by the year 2030, thus numerous research was devoted to complications, deterrence, and management of DM[1]. DM is a polygenic metabolic disorder leading to abnormalities in carbohydrate, lipid, and protein metabolism. Besides, a defect in insulin secretion by the pancreas β-cells plays a significant role in the pathogenesis of DM[2]. The outcome of the imbalance between radical generating and radical scavenging mechanisms results in oxidative stress. Several studies have proved that DM is associated with increased free radical production and decreased antioxidant capacity, which led to the oxidative damage of cell components[3].

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Both experimental and clinical studies suggest that oxidative stress is considered a unifying mechanism for cell injury in many diseases including DM[4]. The use of antioxidants could elicit a beneficial effect in the management of hyperglycemia-induced complications or oxidative stress[5]. The treatments ordinarily use synthetic drugs throughout their lifetime. However, long term treatment had adverse effects, for instance, gastrointestinal disorders and edema with hyponatremia. According to WHO reports, most of the global population employs diverse medicinal plant species to manage a variety of illnesses including DM[6]. Over a while, the rise in blood glucose can lead to severe damage to many of the organ systems, specifically the nerves and blood vessels[7].

In Southeast Asia, *Durio zibethinus* (Murr.), commonly, known as Durian, is considered the king of fruits[8]. The bioactive compounds, including flavonoids, polyphenols, anthocyanins, flavanols and carotenoids have been reported from durian pulp[8,9].

A few durian cultivators are grown in Thailand and they exhibited different free radical scavenging capacities. The leaves, hull, fruit and even the roots have been traditionally used in various ailment treatments[10].

The ethanol extract of durian fruit peel had proven to have hyperglycaemic inhibition and ethanol extract of durian rind had high potential antioxidant activity[11]. Increasing evidences suggest that flavonoids and polyphenols demonstrate several positive health benefits such as antioxidant and antidiabetic effects[12]. InF Malaysia, there are around 15 registered varieties of Durian. Even though Durian is rich in medicinal benefits much less investigation is carried out on leaves of few varieties from Malaysian origin. Till date, much research has gone into fruits, pulp and peels of Durian from Indonesian and Thailand origin[13] but not from Malaysian varieties of Durian, particularly its leaves. It would be more beneficial if extract from leaves is used as a source instead of fruits and pulp since the availability of the leaves is independent of any season or weather and storage, drying, processing and extraction protocol for leaves is easier and safer compared to fruit and pulp where there is a chance of fungal growth. Moreover, the distinctive, robust aroma which is notorious sometimes still exists in fruit and pulp extracts whereas in leaf extract such problems do not exist. As the diabetes-induced hyperglycemia triggers oxidative stress in various parts of the brain[14] and predicted to increase the chances of neurological disorders by inhibiting the associated enzymatic activities associated with neurotransmission, here in the current study, we investigated the antioxidant and antidiabetic effects of the ethanol extract of *Durio zibethinus* leaves (DZL) obtained from the Malaysian geographical zone.

Materials and Methods

Regents and chemicals

Gallic acid, rutin, 2-diphenyl-1-picrylhydrazyl (DPPH), 2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), α-amylase, α-glucosidase, and streptozotocin (STZ) were obtained from Sigma-Aldrich Co. (USA). Solvents and all other chemicals used were of analytical grade and obtained from Fischer Scientific (UK).

Plant material

The plant leaves of *D. zibethinus* were collected from the areas of Baling, Kedah, Malaysia, and authenticated at the Department of Pharmacognosy, AIMST University, Malaysia (Ref. No: AIMST/ FOP/03). Healthy and mature leaves were selected by visual observation and carefully handpicked, brought in sterile bags, and then processed for extraction.

Preparation of extract

The collected leaves were rinsed in running water and shade dried for at least 2 days, thus avoiding chemical decomposition. After drying, the leaves were ground in a blender. The extraction was carried out by the maceration technique using a single solvent system, 70% ethanol (v/v)[15]. Accurately 200 g of sample was weighed and placed in a 1.0 L flask. To the sample, 500 mL of the solvent (70% ethanol) was added and covered. The sample was macerated for 5 days and a stepwise extraction from residual plant material was performed[16]. The above procedure was repeated till a clear, colorless supernatant was obtained. Then the extract solution was filtered through a muslin cloth. The filtrate obtained was pooled and evaporated using a rotary flash evaporator. The resulting extract (DZL) was freeze-dried and transferred to an airtight container and stored in the desiccator. The percentage yield of the extract was calculated.

Qualitative phytochemical screening

Qualitative phytochemical analysis of the DZL was performed to identify the presence of phytoconstituents like saponins, flavonoids, alkaloids, steroids, mucilage, phenols, glycosides, tannins, proteins/amino acids, carbohydrates, reducing sugars, monosaccharides, starch, anthocyanins and gum utilizing standard analytical techniques[17].

Quantitative phytochemical analysis

Total phenolic content

The total phenolic content (TPC) in DZL was determined using the modified spectrophotometric method[18]. Ten mg of DZL was dissolved in 10 mL of 70% ethanol and various concentrations (0.1-1.0 mg/mL) have been prepared by serial dilution. The reaction has been prepared by adding 100 µL of the sample, 100 µL of Folin-Ciocalteu's reagent, and 2 mL of 2.5% Na_2CO_3 solution. The samples were incubated for 30 min at room temperature (30°C)[19]. The absorbance was measured at 750 nm. The process was repeated for gallic acid as a standard and the calibration curve was constructed. Depending on the absorbance values, the phenolic concentration was expressed as mg/mL from the calibration curve. The

TPC of DZL was articulated as gallic acid equivalents (GAE, mg/g)[20].

Total flavonoid content

The total flavonoid content (TFC) of DZL was determined using the modified spectrophotometric method[18]. Different concentrations of DZL were prepared as mentioned in the total phenolic content. The reaction mixture was prepared by mixing 1.0 mL of sample, 10 mL of 30 % ethanol, and 0.7 mL of 10% $AlCl_3$ solution[19]. The sample was kept at room temperature for 6 min. Ten mL of 1.0 M/L NaOH solution was added and 30% ethanol was added till the volume is made up to 25 mL and kept for 10 min. The absorbance was measured at 450 nm. The method was repeated for standard, rutin and the calibration curve was constructed. The flavonoid concentration was articulated as rutin equivalents (RUE, mg/g).

***In vitro* antioxidant activity**

DPPH assay

The capability of DZL to scavenge DPPH free radicals have been evaluated using the procedure described earlier[21]. Five hundred µL of DZL of varying concentration was added to 500 µL of DPPH solution (2 µM); the absorbance was observed at 517 nm. A similar technique was repeated for ascorbic acid as a standard[22]. The percentage of DPPH free radical scavenged was calculated using Equation 1.

% Scavenging: (Absorbance Control – Absorbance Sample)/Absorbance Control × 100 ... (1).

ABTS assay

Scavenging activity of cation of 2, 2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid [$ABTS^{*+}$] free radical by DZL was determined using the procedure described earlier[23], and the absorbance was observed at 734 nm. A similar method was repeated for ascorbic acid as a standard and the percentage of ABTS radical cation scavenged was calculated using Eq. 1.

***In vitro* antidiabetic activity**

α-amylase inhibition assay

The α-amylase inhibitory activity was performed by the modified assay[24]. Ten mg of DZL was dissolved in 10 mL of 70% ethanol and various concentrations (100 to 1000 µg/mL) were prepared by serial dilution. An equal volume (500 µL) of the sample and 0.5 mg/ mL α-amylase solution (dissolved in 0.2 mM/L phosphate buffer, (pH 6.9) was incubated for 10 min at 25°C. Five hundred µL of 1% starch solution (in 0.02 M/L) sodium phosphate buffer, (pH 6.9) was added to each tube after the pre-incubation period[25]. The samples were then incubated at 25°C for 10 min. One mL of dinitrosalicylic acid color reagent was added to arrest the reaction. The solution was kept incubating in boiling water for 5 min and subsequently cooled to room temperature. Ten mL of water was added, and the absorbance was measured at 540 nm. Acarbose was used as a standard drug[26]. The percentage of inhibition has been calculated using Eq. 1.

α-Glucosidase inhibition assay

The α-glucosidase inhibitory activity was identified by a modified assay[27]. The sample solutions of DZL were prepared as described in the α-amylase inhibition assay. One mL of sample and 1.0 mL of sucrose (2%) in Tris buffer (pH 8) was incubated at 37°C for 5 min. After pre-incubation, 1 mL of α-glycosidase (1.0 U/ mL) was added and incubated for 10 min at 37°C. The reaction was detained by heating in boiling water for 2 min. The amount of glucose was measured by the glucose peroxidase method[28]. Acarbose was used as a standard drug. The percentage of inhibition has been calculated using Eq. 1.

***In vivo* study**

Experimental animals

Healthy, either gender of Sprague Dawley (SD) rats weighing 150-180 g were obtained from the central animal house, AIMST University (Malaysia), and used in the experiments. The experimental protocol was approved by the AIMST University Human and Animal Ethics Committee (AUHAEC7/ FOP/2017). Animals were kept in the animal house at an ambient temperature of 25±2°C and 45-55 % relative humidity, with 12 h each of dark and light cycles. Animals were fed pellet diet and water ad libitum. All the experiments are conducted as per AIMST University animal care guidelines which are based on the guidelines of the animal research review panel.

Acute oral toxicity

Acute oral toxicity testing of DZL was carried out as per the methods described in the OECD test guideline[29]. The DZL extract was suspended in carboxymethyl cellulose (0.5% CMC) solution and 2000 mg/kg orally fed to overnight fasted female SD rats. The SD rats were observed for mortality and clinical signs for 24 h after dosing. After a period of

24 h, animals were observed (at least once a day) for 14 days for mortality and clinical signs[30].

Effect of DZL in normoglycemic rats

The effect of DZL was tested in fasted male SD rats for the changes in blood glucose levels at different time intervals after the single oral dose of the extract. The overnight fasted SD rats were randomly divided into 4 groups (n =5 each). The normal control (Gr.I) received CMC solution (0.5% 10 mL/kg, *per os*). The second group (Gr. II) of animals was treated with glibenclamide (5 mg/kg *per os*). The third and fourth group of rats (Gr III & IV) received DZL (100 and 200 mg/kg *per os*), respectively. Except for normal control animals, all the other groups received glucose (2 g/kg, *per os*) 1 h before the respective treatment. The animals with glucose level ≥7 mM/ L were eliminated from the study.

All the drug samples were freshly prepared an hour before dosing and administered orally using an oral gavage needle. The basal blood glucose levels were recorded using a one-touch glucometer in all the groups from the blood sample collected from the tail vein under light ether anesthesia[31]. The blood glucose levels were estimated in blood samples collected at 0, 2, 4, 8 and 12 h after treatment.

Effect of DZL in STZ-induced diabetic rats

Diabetes mellitus was induced in overnight-fasted male SD rats by a single dose of freshly prepared STZ (55 mg/kg, intraperitoneal) in ice-cold 0.01 M/ L citrate buffer (pH 4.5). After 6 h of DM induction, the rats were given a 5% glucose solution (2 mL/kg *per os*) for the next 24 h to prevent hypoglycemic shock. The fasting blood glucose was determined after 48 h to confirm the DM induction. The blood glucose level of rats ≥12 mM/ L was considered diabetic and was selected for treatment[32]. The rats were randomly divided into four groups (n=5). The Gr. I animals were normal non-diabetic rats and groups 2 to 4 were STZ-induced diabetic rats. Normal non-diabetic rats (Gr. I) and diabetic rats (Gr. II) received 0.5% CMC solution (10 mL/kg). The third and fourth group of animals received glibenclamide (5 mg/kg) and DZL (200 mg/kg), respectively. The blood samples were collected at 0, 2, 4, 8 and 12 h after drug administration through the tail vein and immediately estimated for blood glucose level using a glucometer[33].

Statistical analysis

All the *in vitro* experiments were performed in triplicate and the values were expressed as means ± SEM. The concentration required for 50% inhibition of free radicals and enzyme activity was computed using Graph Pad Prism Software (Version 5) by a non-linear regression graph plotted between the percentage of inhibition (x-axis) versus concentration (y-axis). The data obtained from the *in vivo* studies were expressed as mean ± SEM (n=5). The statistical significance between the groups was tested using a one-way analysis of variance followed by Tukey's multiple comparison *post-hoc* test. A *P*-value < 0.05 was considered significant.

Results and Discussion

There are nine edible Durian species, however, only *Durio zibethinus* Murr. species have been extensively grown and harvested in Malaysia. Various parts of durian like fruits, peel, pulp, seeds and leaves are abundant with polyphenols such as flavonoids, phenolic acids, tannins, and other bioactive components such as carotenoids and ascorbic acid[34]**.** In the present research, we have mainly focused on the pharmacological benefits of leaves of durian plants from Malaysian origin as their medicinal properties are yet to be explored.

Qualitative and quantitative phytochemical analysis

The maceration technique was adopted for extraction to avoid the high-temperature effects on the phytochemical constituents. In practice, ethanol is typically more selected for pharmaceutical and food processing compared with other solvents due to its safety and affordability[35]. Earlier investigations determined that the extractions with aqueous alcoholic solvents made a significant contribution to the high antioxidant abilities[36]. Pure ethanol (100%) was unable to extract 100% phenolic constituents, and the presence of water in the solvent helps the release of hydrophilic antioxidants. So, in the present study, we selected 70% v/v ethanol solvent for extraction, maceration is a simple and economical technique for the extraction of antioxidant secondary metabolites from Durian leaves which permits to maintain good extraction parameters such as time of extraction, temperature as well as a solvent ratio. Furthermore, extraction conditions play an important role in pharmaceutical inventions, especially for extracts that are obtained in low yields[37]. The percentage extraction yield of DZL with 70 % ethanol was 29.7% (m/m) after three cold macerations in a stepwise manner. Various parts of the Durian plant including the endophytes of durian leaves were reported to contain both flavonoids and polyphenols[38].

Preliminary qualitative phytochemical analysis of DZL revealed the presence of various phytoconstituents such as phenols, carbohydrates, alkaloids, flavonoids, steroids, mucilage, and glycosides. The concentration total phenolic content in the DZL extract was determined from the calibration curve and the coefficients of determination (R^2) were found to be 0.8104. The total phenolic content in the DZL extract was expressed as GAE (1.80 mg GAE/g of extract). Similarly, for total flavonoid content, the R^2 was found to be 0.9723 and the total flavonoid content was expressed as RUE (1.34 mg RUE/g of extract. Evary *et al*., applied similar extracting methods and biological screening methods adopted in this study on various parts of *D. zibethinus*[39,40]. However, the biological activity, chemical composition differs from the plant extracts obtained from the Malaysian origin and it may also depend on various other factors such as plant variety, climate and geographical origin[41]. Climacteric fruits, such as Durian go through quick postharvest chemical changes resulting in a short shelf life at ambient temperature[42].

In vitro antioxidant activity

Oxidative damage has been projected as the main offender in the pathophysiology of DM[43]. The overall antioxidant effect of durian fruit was attributed due to its high phenolic contents[10,44]. Scientific investigations have also proved that there is a direct relation between phenolic and flavonoids content with antioxidant properties of Durian[45,46]. Figs. 1A & 1B show the DPPH and ABTS radical scavenging ability of DZL extract and their extract inhibitory concentration 50% was found to be 1.61±0.07 and 1.47±0.07 µg/mL, respectively. The inhibitory concentration of 50% for ascorbic acid was found to be 1.07±0.09 µg/mL in both the assays.

In vitro antidiabetic activity

Most of the research reports revealed the various biological effects of Durian fruits, rind and its seeds, and only limited studies[39,45,46] are recently reported on leaves using organic slovents for extraction. The antidiabetic activity of ethanol extract of *D. zibethinus* fruit peel was reported before and the effect was attributed due to its high flavonoid content[47]. In humans, the studies proved that that durian fruit extracts had the lowest glycaemic index (GI = 49) in comparison with papaya, pineapple, and watermelon whose GI = 58, 90, 55, respectively[48]. The low GI value for durian could be due to the fiber and fat

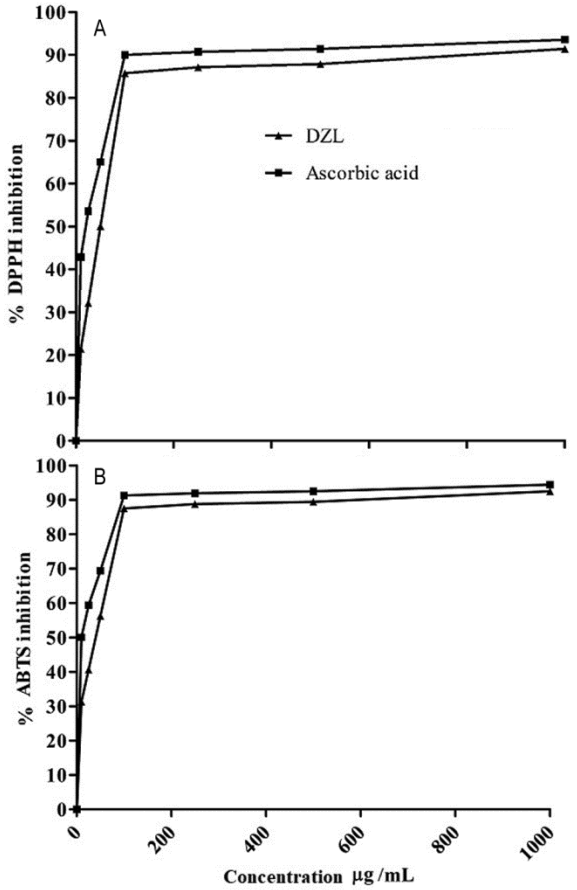

Fig. 1 — (A) Radical scavenging DPPH assay of DZL and ascorbic acid; (B) ABTS free radical cation scavenging assay of DZL and ascorbic acid. [The values are expressed as means ± S.E.M (n=3)]

content. Fibre slows the process of digestion in the gastrointestinal tract and will decelerate the conversion of the carbohydrate to glucose, thus decrease the GI of food[49]. Fat does not contain a direct effect on blood glucose response, but it may affect glycaemic response indirectly by prolonging gastric emptying and thus reducing the rate of glucose absorption[43]. In the present study, ethanolic extract of leaves was used for antidiabetic investigations. Figs. 2 A & B show the α-amylase and α-glucosidase inhibitory effect of DZL extract and their extract inhibitory concentration 50% was found to be 2.58±0.08 and 2.41±0.08 µg/mL, respectively. The inhibitory concentration 50% for acarbose was found to be 2.25±0.15 and 2.22±0.04 µg/mL in the above assays, respectively.

In vivo study

It's the first report to establish the *in vivo* acute oral toxicity and antidiabetic effect of durian leaves. In the acute oral toxicity study, no mortality was observed

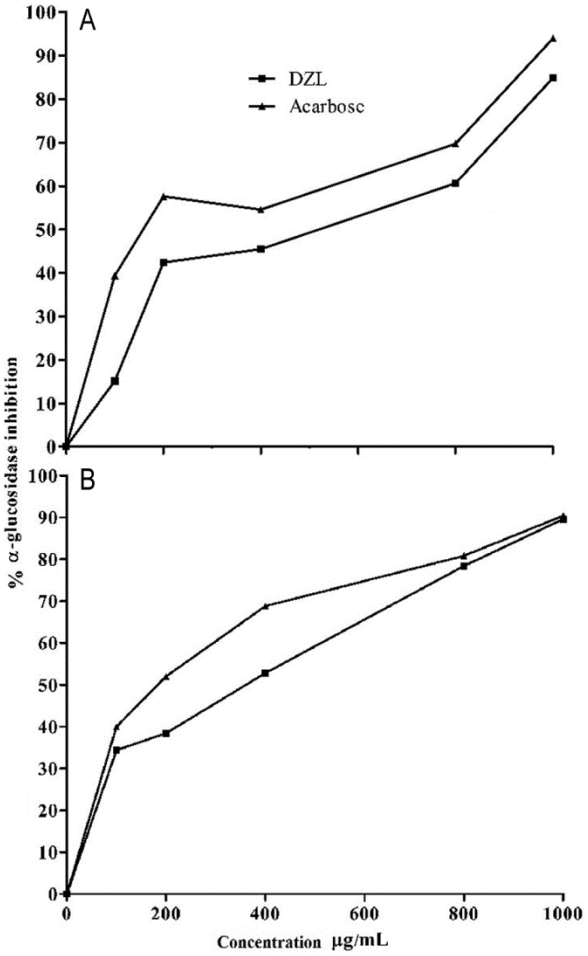

Fig. 2 — (A) Effect of DZL and acarbose on α-amylase inhibition; (B) Effect of DZL and acarbose on α-glucosidase inhibition. [The values are expressed as means ± S.E.M (n=3)]

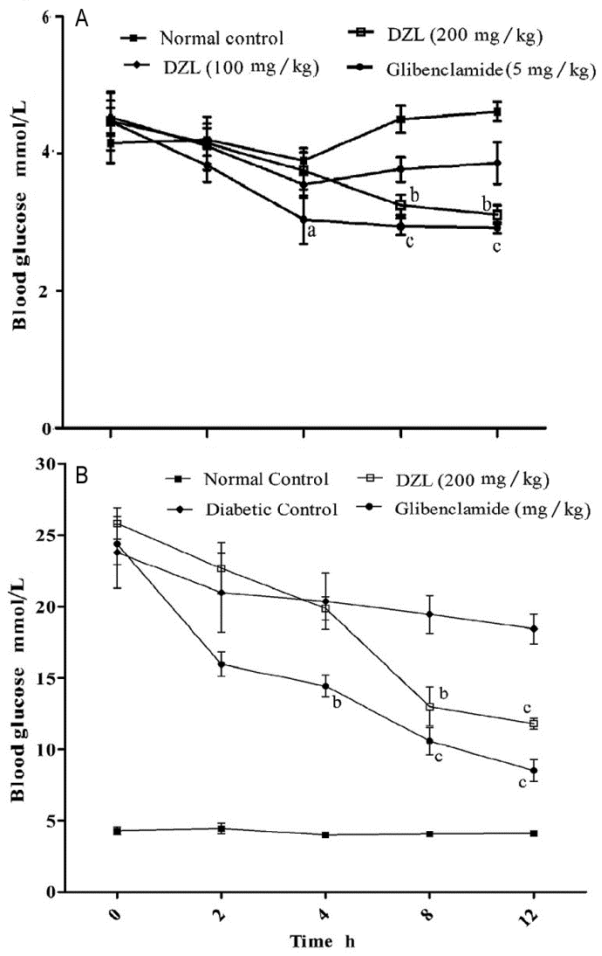

Fig. 3 — (A) Effect of a single dose of DZL on blood glucose level in normal rats. Values are mean ± SEM; n=5 in each group. Significant difference versus control: [a]*P* <0.05; [b]*P* <0.01; [c]*P* <0.001; (B) Effect of a single dose of DZL on blood glucose level in STZ-induced diabetic rats. [Values are mean ± SEM; n=5 in each group. Significant difference versus diabetic control: [a]*P* <0.05; [b]*P* <0.01; [c]*P* <0.001]

with the DZL (2000 mg/kg) treated animals. Lethal dose 50 (LD_{50}) of DZL was found to be >2,000 mg/kg when administrated orally to female SD rats. Hence, DZL could be regarded as orally safe[32]. The doses for diabetic studies were derived based on acute toxicity studies. Two dose levels were selected for the diabetic study 100 and 200 mg/kg which are derived from the $1/20^{th}$ and $1/10^{th}$ dose of 2000 mg/kg.

The effect of DZL in normoglycemic rats is shown in Fig. 3A. The normal rats (Gr. I) showed a mild increase in the blood glucose levels at 8 and 12 h post-dose of vehicle treatment when compared to their basal blood glucose levels measured at 0 h. The normal rats did not receive any per oral glucose (2 g/kg) treatment. This increase in blood glucose levels might be attributed to the stress of animals during continuous blood withdrawal procedures. DZL (200 mg/ kg) pre-treatment exhibited significant (*P* <0.01) reduction in blood glucose levels at 8 and 12 h post-dose. The ability of DZL to control blood glucose homeostasis might be attributed due to the presence of flavonoids and polyphenols[10]. Glibenclamide treated rats showed a significant decrease in blood glucose levels after 4 h (*P* <0.05) and 8, 12 h (*P* <0.001) of dosing.

The effect of DZL in STZ-induced diabetic rats is shown in Fig. 3B. Since DZL (200 mg/kg) responded better in normoglycemic rats, the dose was selected and tested in STZ-induced diabetic rats. Diabetic rats treated with DZL (200 mg/ kg) exhibited a significant post-dose reduction in blood glucose levels (*P* <0.01 at 8 h and *P* <0.001 at 12 h) when compared to diabetic control rats. Glibenclamide treatment in diabetic rats also showed

a significant post-dose decrease in blood glucose levels (P <0.01 at 4 h and P <0.001 at 8 and 12 h).

The DZL (200 mg/kg) showed remarkable dose and time-dependent changes in both glucose-loaded normoglycemic and STZ-induced diabetic rats. Further antidiabetic studies on DZL extract would identify its mechanism of action.

Conclusion

From the current findings, it is concluded that the leaves of Durian could be a good source of medicinal investigations. The free radical scavenging activity of *D. zibethinus* leaves (DZL) might be due to rich phytoconstituents like phenols and flavonoids in the leaves obtained from *D. zibethinus* from Malaysian origin. Total phenol and flavonoid contents were abundantly found high in DZL. The extract exhibited appreciable α-amylase and α-glucosidase inhibition activity, which might be associated with the presence of high phenolic compounds. The DZL (200 mg/kg) showed remarkable dose and time-dependent changes in both glucose-loaded normoglycemic and STZ-induced diabetic rats. The results of the studies appear to affirm the asserted antioxidant and antidiabetic activities by traditional medicine. Henceforth, these findings show that DZL can be the source of natural antioxidants and a remedy for diabetes. Therefore, DZL can be recommended for future natural medicine in the counteractive action of oxidative stress-related hyperglycaemic complications.

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Conflict of interest

I ensure that there is no conflict of interest concerning the authorship or any other matters relating to this manuscript.

Ethical approval for animal studies

The experimental protocol was approved by the AIMST University Human and Animal Ethics Committee, Malaysia. Ref no: (AUHAEC7/ FOP/2017).

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