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Antidiabetic and Hypolipidemic Potentials of Extract of *Picris Babylonica* in Streptozotocin-Induced Diabetic Model in Rats

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To investigate the hypoglycemic and hypolipidemic potentials of Picris babylonica extract in streptozotocin (STZ) induced diabetes in rats. Animals were injected with 40mg/kg of STZ to induce diabetes, a common diabetic model. Development of the disease were assessed by measuring blood glucose level 3 days prior systemic administration of STZ and following STZ injection. Animals received 200mg/kg and 400mg/kg of Picris babylonica extract and 0.6mg/kg of glibenclamide, standard, by oral rout for 14 consecutive days. Administration of the Picris babylonica extract significantly decreased serum blood glucose, total cholesterol, triglycerides, and low-density lipoprotein-cholesterol. In addition, high density lipoprotein-cholesterol level significantly enhanced as compared to standard. Picris babylonica extract demonstrated beneficial effects in lowering blood glucose and improving lipid profile, therefore, Picris babylonica extract could be developed as hypoglycemic and hypolipidemic therapy.

Keywords: Asteraceae; DPPH; Hypolipidemic; Streptozotocin Antidiabetic; Picris babylonica.

One of the challenging health concerns is Diabetes mellitus (DM), which affects approximately 537 million adults globally with an estimated 6.7 million deaths in 2021. The number of incidence is anticipated to increase up to 643 million in 2030 and 784 million in 2045.[1]. DM is a metabolic disorder occasioned by abnormally increased-blood sugar level (hyperglycemia). In addition, it is very often correlated with disturbances in metabolism of carbohydrate, protein, and lipid[2, 3]. These metabolic disturbances are triggered by either insulin deficiency and/or insulin resistance[4]. It is well-known that there is an association between hyperglycemia and diabetic dyslipidemia, which leads to numerous complications including microvascular damages and functional impairments of organs such as the heart, the kidney, and central nervous system[3, 5].

Large body of evidence indicated that type 2 diabetes mellitus represents greater than 90% of all cases[1]. Usually, pharmacological interventions are required to control blood glucose level in most of these cases. However, the most used antidiabetic agents have limited efficacy and serious side effects such as hypoglycemia and diabetic keto-acidosis[6, 7]. Therefore, identifying effective antidiabetic and hypolipidemic agents with fewer side effects are warranted. Furthermore, tremendous efforts have been utilized on finding an alternative medicine from naturally existing products such as herbal

remedies due to their enhanced efficacy and limited undesirable effects[8, 9].

Compositae, also known as Asteraceae, is considered as one of the largest families of flowering plants and comprises around 22,000 species, distributed into 1620 genera. Some of these genera were reported to have an antidiabetic activity[10, 11]. Among these genera, *Picris* known as an important genus comprises around 40 species[12, 13]. Many plants of genus *Picris* were investigated previously and reported to contain different types of biologically active constituents like, phenolic constituents, flavonoids, and various types of terpenoids[14, 15]. Some species of *Picris* were found to have an antidiabetic activity[16]. *Picris babylonica* (*P. babylonica*) spreads in many parts of Saudi Arabia, including Riyadh region. According to the recent reports, *P. babylonica* was investigated for its volatile constituents and its phytochemical contents for various plant parts[12, 15]. These findings encourage us to carry out this experimental work, in which we explore the antidiabetic and hypolipidemic potentials of *P. babylonica* in diabetes induced rats.

In this study, we aimed to evaluate the role of *P. babylonica* extract on serum blood glucose, total cholesterol, triglycerides, and low- and high-density lipoprotein-cholesterol in STZ-induced diabetes in rats.

MATERIALS AND METHODS

Drugs, Reagents, and Instruments

1,1-diphenyl-2-picrylhydrazyl (DPPH) and streptozotocin (STZ) were purchased from sigma-Aldrich Inc. Standard kits for total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TGs) were purchased from Labtest® diagnostica. All other chemicals of analytical grade were purchased from standard commercial suppliers.

Plant Materials

P. babylonica was collected from Riyadh region, Saudi Arabia. Aerial parts of plant material were air-dried in accordance with the universal standard herbarium procedures. A plant voucher specimen is kept in Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University for future research and reference.

Plant Extract Preparation

The air-dried ground of *P. babylonica* aerial parts (1 kg) was exhaustively extracted three times with 3 days time interval at the room temperature (21-23 °C) using 10 Liters of 70% methanol in water through cold maceration method at the room temperature. The solvent was removed by rotary evaporator[12]. The resultant extract was directly freeze-dried to yield the total extract (90 g).

Radical scavenging DPPH assay

The protocol of the DPPH free radical scavenging assay was adapted with some modifications from[17-19]. Briefly, the tested extract was initially dissolved in 100 µl of methanol in a 96-well microplate, The absorbance (Ab) of the test extract was recorded at 515 nm at zero time (t0) as Ab blank. Then, 100 µl of 200 µM DPPH solution was added to every well, and then was kept in the darkness at the room temperature for 30 minutes. Subsequently, the absorbance of the tested extract was measured again as Ab sample. The inhibition percentage (% of inhibition) was measured using the following equation:

% of inhibition = (1 – [Ab sample - Ab blank] / [Ab control - Ab blank]) ×100

Where Ab control is the absorbance of a mixture of all other reactants and DMSO without the tested extract. Half-maximal inhibitory concentration (IC_{50}) was determined as the required concentration of tested sample to cause inhibition of 50 % DPPH free radicals in the method of DPPH radical scavenging.

Experimental Animals

Thirty Wistar rats of both sexes weighing between 150-200 g were obtained from the animal care facility, King Faisal University, Saudi Arabia. Animals were maintained for 1 week to be acclimatized, *i.e.,* ambient room temperatures of (23±2) ºC, at relative humidity of 45-55% for 12 hr time intervals, each of dark and light cycle. The animals were fed with standard rodent pellets and water *ad libitum* before the start of experiment. All procedures that involve experimental animals were carried out in according to the guidelines on the usage and caring of experimental animals, published by the US National Institutes of Health (NIH) and approved by the Committee of Institutional Research Ethics (with protocol ID:

KFU-REC-2021-NOV-EA000166) at King Faisal University, Saudi Arabia.

Induction of diabetes

Experimental animals were exposed to a high fat diet for two weeks and subsequently a single intraperitoneal (IP) dose of 40 mg/kg body weight of STZ to induce diabetes as described in Furman et.al with some modifications[20]. The fresh preparation of STZ was in 0.1 mol/L of cold sodium citrate buffer at a pH of 4.5 for stability enhancement[21, 22]. The confirmation of diabetes development was by measuring the blood glucose level before and 72 hours after the injection of STZ. Rats with a basal blood glucose level more than 200 mg/dL were used in the experimental study[23].

Experimental design

A total of 30 experimental rats, including 6 normal control and 24 STZ-induced diabetic surviving rats, were randomly divided in the following five groups with 6 animals per group:

Group I: Normal healthy control rats.

Group II: Diabetic control rats.

Group III: Diabetic rats received *P. babylonica* extract with a daily dose of 200 mg/kg body weight.

Group IV: Diabetic rats treated with *P. babylonica* extract with a daily dose of 400 mg/kg body weight.

Group V: Diabetic rats received Glibenclamide with a daily dose of 0.6 mg/kg body weight[24].

The treatment by the *P. babylonica* extract was dissolved in 5% carboxy methyl cellulose (CMC) solutions and given orally for two weeks in Group III and Group IV, and Glibenclamide in Group V.

The experimental animals were euthanized at the end of the experiment. The blood glucose level was measured by blood glucometer (One Touch Ultra, LifeScan, Milpitas, CA, USA). The level determination of some parameters of lipid profile in serum that includes total cholesterol, serum triglycerides (TGs), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels were performed by enzymatic colorimetric methods (UV/Vis) using commercial kits (Labtest® diagnostica) according to the manufacturer's instructions.

RESULTS

DPPH radical scavenging activity

The examination of the radical scavenger activity of plant total extract was performed by using DPPH free radical scavenging assay. It showed marked scavenging activity (IC_{50}:29.4 µg/mL), comparable with the standard trolox (IC_{50}:21.8 µM).

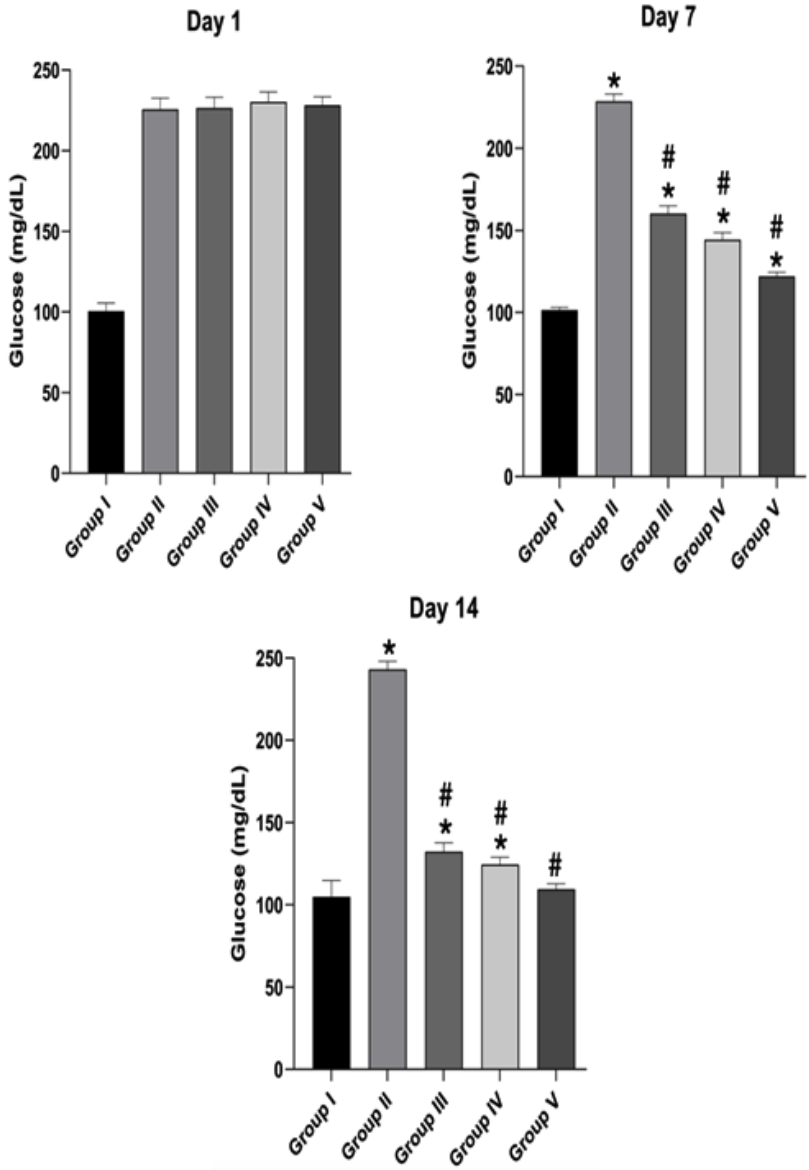
Effect of *P. babylonica* on glucose level after 1 and 2 weeks of treatment

The potentials of antihyperglycemic effect of *P. babylonica* extract-treated groups compared to healthy control, diabetic control and standard glibenclamide-treated groups were investigated in STZ-induced diabetic rats at different time intervals (Figure 1). Results revealed that the measured level of blood glucose in diabetic control (Group II) was slightly increasing with time from 225.58 ± 6.97 to 243.12 ± 4.89 mg/dL in comparison with the healthy control group (Group I). Generally, the highest blood glucose level was found in diabetic control (Group II) compared to the groups of *P. babylonica* extract 200 mg/kg (Group III), *P. babylonica* extract 400 mg/kg (Group IV), and standard glibenclamide (Group V) at all time intervals after the diabetes induction. Our major observation from the obtained results is that the oral administration of 200-400 mg/kg *P. babylonica* extract exhibited a significant antihyperglycemic effect. Moreover, experimental animals treated with 200 mg/kg dose of *P. babylonica* extract (Group III) showed a substantial reduction in the measured blood glucose concentrations between day 1 and day 14, which was 226.45 ± 6.71 to 132.43 ±5.28 mg/dL in comparison with diabetic control (Group II). Similarly, the experimental rats treated with 400 mg/kg dose of *P. babylonica* extract (Group IV) had a decrease in the measured blood glucose level in the allocated time-period from 230.25 ± 6.34 to 124.52 ± 4.33 mg/dL in comparison with diabetic control (Group II). Therefore, we can attribute that the observed antihyperglycemic effect to be because of the administration of the extract of *P. babylonica* plant. However, when compared to the rats treated with standard glibenclamide, the animals treated with *P. babylonica* in both III and IV groups had less antihyperglycemic effect.

Effect of *P. babylonica* on dyslipidemia

The lipid profile of all groups was determined on the last day of the experiment (after 14 days of treatment), as shown in Figure 2. Biochemical analysis of the blood serum, from diabetic control (Group II), has shown a

substantial increase in levels of total cholesterol, TGs, as well as LDL, but there was a decrease in HDL level compared to the healthy rats (Group I). Generally, our observation is that animals treated with *P. babylonica* extract (Group III and IV) had a significant reduction in LDL, TGs, and total cholesterol, however, level of HDL was higher, compared to diabetic control (Group II). As shown in the results, it appears to exhibit a dose-dependent effect with *P. babylonica* extract 400 mg/kg (Group IV) have the highest antihyperlipidemic effect and *P. babylonica* extract 200 mg/kg (Group III) have the least antihyperlipidemic effect, but it is still significant different when compared to diabetic control (Group II). Moreover, the animals treated with *P. babylonica* extract at



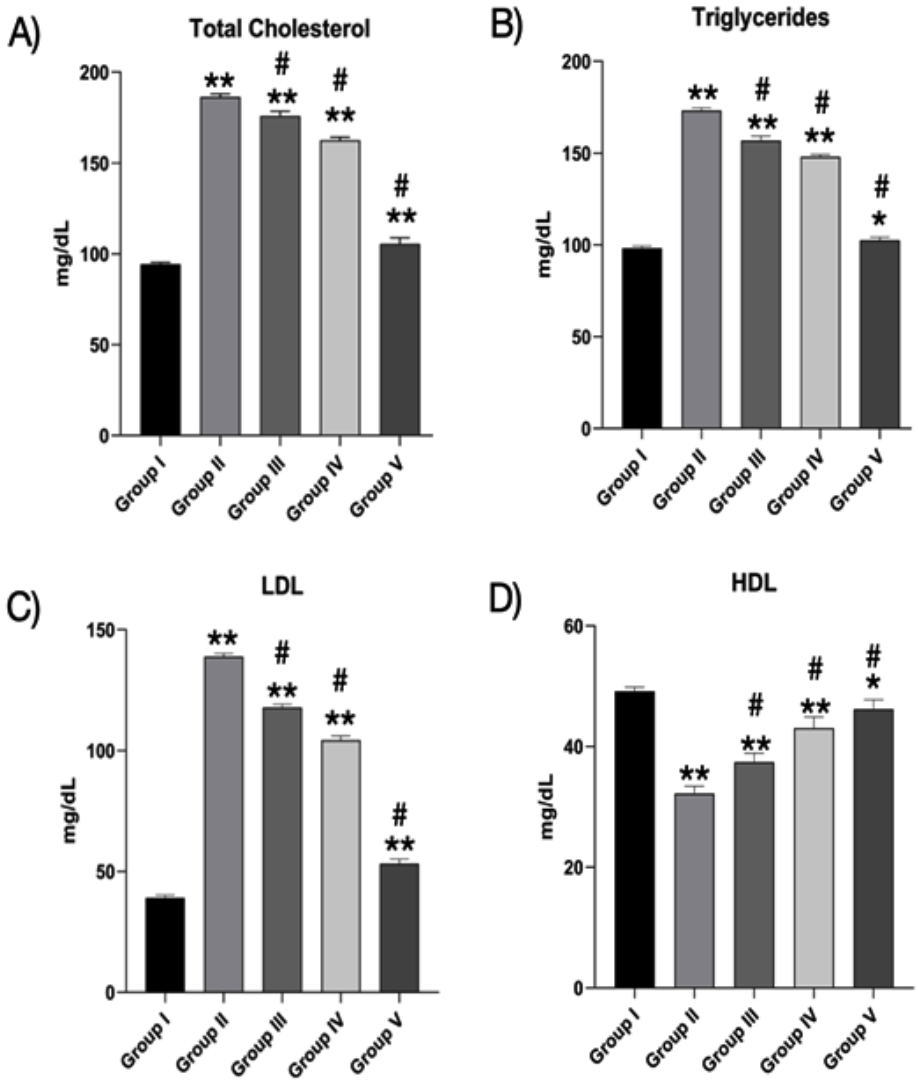
Values are expressed as means ± SD, n= 6. *: $P < 0.0001$ compared to normal control; #: $P < 0.0001$ compared to diabetic control

Fig. 1. Effect of daily oral administration of the extract of *P. babylonica* on blood glucose in STZ-induced diabetic rats

200 and 400 mg/kg doses (Group III and IV) had less antihyperlipidemic effect in comparison with the rats treated with standard glibenclamide. Therefore, these results indicate that *P. babylonica* extract might have contributed to lowering total cholesterol, LDL, and TGs levels.

DISCUSSION

Type 2 DM accounts for approximately 90% of all diabetes and considered one of the most prevalent metabolic disease in the world[1]. Moreover, there is an association between the



A) Serum total cholesterol; B) Serum triglycerides; C) Serum low-density cholesterol; D) Serum high-density cholesterol. Values are expressed as means ± SD, n= 6. **: $P < 0.0001$ compared to normal control, *: $P < 0.001$ compared to normal control; #: $P < 0.0001$ compared to diabetic control.

Fig. 2. Effect of oral administration of extract of *P. babylonica* on lipid profile in STZ-induced diabetic rats after 14 days

uncontrolled type 2 DM, due to treatment failure, and a high risk of developing dyslipidemia, as well as cardiovascular diseases[3, 5]. This increases the necessity to investigate for an effective antidiabetic from natural products with little side effects. Previously, numerous experiments have been carried out to investigate antidiabetic and hypolipidemic potentials of natural extracts in experimental animal models using rats and mice. It is well known that STZ, a nitrosourea compound produced by *Streptomyces achromogenes,* can cause DM by inducing DNA strand breakage in pancreatic â-cells[25]. As a result, the level of insulin will decline, leading to augmentation of glucose level in the blood. In current study, *P. babylonica* extract demonstrated antidiabetic potential by significantly reducing the level of plasma glucose to 132.43 ± 5.28 mg/dL and 124.52 ± 4.33 mg/dL with both doses of 200 mg/kg and 400 mg/kg, respectively, in a dose-dependent manner.

Several reports indicated that DM is highly associated with disturbance in lipid profiles. Indeed, DM considered the main risking factor in hypertriglyceridemia and hypercholesteremia. In addition, we have shown that total cholesterol, LDL and TGs levels were significantly increased in diabetic control (Group II) with the following values: 186.43 ±1.61 mg/dL; 138.9 ± 1.26 mg/dL; and 173.2 ± 1.53 mg/dL, respectively, while the HDL level was reduced. We demonstrated that extract-treated groups remarkably diminished total cholesterol, LDL and TGs levels. Also, we elucidated that extract-treated groups improved HDL level, which was 37.39 ± 1.5 mg/dL with *P. babylonica* extract 200 mg/kg and 43.07 ± 1.83 mg/dL with *P. babylonica* extract 400 mg/kg. These results indicate the potential hypolipidemic effects of *P. babylonica* extract.

Insulin normally activates lipoprotein lipase enzyme and hydrolyses TGs, but in insulin deficiency will hinder these physiological processes causing hypertriglyceridemia. The mechanism of anti-hyperlipidemic effect by *P. babylonica* extract is proposed to be by inhibiting fatty acid synthesis, However, further research is necessary to fully examine the precise mechanism. It is important to mention that one of this study limitations is that the measurement of the subjects' body weight were not reported before and after the treatment. From these findings, we can conclude that *P. babylonica* extracts have significant antidiabetic and hypolipidemic properties. Nevertheless, more confirmatory research is recommended to investigate the plausible involvement of *P. babylonica* active constituents pertaining these properties.

CONCLUSION

The present study revealed that the *P. babylonica* extract could be developed as an antidiabetic and anti-dyslipidemic agent. However, further research is warranted to discover the active constitutes as well as to investigate the possible molecular mechanism.

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Conflict of interest

The author reports no conflicts of interest.

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