

Effects of Ya Khao, a Thai traditional herbal formula extract, on hyperglycemia and associated biochemical and histopathological changes in streptozotocin-induced diabetic rats

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Abstract

Diabetes mellitus (DM) was a chronic metabolic disorder marked by hyperglycemia and affected millions of individuals globally. Ya Khao (YK) was a Thai traditional herbal formula inscribed on the stone slabs of Wat Pho. It consisted of 15 different herbs in equal proportions and had been traditionally used to treat various fevers for a long time. This study aimed to evaluate the anti-hyperglycemic, biochemical, and histopathological effects of Ya Khao formula extract (YKFE) in streptozotocin (STZ)-induced diabetic rats. Forty male Sprague-Dawley rats were classified into 5 groups (n = 8): NDM (non-diabetic), DM, DM+GB (glibenclamide), DM+YKFE250, and DM+YKFE500. Rats in the DM groups were induced to develop the disease by receiving an intraperitoneal injection of STZ (65 mg/kg BW), whereas rats in the NDM group were injected with citrate buffer solution. All rats were administered orally once daily for 2 weeks. Body weights were monitored daily, and fasting blood glucose (FBG) levels were assessed weekly. At the end of the treatment, all rats were euthanized, and their blood samples were collected for FBG and biochemical analyses. Vital organs (pancreas, liver, and kidneys) were removed and weighed, and the pancreas was fixed in 10% formalin for histopathological evaluation. Treatment with both doses of YKFE for 2 weeks significantly decreased FBG levels in diabetic rats (* P < 0.05, ** P < 0.01 compared with the DM group) and ameliorated pancreatic histopathological changes. However, there were no differences in body weight gain and relative organ weight among the groups. Besides, the treatment duration was insufficient to normalize hepatic and renal functions to levels comparable to the NDM group. Collectively, the results suggested that YKFE exhibited anti-hyperglycemic and pancreatic protective effects in STZ-induced diabetic rats and showed potential for further development as a therapeutic agent for DM.

Keywords: Ya Khao formula extract, Diabetes mellitus, Anti-hyperglycemic effect, Pancreatic protective effect, Streptozotocin

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1. Introduction

Diabetes mellitus (DM) was recognized as a chronic metabolic disorder characterized by

elevated blood glucose levels (hyperglycemia) due to the body's inability to produce or utilize insulin effectively [1]. DM was classified into 2 types: type 1 and type 2. Type 1 DM resulted

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from the autoimmune-mediated destruction of pancreatic β -cells in the islets of Langerhans, leading to insulin deficiency. In contrast, type 2 DM was marked by a diminished or ineffective response to insulin, commonly described as insulin resistance [2]. Insulin deficiency in patients with type 1 DM developed several complications, including cardiovascular diseases, neuropathologic diseases, and renal damage [3-5]. Notably, DM-related complications were significant contributors to morbidity and mortality in individuals with DM [6]. In 2016, the International Diabetes Federation (IDF) reported that 415 million people worldwide were living with DM, and the number was expected to increase to 642 million by 2040 [7]. Even though anti-diabetic agents such as glibenclamide were administered to patients with DM, serious adverse effects were documented, particularly hypoglycemia and increased cardiovascular mortality [8, 9]. Several previous investigations explored the potential of herbal formulations or plant extracts to lower blood glucose levels in diabetic animal models. It was reported that oral administration of Madhurameha formula extract at doses of 12.5, 25, and 50 mg/kg body weight (BW) for 2 weeks reduced 2-hour postprandial plasma glucose levels in streptozotocin (STZ)-nicotinamide-induced diabetic rats [10]. Similarly, oral administration of *Caesalpinia bonduc* (L.) Roxb. leaf extract at doses of 150, 200, and 400 mg/kg BW for 2 weeks decreased blood glucose levels in STZ-induced diabetic rats [11]. Moreover, a rhinacanthins-rich extract derived from *Rhinacanthus nasutus* (L.) Kurz. leaves, given orally at 15 mg/kg BW for 4 weeks, lowered fasting blood glucose (FBG) levels in STZ-nicotinamide-induced [12]. Considering previous research demonstrating the anti-hyperglycemic effect of herbal formulations in diabetic animal models, such as STZ-induced type 1 diabetic rats and STZ-nicotinamide-induced type 2 diabetic rats, this study selected the STZ-induced type 1 diabetic rat model. The model was chosen to specifically evaluate the blood glucose-lowering effect of the herbal formula while minimizing confounding variables and comparing its therapeutic efficacy with glibenclamide, a standard antidiabetic drug.

Ya Khao (YK) was known as a Thai traditional herbal formula inscribed on the stone

slabs of Wat Phra Chetuphon Wimon Mangkhalaram Ratchaworamahawihan (Wat Pho) in the Phra Nakhon district, Bangkok, Thailand. It had long been used in Thai traditional medicine to treat various types of fever, such as scrub typhus, black fever, red fever, Mahamekh fever, and Mahanil fever, and so on [13]. The formula was composed root and stem of 15 medicinal plants in equal proportions, including *Hydnophytum formicarum* Jack., *Donax arundastrum* Lour., *Rhinacanthus nasutus* (L.) Kurz., *Camellia sinensis* (L.) O. Kuntze., *Dregea volubilis* (L.f.) Hook.f., *Glochidion lutescens* Blume. *Diospyros wallichii* King & Gamble. *Merremia umbellata* (L.) Hallier f., *Caesalpinia bonduc* (L.) Roxb., *Combretum quadrangulare* Kurz., *Citrus aurantiifolia* (Christm.) Swingle., *Tiliacora triandra* (Colebr.) Diels., *Momordica cochinchinensis* (Lour.) Spreng., *Adenia viridiflora* Craib., and *Sauropus androgynus* (L.) Merr. An earlier study indicated that a 1-week administration of YK in combination with *Andrographis paniculata* (Burm.f.) Nees., Ammaruekhawathi cough syrup, and Makhampom cough syrup effectively treated COVID-19 patients in the sample population [14]. Moreover, a 12-week administration of 500 mg/kg BW of YK formula extract (YKFE) to adult male Sprague-Dawley rats did not cause any toxicological damage and was considered safe for use [15]. Furthermore, research on individual herbal constituents of YK formula indicated that extracts of *Camellia sinensis* (L.) O. Kuntze. and *Caesalpinia bonduc* (L.) Roxb. lowered blood glucose levels in type 1 diabetic rats [11, 16], while the active compound of *Rhinacanthus nasutus* (L.) Kurz. produced comparable effects in type 2 diabetic rats [12, 17]. In addition, *Hydnophytum formicarum* Jack. extract demonstrated inhibitory activity against α -amylase and α -glucosidase, an important mechanism in type 2 DM management [18]. These studies emphasized the importance of further evaluating the anti-hyperglycemic efficacy of this formula.

Although the Ya Khao formula had long been used in Thai traditional medicine and some of its therapeutic effects had been investigated in both humans and animals, research on its ability to reduce blood glucose levels was still limited. Therefore, this study aimed to investigate the anti-hyperglycemic,

biochemical and histopathological effects of YKFE in STZ-induced type 1 DM rats.

2. Methodology

2.1 Chemicals and drugs

Streptozotocin (STZ) was purchased from Sigma-Aldrich (St. Louis, MO, USA), and glibenclamide (GB) was sourced from Siam Bheasach Co., Ltd. (Bangkok, Thailand).

2.2 Preparation of Ya Khao formula extract (YKFE)

Ya Khao formula was supplied by the Department of Thai Traditional and Alternative Medicine and extracted at the Center for Research and Development of Herbal Health Products (CRD-HHP), Faculty of Pharmaceutical Sciences, Khon Kaen University. Approximately 5 kg of dried Ya Khao formula powder was macerated in 50% ethanol at a 1:5 (w/v) ratio and stirred intermittently at room temperature for 7 days. The extract was then filtered and concentrated to dryness at 50 °C using a rotary evaporator, followed by lyophilization with a freeze dryer. The dried crude extract was stored at 0 °C until further use, with an extraction yield of 10.80% (w/w, dry-weight basis).

2.3 Experimental animals and treatment

Six-week-old male Sprague-Dawley rats were obtained from Nomura Siam International Co., Ltd. (Bangkok, Thailand). All rats were housed at the Northeast Laboratory Animal Center, Khon Kaen University, under standard laboratory conditions (temperature 23 ± 2 °C, 12/12 h light-dark cycle, and relative humidity 30-60%). The rats were allowed free access to food and water throughout the experimental period. All experimental procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals under the supervision of the Northeast Laboratory Animal Center, Khon Kaen University, Thailand. Ethical approval for the study was granted by the Institutional Animal Care and Use Committee of Khon Kaen University (Approval No. ACUC-KKU-63/61).

Forty rats with an average fasting blood glucose (FBG) level of 99.17 ± 10.22 mg/dl were divided into 5 groups (n = 8 per group), with comparable baseline FBG levels. Group I (NDM) consisted of non-diabetic rats receiving distilled water as the vehicle. Group II (DM) included diabetic rats receiving the vehicle. Group III (DM+GB; positive control group) comprised diabetic rats administered glibenclamide at a dose of 0.5 mg/kg BW [19]. Group IV (DM+YKFE250) and Group V (DM+YKFE500) consisted of diabetic rats treated with Ya Khao formula extract at doses of 250 and 500 mg/kg BW, respectively.

After 1 week of acclimatization, all rats were fasted overnight for 16 h [20]. Type 1 DM was induced in rats by intraperitoneal injection of freshly prepared streptozotocin (STZ; 65 mg/kg BW) dissolved in 0.1 M citrate buffer (pH 4.5) [21], while non-diabetic rats were injected with an equivalent volume of citrate buffer. Subsequently, diabetic rats were provided with a 5% glucose solution via feeding bottles to prevent early hypoglycemia and were allowed to stabilize for 2 weeks [22]. Two weeks after STZ injection, FBG levels were reassessed, and rats with FBG levels greater than 300 mg/dl were considered diabetic and included in the study [19].

After diabetes was confirmed in the rats, the entire substances were administered orally once daily for 2 weeks. All rats were weighed once a day, and their FBG levels were monitored once a week. At the end of the study, all rats were completely anesthetized by intraperitoneal injection of thiopental sodium (120 mg/kg BW; Jagsonpal Pharmaceuticals Ltd., India). The abdominal and thoracic cavities were then opened to collect blood samples from the abdominal vein for biochemical investigations. Thereafter, the rats were euthanized by transcardial perfusion with 0.9% normal saline. Vital organs, including the pancreas, liver, and kidneys, were removed and weighed. Only the pancreas was fixed in a 10% formalin solution for subsequent histopathological examination.

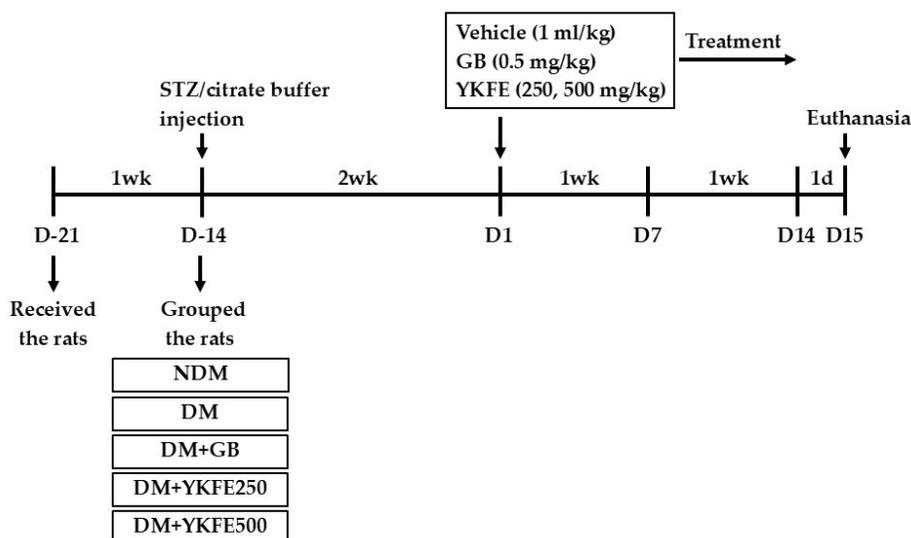


Figure 1. Schematic diagram of experimental animals and drug treatment. DM: Diabetic; GB: glibenclamide; NDM: Nondiabetic; STZ: streptozotocin; YKFE: Ya Khao formula extract.

2.4 Measurement of body and organ weights

The body weight of all rats was tracked and reported as an average every two days. The weights of vital organs (pancreas, liver, and kidneys) for each rat, along with the final body weight obtained on the last day of the study, were used to determine the relative organ weight (%) using the following calculation:

$$\text{Relative organ weight (\%)} = \left[\frac{\text{Organ weight (g)}}{\text{Body weight (g)}} \right] \times 100$$

2.5 Assessment of FBG levels

FBG levels were determined 4 times: before STZ injection, before treatment, 1 week after treatment, and before euthanasia. After the rats were fasted overnight [20], blood samples were collected from the tail vein and analyzed using a glucometer (Apex Biotechnology Corp., Hsinchu, Taiwan), and the values were expressed in mg/dl [23].

2.6 Biochemical investigations

Blood samples collected from the abdominal veins were centrifuged at 3,000 rpm for 10 minutes at 4 °C to isolate serum. The serum samples were then submitted to the Kaen Nakhon Laboratory (Khon Kaen, Thailand) for

analysis of albumin (A), globulin (G), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (Cr) levels.

2.7 Histopathological examination

Fixed tissues were paraffin-embedded and sectioned at a thickness of 5 μm using a microtome. The sections were stained with hematoxylin and eosin (H&E), and histopathological changes were examined under a light microscope (Nikon ECLIPSE E200 MVR microscope) at magnifications of 10X and 40X.

2.8 Statistical analysis

Data were presented as mean ± standard deviation (SD). All statistical analyses were performed using a one-way analysis of variance (ANOVA) followed by a Tukey post-hoc test for multiple comparisons. A level of $P < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1 Effects of YKFE on average body weight and relative organ weight changes in STZ-induced diabetic rats.

Figure 2 and Table 1 showed the changes in average body weight and relative organ weights in STZ-induced diabetic rats over the study period. Initially, the average body weight was similar among all experimental groups. During the 2-week treatment period, all groups demonstrated a progressive increase in average body weight. The NDM group exhibited a relatively higher average body weight than all diabetic groups; however, this difference was not statistically

significant (Figure 2). The result suggested that diabetic rats had a lower growth rate than normal rats. It was possible that the slower weight gain in diabetic rats was due to insulin deficiency caused by the pancreas's inability to produce insulin, which impaired glucose utilization for energy production. Therefore, they relied on the breakdown of fat and muscle protein for energy, resulting in reduced growth [24]. This was consistent with the study published by Huang et al. in 2022 [25].

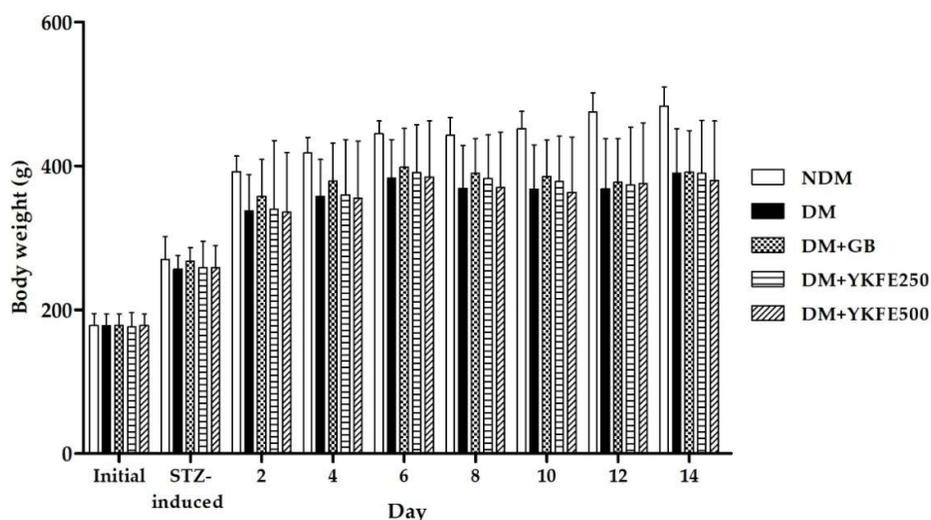


Figure 2. Effects of YKFE on average body weight changes in STZ-induced diabetic rats for 2 weeks of treatment. Groups included non-diabetic control (NDM), diabetic control (DM), diabetic rats treated with the positive control (DM + GB), and diabetic rats treated with the herbal formula (DM + YKFE250 and DM + YKFE500). Data were presented as mean \pm SD (n = 8).

Table 1. Effects of YKFE on relative organ weight changes in STZ-induced diabetic rats after 2 weeks of treatment. Groups included non-diabetic control (NDM), diabetic control (DM), diabetic rats treated with the positive control (DM + GB), and diabetic rats treated with the herbal formula (DM + YKFE250 and DM + YKFE500). Data were presented as mean \pm SD (n = 8).

Groups	Relative organ weight (%)		
	Pancreas	Liver	Kidney
NDM	0.48 \pm 0.13	4.21 \pm 0.31	0.78 \pm 0.06
DM	0.59 \pm 0.10	4.05 \pm 0.37	1.10 \pm 0.16
DM+GB	0.49 \pm 0.08	3.86 \pm 0.27	1.11 \pm 0.14
DM+YKFE250	0.53 \pm 0.07	4.14 \pm 0.43	1.11 \pm 0.19
DM+YKFE500	0.50 \pm 0.10	4.16 \pm 0.46	1.08 \pm 0.19

Moreover, the relative organ weights of the pancreas, liver, and kidneys in all diabetic groups were not significantly different from those of the NDM group (Table 1). This might have been because, under normal conditions, the body possessed a tightly regulated system for distributing energy to preserve vital organs. When it lacked energy derived from glucose, it first broke down fat and muscle protein to generate energy. Therefore, the weights of these organs remained unchanged during a short experimental period (e.g., 14-28 days), although overall body weight decreased [24].

3.2 Effects of YKFE on fasting blood glucose levels in STZ-induced diabetic rats.

Figure 3 showed the fasting blood glucose (FBG) levels in STZ-induced diabetic rats over the study period. Before treatment initiation, FBG levels in all diabetic groups were significantly higher than those in the NDM group. This study revealed that type 1 DM could be successfully induced in rats by a single intraperitoneal injection of STZ (65 mg/kg BW), in agreement with the report by

Huang et al. in 2022 [25]. Interestingly, administration of YKFE (250 and 500 mg/kg BW) for 2 weeks significantly decreased FBG levels compared with the DM group. The effect was similar to those observed with glibenclamide. The finding indicated that both doses of YKFE might have exerted antihyperglycemic effect in diabetic rats similar to those observed with glibenclamide, an antidiabetic drug. This effect was possibly attributed to the pharmacological properties of several herbal components contained in the formula. Previous studies supported this assumption by showing that extracts of *Camellia sinensis* (L.) O. Kuntze. and *Caesalpinia bonduc* (L.) Roxb. effectively reduced blood glucose levels in type 1 diabetic rats [11, 16, 26], while the active constituent of *Rhinacanthus nasutus* (L.) Kurz. displayed similar effect in type 2 diabetic rats [12, 17]. Additionally, *Hydnophytum formicarum* Jack. extract presented anti- α -amylase and anti-glucosidase activities, a key mechanism underlying type 2 DM therapy. [18]. These findings appeared to support the antihyperglycemic effect of YKFE.

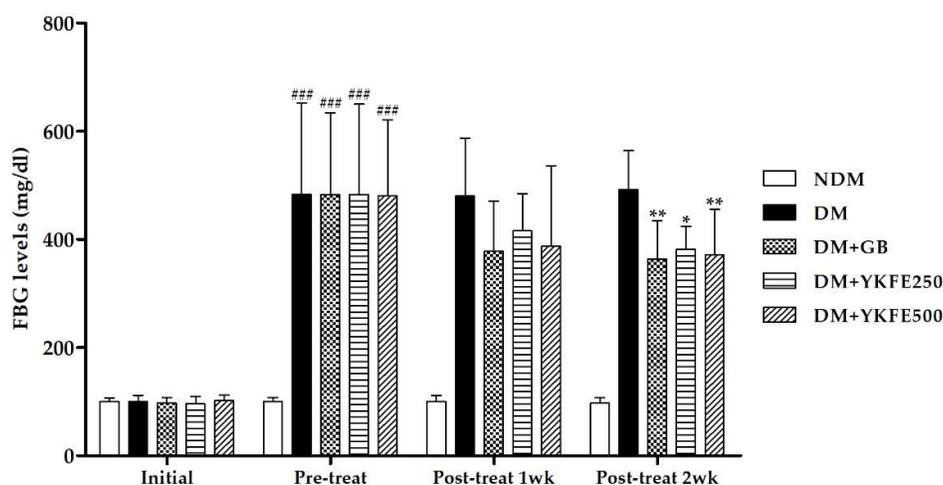


Figure 3. Effects of YKFE on FBG levels in STZ-induced diabetic rats for 2 weeks of treatment. Groups included non-diabetic control (NDM), diabetic control (DM), diabetic rats treated with the positive control (DM + GB), and diabetic rats treated with the herbal formula (DM + YKFE250 and DM + YKFE500). Data were presented as mean \pm SD (n = 8). ### $P < 0.001$ compared with NDM, * $P < 0.05$, ** $P < 0.01$ compared with DM.

3.3 Effects of YKFE on serum biochemical parameters in STZ-induced diabetic rats.

Table 2 showed the serum biochemical parameters in STZ-induced diabetic rats after 2 weeks of treatment. The diabetic groups treated with YKFE (250 and 500 mg/kg body weight) had significantly elevated hepatic function parameters, particularly globulin levels, compared with the NDM group. Similarly, the DM group as well as the diabetic groups treated with YKFE at both doses displayed significant increases in renal function parameters, notably creatinine levels, compared with the NDM group. These study results clearly demonstrated that higher creatinine and globulin levels in diabetic rats and in those treated with YKFE

compared with normal rats, consistent with previous studies. Their research reported that inducing type 1 DM with STZ might have been associated with nephrotoxicity [27] and enhanced muscle protein breakdown for energy production due to insulin deficiency [24], which contributed to impaired excretory function. Furthermore, elevated globulin levels may have suggested an immune response associated with chronic inflammation in diabetic rats [28]. Although YKFE could possibly have been associated with protective effects in vital organ tissues, the 2-week treatment period was unlikely to have been long enough to achieve full restoration of hepatic and renal functions to the same level as the NDM group.

Table 2. Effects of YKFE on serum biochemical parameters in STZ-induced diabetic rats after 2 weeks of treatment. Groups included non-diabetic control (NDM), diabetic control (DM), diabetic rats treated with the positive control (DM + GB), and diabetic rats treated with the herbal formula (DM + YKFE250 and DM + YKFE500). Data were presented as mean \pm SD (n = 8). # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ compared with NDM.

Groups	Hepatic functions				Renal functions	
	Albumin (g/dl)	Globulin (g/dl)	ALT (U/l)	AST (U/l)	BUN (mg/dl)	Creatinine (mg/dl)
NDM	3.29 \pm 0.24	1.98 \pm 0.50	127.79 \pm 64.69	196.00 \pm 59.47	23.77 \pm 5.19	0.46 \pm 0.14
DM	3.19 \pm 0.11	2.26 \pm 0.30	125.71 \pm 101.78	200.00 \pm 50.01	32.64 \pm 3.87	0.75 \pm 0.09 [#]
DM+GB	3.20 \pm 0.08	2.13 \pm 0.26	131.86 \pm 88.24	198.86 \pm 75.48	32.67 \pm 1.77	0.46 \pm 0.07
DM+YKFE 250	3.57 \pm 0.35	2.88 \pm 0.30 ^{##}	89.43 \pm 29.42	211.71 \pm 44.75	34.16 \pm 11.48	0.80 \pm 0.23 ^{###}
DM+YKFE 500	3.51 \pm 0.34	2.82 \pm 0.21 ^{##}	108.57 \pm 49.81	212.57 \pm 72.85	34.61 \pm 9.50	0.88 \pm 0.12 ^{###}

3.4 Effects of YKFE on pancreatic histopathology in STZ-induced diabetic rats.

Figure 4 showed the pancreatic histopathology, particularly the islets of Langerhans, in STZ-induced diabetic rats after 2 weeks of treatment. No histopathological abnormalities were observed in the pancreatic tissue of the NDM group. In the DM group, markedly smaller islets of Langerhans and fewer islet cells were found compared with the

NDM group. The affected cells demonstrated structural damage, poorly defined boundaries, and nuclear degeneration in some cells. Treatment with YKFE (250 and 500 mg/kg BW) and glibenclamide improved these histological features of diabetic groups, as evidenced by larger islets of Langerhans, increased cell numbers, and more distinct cellular boundaries. However, no statistically significant differences in the islets of Langerhans area were detected among the

experimental groups (data not shown). These observations revealed that administration of YKFE for 2 weeks might have contributed to certain improvements in pancreatic histopathology in diabetic rats, in a manner similar to that observed with glibenclamide. These effects could possibly have been correlated with the pharmacological properties of various herbal constituents in the formula. Earlier studies reported that extracts of *Caesalpinia bonduc* (L.) Roxb. and *Rhinacanthus nasutus* (L.) Kurz. restored damaged pancreatic tissue and islets of

Langerhans in diabetic rats [11, 12]. In addition, the active constituent of *Rhinacanthus nasutus* (L.) Kurz., especially rhinacanthin-C, enhanced the levels of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while suppressing malondialdehyde (MDA), TNF- α , and caspase-3 levels in the pancreatic tissue of diabetic rats [17]. This evidence suggested that the pancreatic protective effects of YKFE might have been linked to its antioxidant, anti-inflammatory, and anti-apoptotic properties.

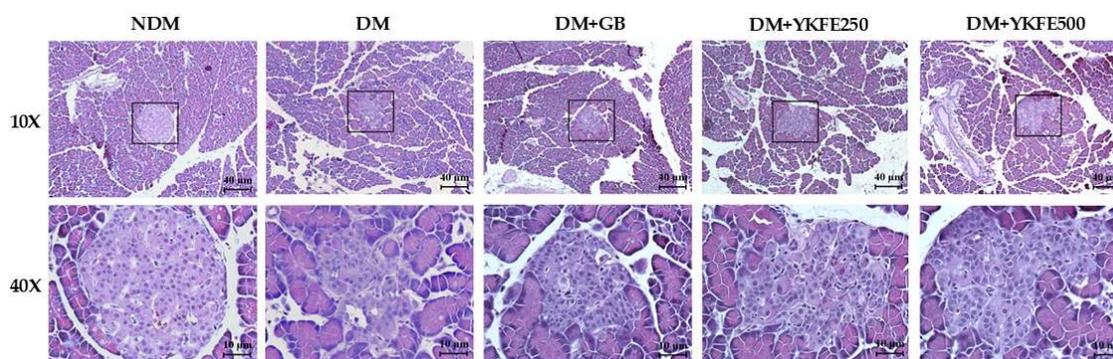


Figure 4. Effects of YKFE on pancreatic histopathology in STZ-induced diabetic rats after 2 weeks of treatment. Groups included non-diabetic control (NDM), diabetic control (DM), diabetic rats treated with the positive control (DM + GB), and diabetic rats treated with the herbal formula (DM + YKFE250 and DM + YKFE500).

4. Conclusion and Recommendations

The findings demonstrated that 2-week treatment with YKFE at both doses produced anti-hyperglycemic and pancreatic protective effects in STZ-induced diabetic rats. Nevertheless, this treatment period was not sufficient to return hepatic and renal functions to normal levels comparable to the NDM group. Accordingly, future studies were recommended to increase the treatment duration, and YKFE was proposed as a promising candidate for future antidiabetic drug development.

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