Original Article

Antioxidant and Anti-inflammatory Roles of Yacon Leaf Extract (*Smallanthus sonchifolius* [Poepp.] H. Rob.) Mitigated Diabetes in a Rat Model

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Abstract

Background: Diabetes mellitus (DM), which is characterized by hyperglycemia, has a high prevalence and requires a serious treatment. Yacon is promoted as an antidiabetic. **Aim:** This study examined the antidiabetic potential of yacon leaf extract (YLE, *Smallanthus sonchifolius* [Poepp.] H. Rob.). **Materials and Methods:** YLE compounds were analyzed using liquid chromatography-electrospray ionization-tandem mass spectrometry. YLE was administered orally (150, 300, and 450 mg/kg BW) to Wistar rats induced with alloxan for 21 days. Serum glucose and insulin as well as pancreatic catalase (CAT) and malondialdehyde (MDA) were measured using colorimetric and enzyme-linked immunosorbent assay methods. Pancreatic histopathological analysis was done using hematoxylin and eosin staining. Immunohistochemistry assay was used to detect protein expression of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and pancreatic duodenal homeobox factor-1 (PDX-1). **Results:** YLE contained apigenin, caffeic acid, gallic acid, and coumaric acid. YLE decreased serum glucose and increased serum insulin levels, increased pancreatic CAT, and decreased pancreatic MDA levels. The YLE repaired Langerhans damage. It decreased TNF-α and IL-1β and increased PDX-1. All effects were in a dose-dependent manner. **Conclusions:** YLE ameliorated DM by mitigating pancreatic inflammation and stimulating blood glucose control.

Keywords: Anti-inflammatory, antioxidant, diabetes, *Smallanthus sonchifolius*

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to pancreatic β-cell dysfunction and insulin secretion impairment.[1] Oxidative stress and increased level of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) contribute to β-cell damage,[2,3] increasing malondialdehyde (MDA) levels and reducing antioxidant enzymes such as catalase (CAT) and pancreatic duodenal homeobox factor-1 (PDX-1).[3-5] Current treatments, glibenclamide, have adverse effects, prompting interest in natural alternatives.[6] Yacon leaf (*Smallanthus sonchifolius*)[7] has shown antioxidant and anti-inflammatory potential.[8] This study aims to analyze the bioactive compounds in yacon leaf extract (YLE) using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS) and investigate its effects on Langerhans islet histopathology, glucose, insulin, CAT, MDA, TNF-α, IL-1β, and PDX-1 in DM treatment.

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Materials and Methods

Yacon leaf extraction

The yacon plant (*S. sonchifolius* [Poepp.] H. Rob) is obtained from Cibodas and determined by Mr. Djuandi from Bandung Institute of Technology, Indonesia (0220419-A008). The extraction method followed our previous work.[9]

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Liquid chromatography-electrospray ionization-tandem mass spectrometric analysis

Quantitative analysis of YLE compounds was performed with LC-ESI-MS (Accela 1250, Thermo Scientific). One gram of sample was diluted in 5 mL of methanol grade gradient, and 1 mL of 0.1 M HCl was added. The solution was sonicated for 1 h at room temperature, dried in an oven at 60°C, added 5 mL of methanol, and sonicated for 20 min. Briefly, 3 mL of petroleum ether was added to the solution and the bottom layer was taken to be filtered with 0.2 µm Polytetrafluoroethylene (PTFE) membrane. The optical density was read with an MS/MS triple Q (quadrupole) mass spectrophotometer, TSQ quantum access MAX triple quadrupole (Thermo Scientific), electrospray ionization (ESI) with a voltage of 3 kV, an evaporation temperature of 50°C, a capillary temperature of 270°C, and 5 psi of nitrogen. Mass calculations use the TSQ tune software which is operated with positive parity.[10]

Animals experimental

This study was carried out in accordance with the Guide for the Care and Use of Laboratory Animals from the Institute of Laboratory Animal Resources. The protocol was approved by Maranatha Christian University's Ethics Committee (No: 102/KEP/V/2019). Male Wistar rats (*Rattus norvegicus*) aged 8–9 weeks and weighed 170–200 g. All rats were acclimatized for 1 week and housed in individual cages in a room temperature 12 dark/light cycle with free access to food and water *ad libitum*.[11]

Blood glucose level was checked using an EasyTouch® glucometer. Alloxan 120 mg/kg BW was injected intraperitoneally for 3 days.[12] Rats with blood glucose more than 200 mg/dL were considered to have DM and then were treated with YLE at doses of 150, 300, and 450 mg/kg BW and glibenclamide 0.45 mg/kg BW (Generic, GKL9520905004A2). The rats were randomly divided into six groups (n = 5 per group): Group 1 – negative control; Group 2 – diabetic model induced by alloxan (120 mg/kg BW); Groups 3, 4, and 5 – diabetic rats treated with YLE at doses of 150, 300, and 450 mg/kg BW for 3 weeks, respectively; Group 6 – diabetic rats treated with glibenclamide (0.45 mg/kg BW).

Sample collection

Serum was collected from sampled retro-orbital blood on day 0, day 10, and day 21 after YLE treatment. On the 21st day, the rats were terminated with minimal suffering using ketamine–xylazine at concentrations of 100 mg/kg BW and 15 mg/kg BW, respectively (Ikapharmindo Putramas and Interchemie, 361453). The pancreas was preserved at -80°C for enzyme-linked immunosorbent assay (ELISA) and colorimetry tests and fixed in formalin (10%) for hematoxylin and eosin (H and E) staining and immunohistochemistry (IHC) test.[13]

Histopathological assay

The fixed pancreas was paraffinized and then sliced into 5 µm sections, which was then processed for H and E staining.[11]

Colorimetric and enzyme-linked immunosorbent assays

Serum glucose and insulin were measured using glucose colorimetric and insulin ELISA kits (Elabsci, E-BC-K234-M and E-EL-R3034), while pancreatic CAT and MDA were measured using CAT and MDA ELISA kits (Elabsci, E-BC-K031-S and E-EL-0060). Those parameters were measured in a Multiskan GO spectrophotometer (Thermo Scientific) at 505, 450, 405, and 450 nm, respectively.

Protein assay

Two hundred microliters of Quick Start Dye Reagent 1X (Bio-Rad, 5000205) was added to 20 µL of each standard solution (2 mg/L bovine serum albumin; Sigma, A9576, Lot SLB2412)) and to each sample in a 96-well plate. The plate was incubated for 5 min and then was read using a Multiskan GO spectrophotometer (Thermo Scientific) at 595 nm wavelength.[14]

Immunohistochemistry assay

The IHC method was done using a two-step plus Poly-HRP Anti Mouse/Rabbit IgG Detection System (with DAB solution) (Elabsci, E-IR-R217). The used primary antibodies were PDX-1 and TNF-α monoclonal antibodies (Elabsci, E-AB-15824 and E-AB-14410) and recombinant mouse IL-1β (Elabsci, PKSM041398), and the secondary antibody was poly-peroxidase-anti-mouse/rabbit IgG (Elabsci, E-IR-R217B). H and E staining was applied as the counterstaining.[13]

Statistical analysis

The statistical significance was obtained using one-way analysis of variance and Tukey's honestly significant difference test at $P \leq 0.05$ on IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Yacon leaf extract compounds

Figure 1 illustrates the chromatographic profile of YLE. The YLE analysis detected peaks resembling standard gallic acid (MS 169.36), caffeic acid (MS 179.03), apigenin (MS 269.60), and coumaric acid (MS 163.14). The major peaks corresponded to these phenolic compounds, which were known for their antioxidant and anti-inflammatory properties. Their presence supported the potential of YLE in mitigated oxidative stress and inflammation in diabetic conditions.

Serum glucose and insulin

Figure 2 demonstrates that alloxan induction significantly elevated serum glucose and decreased insulin levels. Treatment with the YLE alleviated serum glucose [Figure 2a] as well as increased insulin level of the DM rat model [Figure 2b]. These effects were time dependent, hence the YLE most effective activity was observed on day 21. YLE 450 mg/kg BW possessed the most suppressive effect on serum glucose and the most stimulative effect on insulin production among the YLE treatments.

Pancreatic catalase and malondialdehyde

Figure 3 shows that alloxan treatment (positive control group) significantly decreased CAT levels and increased MDA levels compared to the negative control group. YLE significantly

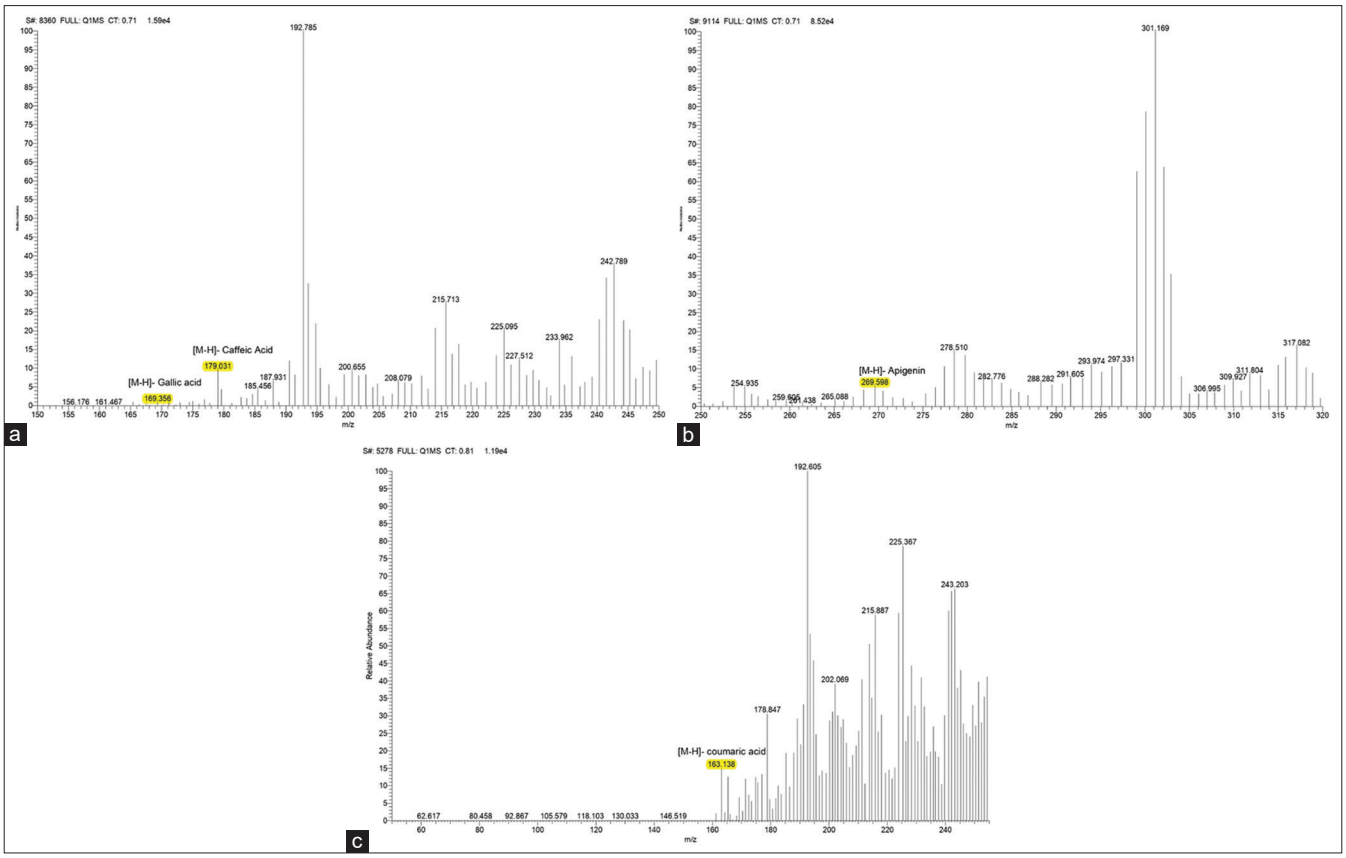

Figure 1: Yacon leaf extract chromatogram with liquid chromatography-electrospray ionization-tandem mass spectrometry (MS): (a) Gallic acid (MS 169.36) and caffeic acid (MS 179.03), (b) apigenin (MS 269.60), (c) coumaric acid (MS 163.14)

elevated the CAT level and suppressed the MDA level compared to the positive control. YLE effectively increased CAT levels and reduced MDA levels at a dose of 450 mg/kg BW.

Pancreatic histopathology

Figure 4 shows that alloxan (PC) caused the Langerhans islet to shrink and the islet cell swelling. Histopathological scoring depicted the decrease of the proportion of Langerhans islet as alloxan induction, and then, it was significantly increased by the YLE treatments.

Pancreatic tumor necrosis factor-α expression

The brown dots indicate TNF-α expression in DM rats' pancreas [Figure 5]. The scoring data depicted that alloxan induction stimulated TNF-α expressions. Subsequently, it was lowered by the YLE treatments. The YLE at a dose of 450 mg/kg BW even possessed a stronger suppressive effect than the comparison control (glibenclamide).

Pancreatic interleukin-1β expression

Figure 6 depicts that the YLE significantly decreased IL-1β protein expression of DM rats' pancreas which initially increased due to alloxan induction. The decreased effect was in a dose-dependent manner; hence, the highest dose resulted in the biggest decrease and was almost similar to glibenclamide.

Pancreatic duodenal homeobox factor-1 expression

Alloxan induction dramatically dropped the expression of PDX-1 protein of DM rats' pancreas. The YLE treatments elevated PDX-1 protein expression in a dose-dependent way. Therefore, YLE at a dose of 450 mg/kg BW improved PDX-1 expression was comparable with glibenclamide treatment [Figure 7].

Discussion

Type 2 DM is characterized by pancreatic β-cell dysfunction to secrete insulin and insulin resistance and then cause hyperglycemia. Targeted therapy on Langerhans inflammation and oxidative stress promises an effectiveness.[15]

Yacon leaf is considered to treat DM due to its bioactive compounds including phenols, flavonoids, saponins, tannins, alkaloids, and steroids/triterpenoids.[9] Similarly, previous studies reported that YLE contains apigenin,[16] caffeic, coumaric, and gallic acids[17] which have been shown to act as antioxidants with 2,2-diphenyl-1-picryl-hydrazyl-hydrate and xanthine oxidase superoxide radical ($O_2^{\cdot}-$) scavenging assays.[18] Other reported compounds are quercetin, rutin, myricetin, ferulic acid, and chlorogenic acid which can repair pancreatic β-cells so that they can increase insulin production.[19]

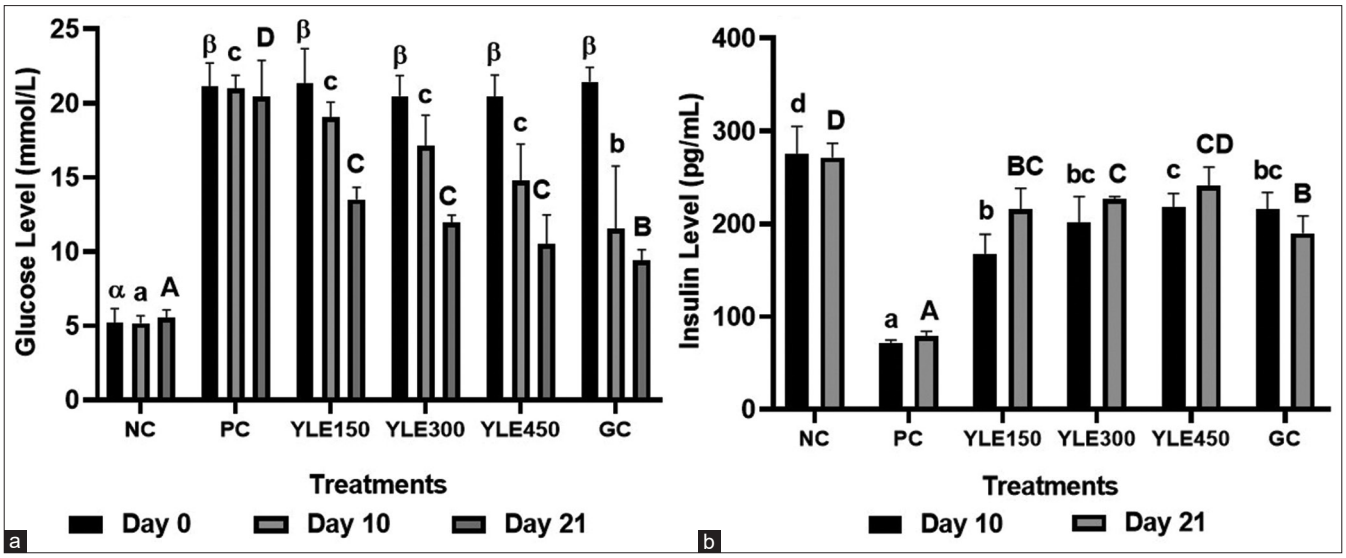

Figure 2: Effects of yacon leaf extract (YLE) on insulin and glucose levels in diabetes mellitus rats' serum. The histograms display mean ± standard deviation. NC: Negative control; PC: Positive control (rats treated with alloxan 120 mg/kg BW); YLE150: PC + YLE 150 mg/kg BW; YLE300: PC + YLE 300 mg/kg BW; YLE450: PC + YLE 450 mg/kg BW; GC: PC + glibenclamide (0.45 mg/kg of BW). The different letters (α, β on day 0; a, b, c, on day 10; and A, B, C, D on day 21 in panel a) a, b, bc, c, d on day 10 and A, B, BC, CD, D on day 21 in panel b) indicate significant differences among treatments based on Tukey's honestly significant difference *post hoc* test ($P \leq 0.05$)

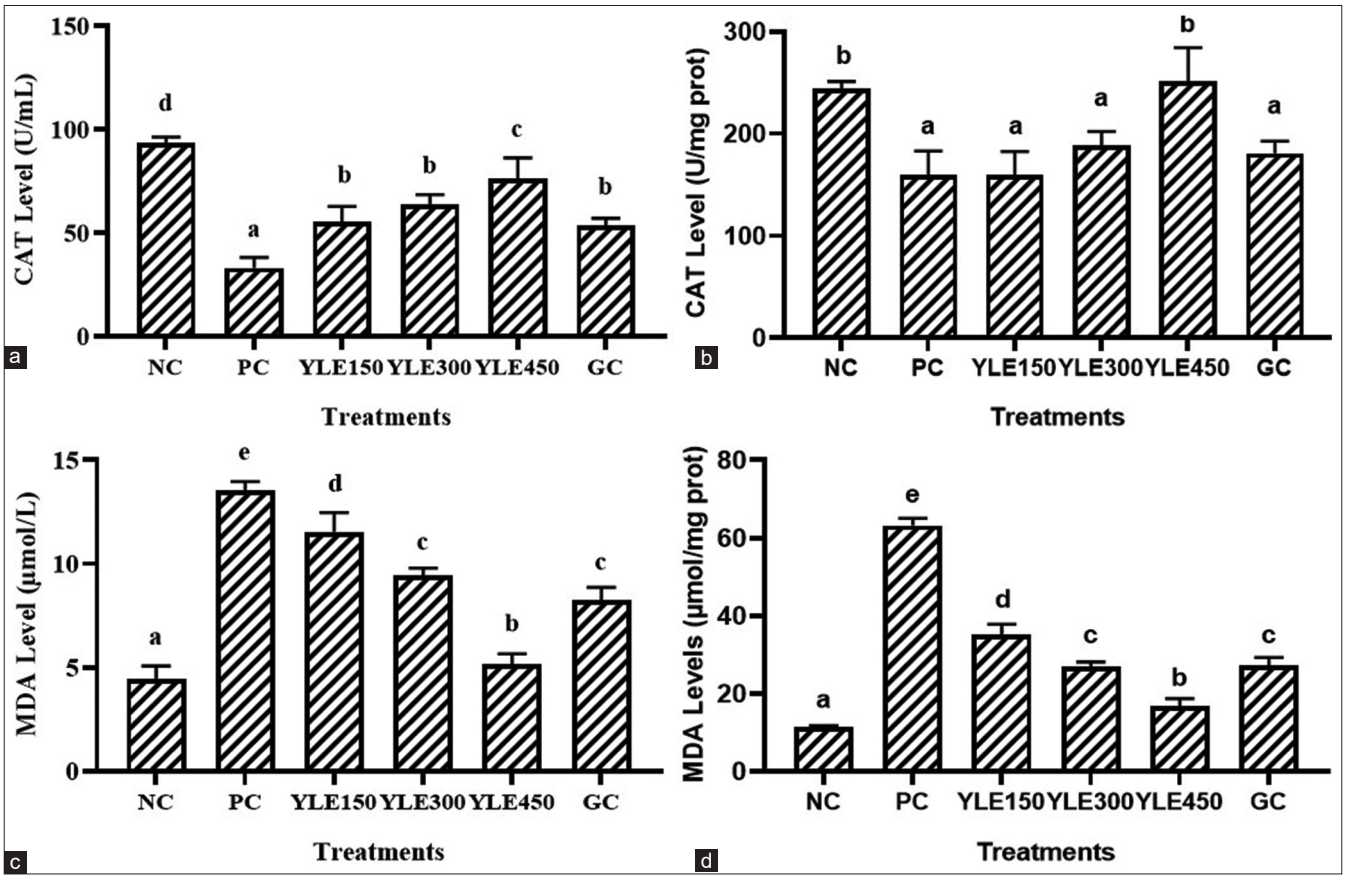

Figure 3: The histograms display mean ± standard deviation. NC: Negative control; PC: Positive control (rats treated with alloxan 120 mg/kg BW); YLE150: PC + YLE 150 mg/kg BW; YLE300: PC + YLE 300 mg/kg BW; YLE450: PC + YLE 450 mg/kg BW; GC: PC + glibenclamide (0.45 mg/kg BW). The different letters (a, b, c, d in panel a; a, b in panel b; a, b, c, d, e in panel c and d) represent significant differences among treatments in accordance to Tukey's honestly significant difference *post hoc* test ($P \leq 0.05$)

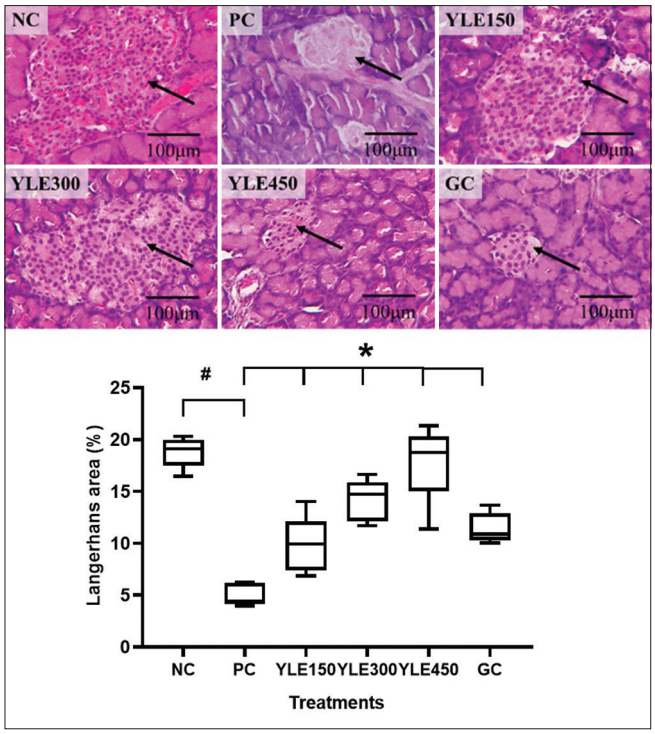

Figure 4: Effects of yacon leaf extract (YLE) on pancreatic histopathology of diabetes mellitus rats. The histological figures are in ×40. The histogram displays mean ± standard deviation. NC: Negative control; PC: Positive control (alloxan 120 mg/kg BW); YLE150: PC + YLE 150 mg/kg BW; YLE300: PC + YLE 300 mg/kg BW; YLE450: PC + YLE 450 mg/kg BW; GC: PC + glibenclamide (0.45 mg/kg BW). The hashtag (#) indicates a significant difference between negative control and positive control, while the asterisk (*) denotes a significant difference between treatments and positive control based on Tukey's *post hoc* test ($P \leq 0.05$)

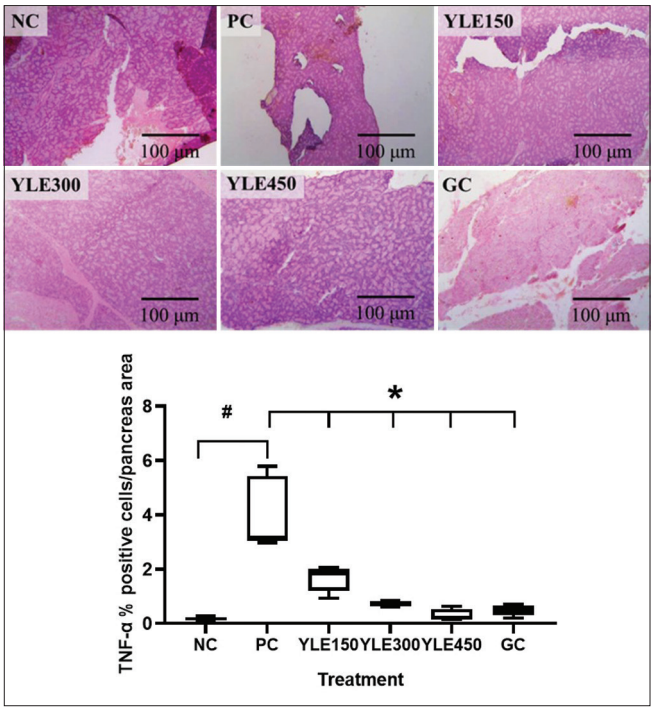

Figure 5: Effects of yacon leaf extract (YLE) on pancreatic tumor necrosis factor-α of diabetes mellitus rats. The histological figures are in ×10. The histogram displays mean ± standard deviation. NC: Negative control; PC: Positive control (alloxan 120 mg/kg BW); YLE150: PC + YLE 150 mg/kg BW; YLE300: PC + YLE 300 mg/kg BW; YLE450: PC + YLE 450 mg/kg BW; GC: PC + glibenclamide (0.45 mg/kg BW). The hashtag (#) indicates a significant difference between negative control and positive control, while the asterisk (*) denotes a significant difference between treatments and positive control based on Tukey's *post hoc* test ($P \leq 0.05$). TNF-α: Tumor necrosis factor-α

Alloxan induction is commonly used to generate DM models[20] due to its action to exaggerate ROS production, damage β-cells by inducing apoptosis, and weaken insulin synthesis.[15] This study demonstrated the YLE mitigation toward the DM progression of the alloxan-induced rats.

YLE treatment reduced blood glucose levels and enhanced insulin production in the rats' serum by modulating antidiabetic enzymes, including α-amylase, α-glucosidase, and glucose 6-phosphatase (G-6-Pase).[9] Caffeic acid in YLE also contributes to decreasing blood glucose levels by modulating glycogenesis.[21] Another study reported YLE flavonoid stimulation on insulin receptor phosphorylation and induction on the adenosine monophosphate-activated protein kinase signaling paths, thereby increasing insulin responsiveness and blood glucose regulation.[22]

The antioxidant potential of YLE, attributed to its flavonoid content, aligns with prior studies demonstrating its ability to counteract oxidative stress in diabetic models.[23] Another study found that YLE treatment alleviated lipoperoxidation and inhibited liver oxidative damage.[8]

YLE administration protected the pancreatic Langerhans islets from inflammation and structural damage. The observed reduction in inflammatory markers aligns with reports that YLE compounds, particularly gallic acid, interfere with NF-κB activation, thereby preserving pancreatic β-cell integrity and function.[24] The gallic acid content in YLE is reported inhibiting TNF-α and NF-κB activities.[25] As a result, it attenuated the islet injury. In addition, it increased PDX-1 expression. A previous study also reported that YLE can increase PDX-1 expression, thereby mitigating pancreatic β-cell dysfunction and hyperglycemia.[26]

This study has limitations, including a small sample size and the use of alloxan-induced diabetic rats, which may not fully represent human diabetes. Further research is needed to explore the molecular mechanisms, pharmacokinetics, and bioavailability of YLE. Before clinical translation, larger sample sizes, diverse diabetic models, and clinical trials are essential to validate its therapeutic potential.

Conclusions

YLE contains apigenin, caffeic acid, gallic acid, and coumaric acid compounds, which are known for their antioxidant and anti-inflammatory properties. YLE 150–450 mg/kg BW treatment reduced serum glucose and increases serum insulin

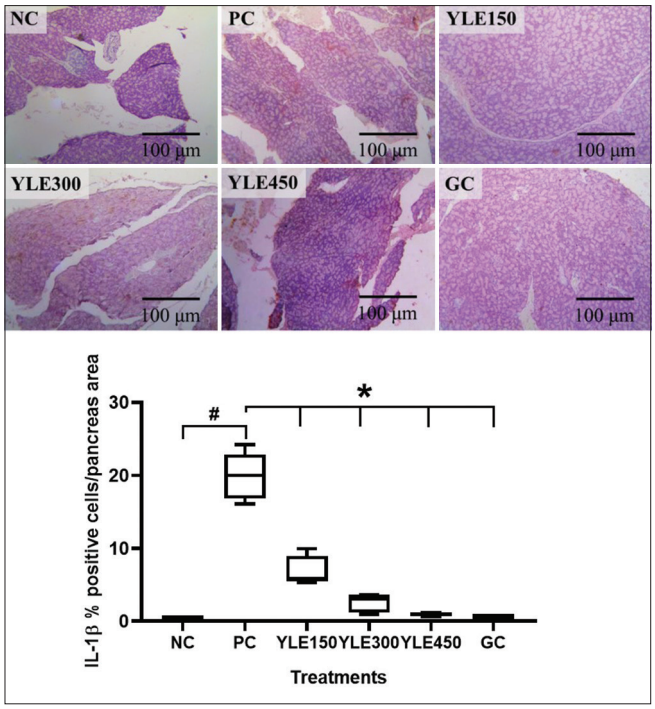

Figure 6: Effects of yacon leaf extract (YLE) on pancreatic IL-1β of diabetes mellitus rats. The histological figures are in ×10. The histogram displays mean ± standard deviation. NC: Negative control; PC: Positive control (alloxan 120 mg/kg BW); YLE150: PC + YLE 150 mg/kg BW; YLE300: PC + YLE 300 mg/kg BW; YLE450: PC + YLE 450 mg/kg BW; GC: PC + glibenclamide (0.45 mg/kg BW). The hashtag (#) indicates a significant difference between negative control and positive control, while the asterisk (*) denotes a significant difference between treatments and positive control based on Tukey's *post hoc* test ($P \leq 0.05$). IL-1β: Interleukin-1β

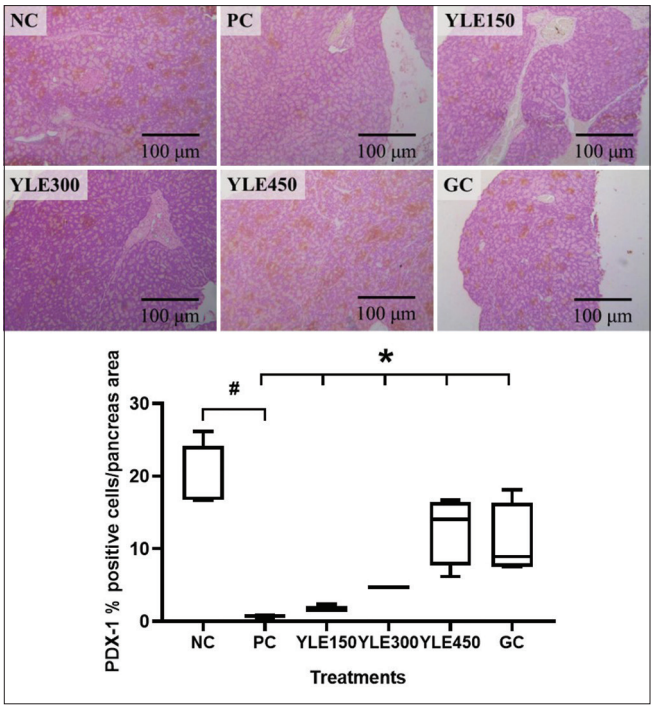

Figure 7: Effects of yacon leaf extract (YLE) on pancreatic duodenal homeobox factor-1 of diabetes mellitus rats. The histological figures are in ×10. The histogram displays mean ± standard deviation. NC: Negative control; PC: Positive control (alloxan 120 mg/kg BW); YLE150: PC + YLE 150 mg/kg BW; YLE300: PC + YLE 300 mg/kg BW; YLE450: PC + YLE 450 mg/kg BW; GC: PC + glibenclamide (0.45 mg/kg of BW). The hashtag (#) indicates a significant difference between negative control and positive control, while the asterisk (*) denotes a significant difference between treatments and positive control based on Tukey's *post hoc* test ($P \leq 0.05$). PDX-1: Pancreatic duodenal homeobox factor-1

levels. YLE repaired pancreatic β-cells and upregulated PDX-1 protein expression by increasing CAT, suppressing MDA levels, and anti-inflammatory mechanisms by decreasing TNF-α and IL-1β expression. Given these promising results, further studies, including mechanistic investigations and clinical trials, are needed to confirm YLE's therapeutic efficacy and safety in human diabetes management.

Ethical considerations

The Institutional Review Board and Ethics Committee of Maranatha Christian University Faculty of Medicine approved this experimental study on 21 May 2019 (Approval No: 102/KEP/V/2019).

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Reporting guidelines

This animal preclinical study followed the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.

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Conflicts of interest

There are no conflicts of interest.

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