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RESEARCH ARTICLE

Glycemic and lipid responses to *Paederia foetida* leaf extract in cats with mild diet-induced blood glucose elevation: A non-randomized sequential crossover study

Jareerat Aiemsaard[1], Eakachai Thongkham[2] and Ranee Singh[1]

1. Division of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
2. Department of Pharmacology, Faculty of Veterinary Medicine, Mahanakorn University of Technology, Bangkok 10530, Thailand.

ABSTRACT

Background and Aim: Plant-derived compounds have attracted interest as potential complementary approaches to feline glycemic management. However, evidence regarding the metabolic effects of *Paederia foetida* in cats remains limited. This study aimed to characterize the phenolic and flavonoid contents and *in vitro* antioxidant activity of *P. foetida* leaf extract and evaluate its effects on glycemic and lipid parameters in cats subjected to a mild dietary carbohydrate challenge.

Materials and Methods: Mature *P. foetida* leaves were extracted using 70% ethanol. Total phenolic and flavonoid contents were determined using colorimetric assays, and antioxidant activity was assessed using the 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay. Eighteen clinically healthy cats participated in a non-randomized, one-sequence crossover study. Following control diet and high-carbohydrate-diet phases, all cats received glipizide (2.5 mg/cat/day) for 4 weeks, underwent a 4-week washout, and subsequently received *P. foetida* extract (500 mg/cat/day) for 4 weeks. Fasting blood glucose, intravenous glucose tolerance, serum triglycerides, and total cholesterol were evaluated.

Results: Total phenolic and flavonoid contents were 2.50 ± 0.33 mg gallic acid equivalents/g extract and 1.69 ± 0.50 mg quercetin equivalents/g extract, respectively. The extract exhibited relatively weak antioxidant activity, with a half-maximal inhibitory concentration of 2,000.00 ± 1.88 µg/mL. The high-carbohydrate diet increased fasting blood glucose from 85.3 ± 3.8 to 98.3 ± 4.3 mg/dL. Extract administration reduced fasting glucose to 88.1 ± 3.0 mg/dL ($p < 0.05$), whereas glipizide reduced it to 52.9 ± 7.7 mg/dL. Glucose tolerance improved following extract administration, although the response was less pronounced than with glipizide. Serum triglycerides were lower during extract treatment than during glipizide treatment, whereas the extract did not significantly reduce cholesterol relative to the high-carbohydrate-diet condition.

Conclusion: *P. foetida* leaf extract was associated with modest improvements in glycemic parameters in cats experiencing mild diet-induced blood glucose elevation. However, its antioxidant activity was limited, and its glucose-lowering effect was smaller than that of glipizide. Randomized studies that optimize dosing, standardize phytochemical characterization, and include longer-term monitoring are needed before establishing clinical applicability.

Keywords: antioxidant activity, feline glucose metabolism, glycemic regulation, high-carbohydrate diet, lipid profile, *Paederia foetida*, plant extract, sequential crossover study.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both, and may be accompanied by glucosuria. It is broadly classified into type 1 and type 2 diabetes mellitus based on underlying pathophysiological mechanisms. Type 1 diabetes mellitus results from destruction or dysfunction of pancreatic β-cells, leading to an absolute insulin deficiency. In contrast, type 2 diabetes mellitus is characterized primarily by reduced insulin sensitivity in peripheral tissues, frequently accompanied by impaired insulin secretion [1]. Type 2 diabetes mellitus is the predominant form reported in cats and shares several pathophysiological characteristics with the corresponding condition in humans, whereas type 1 diabetes mellitus is less common in feline patients [2]. Insulin plays a central role in metabolic homeostasis by regulating glucose uptake and utilization, as well as lipid and protein metabolism. Impaired insulin secretion or action disrupts glucose homeostasis, resulting in elevated circulating glucose concentrations. Persistent

Corresponding Author: Ranee Singh
E-mail: sranee@kku.ac.th

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Co-authors: JA: jaraim@kku.ac.th; ET: eakachai@mut.ac.th
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hyperglycemia may subsequently produce characteristic clinical signs, including polyuria and polydipsia [3]. According to published feline diabetes management guidelines, persistent blood glucose concentrations of approximately 15 mmol/L (270 mg/dL) or greater may support a diagnosis of diabetes mellitus, particularly when accompanied by compatible clinical signs and glucosuria. Abnormalities in serum triglyceride and cholesterol concentrations may also occur in association with altered glucose and lipid metabolism [4].

Although naturally occurring feline diabetes mellitus is characterized by persistent hyperglycemia, disturbances in glucose and lipid metabolism may develop before overt clinical disease becomes apparent. Investigating metabolic responses under controlled dietary conditions may therefore provide preliminary information on interventions that influence glucose regulation. The principal objectives of feline diabetes management are to achieve appropriate glycemic control, alleviate clinical signs, minimize treatment-related complications, and maintain quality of life. Insulin administration, together with dietary management, remains a central component of treatment. Researchers have also investigated oral glucose-lowering agents, including acarbose, chlorpropamide, glimepiride, and glipizide, as alternative or adjunctive interventions in cats. However, their use may be limited by variable therapeutic responses and adverse effects, including hypoglycemia, gastrointestinal disturbances, and, with certain agents, hepatic complications [4, 5]. These considerations have encouraged continued investigation of complementary approaches to glucose regulation. Nevertheless, potential alternatives must be evaluated for efficacy and safety rather than presumed to offer advantages over established treatments.

Medicinal plants have attracted attention as sources of bioactive compounds that may affect glucose and lipid metabolism. Several plants used in Thai traditional medicine, including *Momordica charantia* L., *Terminalia catappa* L., *Tinospora crispa* (L.) Hook. f. and Thomson, *Gymnema inodorum* (Lour.) Decne., and *Paederia foetida* L., have been investigated for their potential glucose-lowering properties [6–8]. However, evidence obtained from traditional use, phytochemical investigations, or experimental studies in other species does not establish equivalent efficacy or safety in cats. Differences in metabolic physiology, compound absorption, biotransformation, and elimination may influence the biological responses to plant-derived preparations.

P. foetida, commonly known as skunk vine or Chinese fever vine, belongs to the family Rubiaceae and is widely distributed in Thailand. The plant has a history of use in traditional medicine and contains various secondary metabolites, including phenolic and flavonoid compounds [9]. Experimental studies in rodents report antihyperglycemic activity and propose mechanisms involving enhanced insulin secretion and preserved pancreatic β-cell function. Other reported biological properties include antioxidant, anti-inflammatory, gastrointestinal motility-modulating, and antipyretic activities [9]. These findings provide a rationale for investigating the metabolic effects of *P. foetida*. However, the composition and biological activity of plant extracts can vary with botanical source, extraction conditions, and phytochemical characteristics. Moreover, the mechanisms proposed from rodent experiments have not been established in cats.

Despite experimental evidence suggesting that *P. foetida* possesses glucose-modulating properties, its effects on feline glucose and lipid metabolism remain insufficiently characterized. Much of the available evidence comes from rodent models, and interspecies differences in carbohydrate metabolism, endocrine regulation, and the disposition of plant-derived compounds limit extrapolation to cats. In particular, it remains unclear whether administration of *P. foetida* extract influences fasting blood glucose concentrations and glucose tolerance in cats experiencing a mild dietary carbohydrate challenge. Such a model is relevant for preliminary investigation of metabolic responses but must be distinguished from naturally occurring feline diabetes mellitus because modest diet-associated changes in blood glucose do not necessarily reproduce the pathophysiological abnormalities of clinical diabetes.

Another important gap concerns the relationship between the phytochemical characteristics of *P. foetida* extract and its biological effects. Phenolic and flavonoid compounds are associated with antioxidant activity, and oxidative processes contribute to metabolic dysfunction. However, the presence of these compounds does not necessarily indicate strong antioxidant activity or show that antioxidant mechanisms explain changes in glucose regulation. Characterizing the total phenolic and flavonoid contents alongside an *in vitro* antioxidant assay may therefore provide useful information about the preparation being investigated. Nevertheless, such measurements cannot independently identify the active constituents or establish their mechanisms of action in cats.

The comparative metabolic responses to *P. foetida* extract and a conventional glucose-lowering agent also require investigation. Glipizide has been studied as an oral hypoglycemic agent in cats [4, 5], providing a

pharmacological reference for evaluating glucose-related responses. However, differences in treatment effects must be interpreted in relation to the experimental design, administered doses, and physiological condition of the animals. Furthermore, changes in fasting blood glucose alone may not fully characterize metabolic responses. Assessment of glucose tolerance together with serum triglyceride and cholesterol concentrations can provide a broader description of the glycemic and lipid changes associated with treatment.

Accordingly, a preliminary feline investigation integrating phytochemical characterization, *in vitro* antioxidant assessment, and *in vivo* metabolic measurements is warranted. Such evidence may help determine whether the extract produces measurable responses under controlled experimental conditions and identify questions requiring further investigation in randomized studies and cats with naturally occurring metabolic disorders.

This study aimed to evaluate the effects of ethanolic *P. foetida* leaf extract on glycemic and lipid parameters in clinically healthy cats subjected to a mild dietary carbohydrate challenge. Specifically, the study aimed to determine the extract's total phenolic and flavonoid contents and assess its *in vitro* antioxidant activity; examine changes in fasting blood glucose and intravenous glucose tolerance after extract administration; and evaluate serum triglyceride and total cholesterol under the experimental dietary and treatment conditions. The metabolic responses observed during extract administration were also compared with those recorded during treatment with glipizide.

By combining phytochemical assessment with measurements of glucose regulation and lipid profiles, this exploratory study sought to provide preliminary evidence regarding the metabolic effects of *P. foetida* in cats. The investigation aimed to characterize responses in a model of mild diet-induced blood glucose elevation, not to establish therapeutic efficacy in cats with naturally occurring diabetes mellitus.

MATERIALS AND METHODS

Ethical approval

The study protocol was approved by the Institutional Animal Care and Use Committee of Khon Kaen University (approval number: IACUC-KKU-102/66). All experimental procedures were conducted in accordance with the ethical principles for animal experimentation established by the National Research Council of Thailand. The study involved clinically healthy domestic cats maintained under controlled housing and husbandry conditions. Animal health and welfare were monitored throughout the experimental period, including daily observations of feed intake, behavior, and general health status, together with periodic physical examinations and body weight assessments. Environmental enrichment and opportunities for social interaction were provided. These measures were implemented to support animal welfare during dietary interventions, treatment administration, and repeated blood sampling.

Study period and location

The study was conducted from September 2023 to April 2024 at the Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, Thailand.

Study design

This preliminary investigation employed a non-randomized, fixed-sequence crossover design involving 18 cats, each exposed sequentially to a control diet, a high-carbohydrate diet, glipizide treatment, a washout period, and *P. foetida* extract treatment. The study comprised five consecutive 4-week phases over 20 weeks. All cats initially received a control diet during weeks 1–4, followed by a high-carbohydrate diet during weeks 5–8. During weeks 9–12, the cats received glipizide in combination with the high-carbohydrate diet. A 4-week washout period followed (weeks 13–16), during which the cats continued receiving the high-carbohydrate diet without pharmacological or herbal supplementation. During weeks 17–20, the cats received *P. foetida* extract in combination with the high-carbohydrate diet.

The sample size was selected with reference to a previous experimental investigation of the antidiabetic activity of a herbal extract that included six rats per treatment group [15]. Because the present study was exploratory and involved a different species, 18 cats were enrolled to permit repeated within-animal assessments. No formal feline-specific sample size calculation was reported. The fixed-sequence design allowed each cat to serve as its own comparator, thereby reducing between-animal variability. However, the absence of treatment-order randomization meant that period effects and residual carryover effects could not be excluded.

Preparation of *P. foetida* leaf extract

Mature leaves of *P. foetida* were collected from a garden in Khon Kaen Province, Thailand. The leaves were

washed, air-dried, and subsequently dried in a hot-air oven at 50°C until a constant weight was achieved. The dried material was pulverized and extracted with 70% (v/v) ethanol (Merck, Darmstadt, Germany) at a plant material-to-solvent ratio of 1:10 (w/v). The resulting mixture was filtered through Whatman No. 1 filter paper (Cytiva, Maidstone, UK), and the filtrate was concentrated under reduced pressure using a rotary evaporator (Heidolph, Schwabach, Germany). The concentrated extract was then freeze-dried using a freeze-drying system (Coolsafe 110-4 and CryoSafe 18–50, Scanvac, Denmark) and stored at –20°C for subsequent analyses within 1 month [10].

A single extraction batch was prepared and used throughout the study to maintain consistency between the phytochemical analyses and biological evaluations.

Determination of total phenolic content

The total phenolic content of the *P. foetida* extract was determined using the Folin–Ciocalteu colorimetric method [11]. The extract was dissolved in 98% (v/v) ethanol (Merck, Darmstadt, Germany) to obtain a 5% (w/v) solution. An aliquot of the extract solution (500 µL) was mixed with 100 µL of Folin–Ciocalteu reagent (Merck, Darmstadt, Germany) and allowed to react for 5 min. Subsequently, 100 µL of 20% (w/v) sodium carbonate solution (Q RëC, Auckland, New Zealand) was added, and the final volume was adjusted to 1 mL using 98% (v/v) ethanol.

The reaction mixture was incubated in the dark at room temperature for 90 min. Absorbance was measured at 746 nm using an ultraviolet–visible spectrophotometer (Epoch 2, BioTek Instruments, Inc., Winooski, VT, USA). Gallic acid (Sigma-Aldrich, Taufkirchen, Germany) was used to construct the calibration curve. Total phenolic content was calculated from the calibration curve and expressed as milligrams of gallic acid equivalents per gram of extract (mg GAE/g extract).

Determination of total flavonoid content

The total flavonoid content of the *P. foetida* extract was determined using the aluminum chloride colorimetric method [11]. A 500 µL aliquot of 5% (w/v) extract solution was prepared and mixed with 50 µL of 0.5% (w/v) sodium nitrite (Merck, Darmstadt, Germany). After 5 min, 50 µL of 10% (w/v) aluminum chloride solution (Merck, Darmstadt, Germany) was added, and the mixture was incubated for another 5 min.

Subsequently, 0.5 mL of 1 M sodium hydroxide (Merck, Darmstadt, Germany) was added, and the final volume was adjusted to 1.5 mL using 98% (v/v) ethanol. Absorbance was measured at 510 nm using an ultraviolet–visible spectrophotometer. Quercetin (Sigma-Aldrich, Taufkirchen, Germany) was used to construct the calibration curve. Total flavonoid content was expressed as milligrams of quercetin equivalents per gram of extract (mg QE/g extract).

Determination of *in vitro* antioxidant activity

The antioxidant activity of the *P. foetida* extract was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, with minor modifications to previously described procedures [12]. The extract was subjected to serial twofold dilutions using absolute ethanol. For each concentration, 0.5 mL of the diluted extract was mixed with 0.5 mL of 0.0004 M DPPH solution (Fluka, Seelze, Germany).

The reaction mixtures were incubated in the dark at room temperature for 25 min. Absorbance was then measured at 517 nm using an ultraviolet–visible spectrophotometer. Butylated hydroxytoluene (Riedel-de Haën, Seelze, Germany) and tocopherol acetate (Loba Chemie, Mumbai, India) were used as reference antioxidants. All measurements were performed in triplicate.

The percentage of DPPH radical scavenging activity was calculated using the following equation:

$$\text{Antioxidant index (\%)} = \frac{(Abs_{control} - (Abs_{sample} - Abs_{blank}) \times 100)}{Abs_{control}}$$

Where $Abs_{control}$ represents the absorbance of the reaction mixture containing all reagents except the antioxidant, Abs_{sample} denotes the absorbance of the mixture containing both the extract and DPPH, and Abs_{blank} corresponds to the absorbance of the extract solution without DPPH.

The half-maximal inhibitory concentration (IC_{50}) was subsequently evaluated by constructing the dose–response curve where 50% DPPH radical inhibition is achieved. The half-maximal inhibitory concentration (IC_{50}), defined as the concentration required to achieve 50% DPPH radical inhibition, was estimated from the concentration–response curve.

Experimental animals and housing conditions

Eighteen clinically healthy domestic mixed-breed cats, comprising nine males and nine females, were enrolled. The cats were 1–5 years old and weighed 2–6 kg. Body condition scores ranged from 2 to 4 on a previously described nine-point scale [13]. Eligibility was based on physical examination findings, the absence of identified infectious diseases, and hematological parameters within the applicable reference ranges.

Before enrollment, all cats underwent routine deworming and rabies vaccination as part of the standardized health management protocol. Hematological status was monitored periodically through packed cell volume measurements. Additional health assessments, including body weight, rectal temperature, heart rate, and respiratory rate, were performed as required.

The cats were housed in group enclosures under controlled laboratory conditions with a 12-h light/12-h dark cycle and unrestricted access to drinking water. Environmental enrichment included daily human interaction, toys, climbing structures, and opportunities for social interaction. Feed intake, behavior, and general health were monitored daily, whereas body weight and physical examination findings were assessed periodically throughout the study.

Experimental diets and feeding protocol

Two experimental diets were used: a control diet providing 31% of metabolizable energy (ME) from carbohydrates and a high-carbohydrate diet providing 45% of ME from carbohydrates. The ingredient compositions of both diets are presented in Table 1. All dietary ingredients were purchased from Chanjao Longevity Co., Ltd. (Bangkok, Thailand).

Table 1: Ingredient composition of the experimental diets used in the study.

Ingredient	Control diet (31% carbohydrate ME) (g/kg diet)	High-carbohydrate diet (45% carbohydrate ME) (g/kg diet)
Corn starch	234.0	372.0
Sucrose	100.0	100.0
Casein	335.0	312.0
Gelatin	40.0	40.0
Lard	142.0	27.0
Soybean oil	20.0	20.0
Cellulose	50.0	50.0
Mineral mix	50.0	50.0
Vitamin mix	20.0	20.0
L-Cystine	3.0	3.0
L-Arginine	3.0	3.0
Taurine	3.0	3.0

ME = metabolizable energy.

During the initial 4-week acclimation period (weeks 1–4), all cats received the control diet to establish baseline metabolic measurements. During weeks 5–8, the cats were transitioned to the high-carbohydrate diet to induce mild blood glucose elevation [14]. The high-carbohydrate diet was subsequently maintained during both treatment phases and the intervening washout period.

Blood samples were collected at the end of weeks 4 and 8 to determine fasting blood glucose, serum triglyceride, and total cholesterol concentrations. Intravenous glucose tolerance testing was also performed at these time points to evaluate glucose handling under the respective dietary conditions.

Treatment administration and washout period

During the first treatment phase (weeks 9–12), all cats received glipizide (Siam Bheasach Co., Ltd., Bangkok, Thailand) orally at a dose of 2.5 mg/cat once daily while continuing the high-carbohydrate diet.

Following glipizide administration, the cats underwent a 4-week washout period (weeks 13–16), during which they received the high-carbohydrate diet without pharmacological or herbal supplementation. The washout period was intended to reduce potential residual effects of glipizide before administration of the plant extract. Fasting blood glucose, triglyceride, and cholesterol concentrations were monitored before the second treatment phase. These measurements were reported to have generally returned toward the values observed during the high-carbohydrate-diet phase.

During the second treatment phase (weeks 17–20), all cats received *P. foetida* extract orally at a fixed dose

of 500 mg/cat/day while continuing the high-carbohydrate diet [7, 15]. Because feline-specific dosing information for *P. foetida* was unavailable, the fixed dose approach was selected for this preliminary investigation.

Blood samples were collected at the end of weeks 12 and 20 to assess fasting blood glucose, serum triglyceride, and total cholesterol concentrations. Intravenous glucose tolerance testing was performed at the same time points.

Assessment of glycemic and lipid parameters

Blood samples were collected between 8:00 and 9:00 a.m. on each sampling day following a fasting period of at least 12 h.

Fasting blood glucose concentrations were measured using capillary blood samples and a veterinary handheld glucometer (AlphaTRAK 2, Abbott/Zoetis, Parsippany, NJ, USA). Serum triglyceride and total cholesterol concentrations were measured using a chemistry analyzer with commercial enzymatic assay kits: Randox Triglycerides (GPO-PAP) and Randox Total Cholesterol (Randox Laboratories Ltd., Antrim, UK), respectively. Measurements were performed according to the manufacturer's instructions.

For the intravenous glucose tolerance test, a baseline blood sample was collected immediately before glucose administration (0 min). Glucose was then administered intravenously at a dose of 1 g/kg body weight. Subsequent blood samples were collected at 15, 30, 60, 90, and 120 min after administration.

Blood glucose concentrations were measured at each sampling time point. Glucose tolerance was assessed using the incremental area under the blood glucose concentration–time curve from 0 to 120 min ($iAUC_{0–120}$ min) [16].

Statistical analysis

Data were expressed as mean ± standard deviation. The normality of paired differences was assessed using the Shapiro–Wilk test. Statistical analyses were performed using IBM SPSS Statistics, version 28 (IBM Corp., Armonk, NY, USA). A p-value ≤ 0.05 was considered statistically significant.

Differences in IC_{50} values among *P. foetida* extract, butylated hydroxytoluene, and tocopherol acetate were analyzed using one-way analysis of variance followed by Tukey's post hoc test when the normality assumption was satisfied. For data that did not satisfy the normality assumption, the Kruskal–Wallis test followed by Dunn's multiple-comparison test was applied.

Fasting blood glucose, serum triglyceride, serum total cholesterol, and $iAUC_{0–120}$ min values were analyzed using within-subject comparisons because all cats underwent the experimental conditions sequentially. Planned comparisons included the control diet versus the high-carbohydrate diet and glipizide treatment versus *P. foetida* extract treatment. Normally distributed paired differences were analyzed using the paired-samples t-test, whereas the Wilcoxon signed-rank test was applied when the normality assumption was not satisfied.

No formal adjustment for multiple testing was applied because the analyses focused on a limited number of predefined metabolic outcomes and planned comparisons.

RESULTS

Phytochemical content and antioxidant activity

The extraction yield of the ethanolic *P. foetida* leaf extract was 13.50% (w/w). The extract contained measurable amounts of phenolic and flavonoid compounds, with a total phenolic content of 2.50 ± 0.33 mg GAE/g extract and a total flavonoid content of 1.69 ± 0.50 mg QE/g extract (Table 2).

Table 2: Total phenolic and flavonoid contents of *Paederia foetida* leaf extract.

Sample	Total phenolic content (mg GAE/g extract)	Total flavonoid content (mg QE/g extract)
P. foetida extract	2.50 ± 0.33	1.69 ± 0.50

Data are presented as mean ± standard deviation from triplicate measurements. GAE = gallic acid equivalents; QE = quercetin equivalents.

The antioxidant activities of the tested substances, assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, are presented in Table 3. Butylated hydroxytoluene exhibited the greatest antioxidant activity, with a half-maximal inhibitory concentration (IC_{50}) of 50.00 ± 3.06 µg/mL, which was significantly lower than those of the other tested substances ($p < 0.05$). In contrast, *P. foetida* extract and tocopherol acetate exhibited comparatively weak radical scavenging activity, with IC_{50} values of 2,000.00 ± 1.88 µg/mL and 3,000.00 ± 1.75 µg/mL, respectively. No statistically significant difference in IC_{50} was observed between *P. foetida* extract and tocopherol acetate ($p > 0.05$).

Table 3: Antioxidant activity of *Paederia foetida* leaf extract and reference antioxidants against 2,2-diphenyl-1-picrylhydrazyl radicals.

Antioxidant	IC_{50} (μg/mL)
Butylated hydroxytoluene	50.00 ± 3.06[a]
P. foetida extract	2,000.00 ± 1.88[b]
Tocopherol acetate	3,000.00 ± 1.75[b]

Data are presented as mean ± standard deviation from triplicate measurements. IC_{50} = half maximal inhibitory concentration. Different superscript letters within the same column indicate statistically significant differences ($p < 0.05$).

Fasting blood glucose concentrations

Fasting blood glucose concentrations differed significantly among the experimental conditions (Figure 1). The mean fasting blood glucose concentration increased from 85.3 ± 3.8 mg/dL during the control diet phase to 98.3 ± 4.3 mg/dL during the high-carbohydrate-diet phase ($p < 0.05$).

Both treatment phases were associated with significantly lower fasting blood glucose concentrations than the untreated high-carbohydrate-diet phase ($p < 0.05$). The lowest concentration was recorded during glipizide treatment (52.9 ± 7.7 mg/dL), which was significantly lower than the concentrations observed during both the high-carbohydrate-diet and *P. foetida* extract phases ($p < 0.05$). During *P. foetida* extract administration, the mean fasting blood glucose concentration was 88.1 ± 3.0 mg/dL, significantly lower than the concentration recorded during the untreated high-carbohydrate-diet phase ($p < 0.05$).

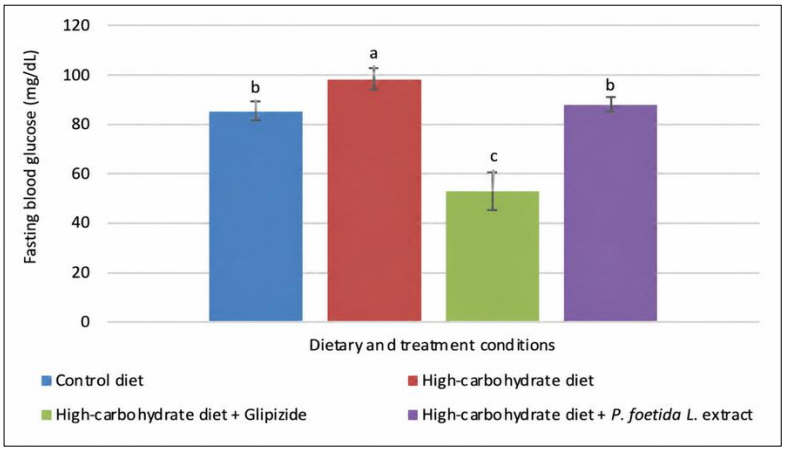


Figure 1: Fasting blood glucose concentrations in cats during the control diet, high-carbohydrate-diet, glipizide treatment, and *Paederia foetida* extract treatment phases. Different letters above the bars indicate statistically significant differences among experimental conditions ($p < 0.05$).

Intravenous glucose tolerance

Intravenous glucose tolerance, expressed as the incremental area under the blood glucose concentration–time curve from 0 to 120 min ($iAUC_{0–120}$ min), differed among the experimental conditions (Figure 2). The mean $iAUC_{0–120}$ min increased from 637.5 ± 8.36 mg·min/dL during the control diet phase to 744.5 ± 7.87 mg·min/dL during the high-carbohydrate-diet phase ($p < 0.05$), indicating reduced glucose tolerance following the dietary carbohydrate challenge.

Both glipizide and *P. foetida* extract administration were associated with significantly lower $iAUC_{0–120}$ min values than the untreated high-carbohydrate-diet phase ($p < 0.05$). The lowest $iAUC_{0–120}$ min was recorded during glipizide treatment (410.5 ± 7.9 mg·min/dL), which was significantly lower than the value recorded during *P. foetida* extract administration (592 ± 6.20 mg·min/dL; $p < 0.05$). The $iAUC_{0–120}$ min during the *P. foetida* extract phase did not differ significantly from that observed during the control diet phase ($p \geq 0.05$).

Serum triglyceride and total cholesterol concentrations

Serum triglyceride concentrations are presented in Figure 3. No statistically significant difference was observed between the control diet and high-carbohydrate-diet phases ($p \geq 0.05$). During glipizide treatment, the mean serum triglyceride concentration was 73.6 ± 4.1 mg/dL, significantly higher than that recorded during the untreated high-carbohydrate-diet phase ($p < 0.05$).

During *P. foetida* extract administration, the mean serum triglyceride concentration was 64.3 ± 6.6 mg/dL, significantly lower than that recorded during glipizide treatment ($p < 0.05$). However, the triglyceride

concentration during extract administration did not differ significantly from that observed during the untreated high-carbohydrate-diet phase ($p \geq 0.05$).

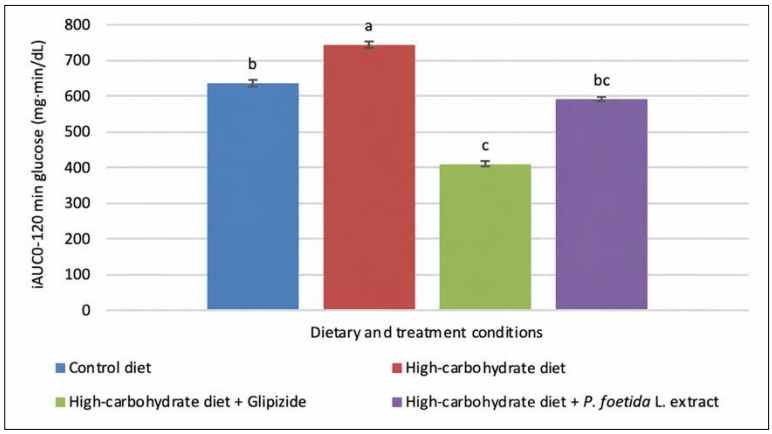


Figure 2: Incremental area under the blood glucose concentration–time curve from 0 to 120 min ($iAUC_{0–120}$ min) during the intravenous glucose tolerance test in cats during the control diet, high-carbohydrate-diet, glipizide treatment, and *Paederia foetida* extract treatment phases. Different letters above the bars indicate statistically significant differences among experimental conditions ($p < 0.05$).

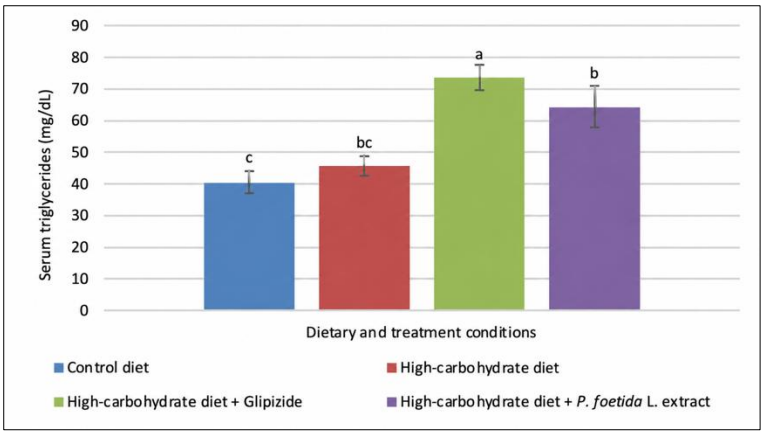


Figure 3: Serum triglyceride concentrations in cats during the control diet, high carbohydrate diet, glipizide treatment, and *Paederia foetida* extract treatment phases. Different letters above the bars indicate statistically significant differences among experimental conditions ($p < 0.05$).

Serum total cholesterol concentrations are presented in Figure 4. The mean total cholesterol concentration increased significantly from 83.8 ± 3.9 mg/dL during the control diet phase to 99.0 ± 5.0 mg/dL during the high-carbohydrate-diet phase ($p < 0.05$).

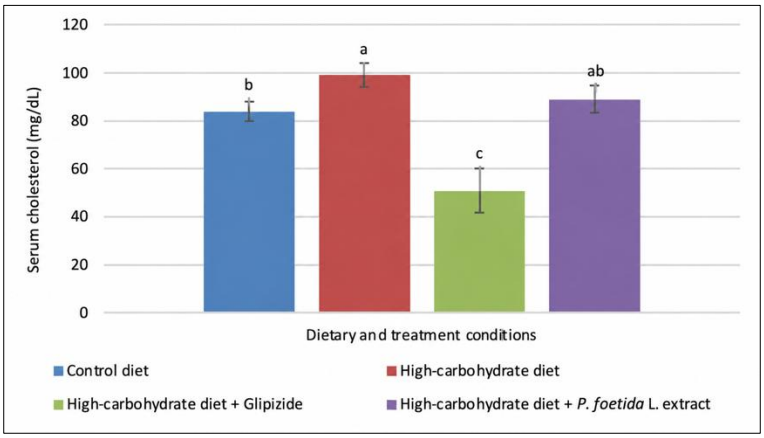


Figure 4: Serum total cholesterol concentrations in cats during the control diet, high carbohydrate diet, glipizide treatment, and *Paederia foetida* extract treatment phases. Different letters above the bars indicate statistically significant differences among experimental conditions ($p < 0.05$).

During glipizide treatment, the mean total cholesterol concentration was 50.9 ± 9.1 mg/dL, significantly

lower than the concentrations recorded under the other experimental conditions ($p < 0.05$). During *P. foetida* extract administration, the mean total cholesterol concentration was 89.0 ± 5.5 mg/dL, which did not differ significantly from that observed during the untreated high-carbohydrate-diet phase ($p \geq 0.05$).

DISCUSSION

Phytochemical composition and antioxidant activity of *P. foetida* extract

The ethanolic *P. foetida* leaf extract exhibited relatively weak antioxidant activity in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, with a half-maximal inhibitory concentration (IC_{50}) of 2,000.00 ± 1.88 µg/mL. Although the extract had a numerically lower IC_{50} than tocopherol acetate, the difference was not statistically significant. Butylated hydroxytoluene exhibited significantly greater radical scavenging activity than either substance. These findings indicate that the extract had limited radical scavenging capacity under the extraction and assay conditions used in this study.

Previous investigations have reported substantially greater antioxidant activity in *P. foetida* extracts. Phankhieo *et al.* [17] identified several phenolic and flavonoid compounds in *P. foetida* leaves, including gallic acid, chlorogenic acid, caffeic acid, ferulic acid, quercetin, and kaempferol. Their extract exhibited IC_{50} values of 1.43 ± 0.08 µg/mL in the DPPH assay and 1.31 ± 0.03 µg/mL in the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay. Similarly, Thankhanithikun and Nikomtat [18] reported total phenolic contents of 14.25 ± 0.24 and 14.08 ± 1.04 mg GAE/g extract in aqueous extracts prepared from fresh and dried *P. foetida* leaves, respectively. The corresponding DPPH IC_{50} values were 440 and 430 µg/mL.

The total phenolic content of 2.50 ± 0.33 mg GAE/g extract and total flavonoid content of 1.69 ± 0.50 mg QE/g extract observed in the present study were comparatively low. Differences in phytochemical composition and antioxidant activity among studies may be associated with extraction solvents, extraction efficiency, geographical origin, growing conditions, harvesting stage, drying procedures, storage conditions, and analytical methods. However, the relative contributions of these factors cannot be determined from the available data. The absence of chromatographic characterization in the present study also prevents identification and quantification of individual compounds that may have contributed to the measured antioxidant activity.

Phenolic and flavonoid compounds may exhibit antioxidant properties through mechanisms involving hydrogen atom donation, electron transfer, and metal chelation. These compounds contribute to plant defense systems, and their concentrations have been associated with radical scavenging activity in experimental investigations [19]. Nevertheless, total phenolic and flavonoid measurements provide broad estimates of compound classes rather than direct measurements of the antioxidant activities of individual constituents.

Oxidative stress, characterized by an imbalance between reactive oxygen species production and endogenous antioxidant defenses, has been implicated in the pathogenesis and progression of type 2 diabetes mellitus. Hyperglycemia may increase reactive oxygen species generation through several metabolic pathways, including glucose autoxidation, the polyol pathway, and protein kinase C activation. Sustained oxidative stress can contribute to cellular injury, pancreatic β-cell dysfunction, and impaired glucose regulation [20, 21]. Previous studies suggest that phenolic and flavonoid compounds may influence oxidative processes by scavenging radicals, modulating endogenous antioxidant enzymes, and regulating redox-sensitive signaling pathways [22, 23].

However, the present study assessed antioxidant activity only through an *in vitro* chemical assay. Circulating oxidative stress biomarkers, endogenous antioxidant enzyme activities, and tissue-level oxidative responses were not measured. Consequently, the observed DPPH radical scavenging activity cannot be directly extrapolated to antioxidant effects *in vivo*. Moreover, the comparatively weak activity of the extract does not establish whether antioxidant mechanisms contributed to the changes in glycemic parameters observed in the cats. The relationship between the extract's phytochemical composition, antioxidant properties, and metabolic effects therefore remains unresolved.

Effects on fasting blood glucose and glucose tolerance

Despite its limited *in vitro* antioxidant activity, *P. foetida* extract administration was associated with measurable changes in glucose regulation. The high-carbohydrate diet increased mean fasting blood glucose from 85.3 ± 3.8 to 98.3 ± 4.3 mg/dL, whereas administration of the extract was associated with a reduction to 88.1 ± 3.0 mg/dL. The extract treatment phase was also associated with a lower incremental area under the blood glucose concentration–time curve from 0 to 120 min ($iAUC_{0–120}$ min) than the untreated high-carbohydrate-diet phase. These findings indicate that glucose-related measurements differed between the dietary challenge and extract treatment phases.

The observed response is broadly consistent with previous experimental evidence suggesting that *P. foetida* possesses glucose-lowering properties. Kumar *et al.* [7] reported dose-dependent antihyperglycemic effects of *P. foetida* extract in rodents, with a dose of 500 mg/kg producing a greater response than doses of 100 and 250 mg/kg. Their toxicological investigation reported adverse effects at doses exceeding 2,000 mg/kg. However, these findings were obtained in a different species and under different experimental conditions. They cannot establish the safety margin, appropriate dose, or therapeutic efficacy of *P. foetida* extract in cats.

In the present study, the extract was administered at a fixed oral dose of 500 mg/cat/day for 4 weeks. Because the enrolled cats weighed 2–6 kg, the dose expressed relative to body weight varied among animals. Furthermore, the administered dose cannot be directly compared with the weight-based doses evaluated in rodents. The present investigation included only one extract dose and therefore could not establish a feline dose–response relationship.

The reduction in fasting blood glucose during extract administration was statistically significant but modest in magnitude. Importantly, the dietary intervention produced only mild blood glucose elevation, and the measured fasting concentrations did not approach those typically associated with clinically overt feline diabetes mellitus. The findings should therefore be interpreted as preliminary evidence of altered glucose regulation during a dietary carbohydrate challenge rather than evidence of therapeutic efficacy in cats with naturally occurring diabetes mellitus.

The reduction in $iAUC_{0–120}$ min during extract administration provides additional evidence of a difference in glucose handling between experimental phases. However, fasting glucose and glucose tolerance measurements alone cannot identify the physiological processes responsible for this response. Potential contributions from altered insulin secretion, insulin sensitivity, glucose absorption, or other metabolic pathways were not directly investigated.

Comparison with glipizide and possible glucose-regulatory mechanisms

Glipizide produced a more pronounced reduction in fasting blood glucose than *P. foetida* extract. The mean fasting blood glucose concentration during glipizide administration was 52.9 ± 7.7 mg/dL, compared with 88.1 ± 3.0 mg/dL during extract administration. The glucose tolerance assessment also yielded a lower $iAUC_{0–120}$ min during glipizide treatment than during extract treatment.

Glipizide belongs to the sulfonylurea class of oral glucose-lowering agents and primarily acts by stimulating insulin secretion from pancreatic β-cells [24]. Although researchers have investigated sulfonylureas for feline diabetes management, their clinical use requires consideration of treatment response, adverse effects, and the patient's physiological status. In the present study, glipizide served as a pharmacological comparator rather than as evidence that either intervention could replace established management of feline diabetes mellitus.

The relatively low fasting blood glucose concentration recorded during glipizide treatment warrants attention. However, the available data do not establish whether individual cats experienced clinical hypoglycemia or associated adverse effects. Interpretation would require individual glucose measurements, information on the duration of low glucose concentrations, and corresponding clinical observations. The group means alone cannot establish the frequency or severity of hypoglycemic episodes.

Rodent studies have proposed that the glucose-lowering effects of *P. foetida* may involve stimulation of insulin secretion or preservation of pancreatic β-cell function [7]. Nevertheless, these mechanisms have not been demonstrated in cats. The present study did not measure circulating insulin concentrations, insulin sensitivity, or pancreatic β-cell function. Consequently, the similarity in the direction of the glycemic responses to glipizide and *P. foetida* extract does not establish a shared mechanism of action.

Furthermore, the fixed treatment sequence complicates direct comparisons between the two interventions. All cats received glipizide before *P. foetida* extract, with a 4-week washout period between treatments. Although metabolic measurements were monitored during the washout period, potential period effects, residual treatment effects, and changes associated with prolonged exposure to the high-carbohydrate diet cannot be completely excluded. The observed differences should therefore be regarded as descriptive comparisons within this exploratory design rather than definitive evidence of comparative efficacy.

Effects on serum triglyceride and total cholesterol concentrations

The experimental conditions were also associated with differences in serum lipid concentrations. Serum triglyceride concentrations did not differ significantly between the control diet and untreated high-carbohydrate-diet phases. However, triglyceride concentrations were significantly higher during glipizide treatment than during

the untreated high-carbohydrate-diet phase.

During *P. foetida* extract administration, the mean serum triglyceride concentration was 64.3 ± 6.6 mg/dL, compared with 73.6 ± 4.1 mg/dL during glipizide treatment. Although this difference was statistically significant, the triglyceride concentration during extract administration did not differ significantly from that observed during the untreated high-carbohydrate-diet phase. Accordingly, these results do not establish a triglyceride-lowering effect of *P. foetida* relative to the dietary challenge alone.

Serum total cholesterol increased from 83.8 ± 3.9 mg/dL during the control diet phase to 99.0 ± 5.0 mg/dL during the high-carbohydrate-diet phase. The lowest reported cholesterol concentration was observed during glipizide treatment (50.9 ± 9.1 mg/dL). During *P. foetida* extract administration, the mean cholesterol concentration was 89.0 ± 5.5 mg/dL and did not differ significantly from that observed during the untreated high-carbohydrate-diet phase.

The lipid findings therefore indicate different patterns of change across the treatment phases, but they do not demonstrate that *P. foetida* extract improved both triglyceride and cholesterol concentrations relative to the untreated high-carbohydrate condition. The magnitude of the reported cholesterol reduction during glipizide treatment also requires careful evaluation, particularly because the source data contain inconsistent values for cholesterol during the high-carbohydrate-diet phase.

The present study did not investigate the mechanisms underlying the lipid responses. Measurements of insulin, additional lipid fractions, and relevant metabolic biomarkers would be needed to clarify whether the observed differences were associated with altered lipid synthesis, utilization, transport, or other physiological processes. In addition, the fixed treatment sequence limits the extent to which these differences can be attributed exclusively to the administered interventions.

Study strengths and limitations

A key strength of this study was integrating phytochemical characterization, *in vitro* antioxidant assessment, and *in vivo* metabolic evaluation within a single exploratory investigation. The use of a single extraction batch reduced variability in the preparation administered to the cats. Repeated assessments of fasting blood glucose, intravenous glucose tolerance, triglycerides, and total cholesterol also provided information on several metabolic outcomes under the experimental conditions. In addition, the within-animal design reduced variability attributable to differences between individual cats.

Nevertheless, several limitations should be considered. First, the study used a non-randomized, fixed-sequence crossover design. Although a 4-week washout period was incorporated, potential period effects and residual carryover effects cannot be excluded. The absence of treatment-order randomization also limits the interpretation of direct comparisons between glipizide and *P. foetida* extract.

Second, the high-carbohydrate diet produced only mild elevations in fasting blood glucose. The experimental condition therefore represents a dietary metabolic challenge rather than naturally occurring feline diabetes mellitus. The findings cannot be directly generalized to cats with persistent diabetic hyperglycemia, impaired pancreatic function, or concurrent metabolic disease.

Third, *P. foetida* extract was administered at a fixed dose per cat because feline-specific dosing information was unavailable. Differences in body weight led to variable exposure when expressed as milligrams per kilogram. The study tested only one extract dose and one treatment duration, preventing determination of an optimal dosing regimen or assessment of dose-dependent responses.

Fourth, the sample size was selected for preliminary exploration without a formal *a priori* power calculation. The number of enrolled cats may therefore have been insufficient to detect smaller metabolic differences or characterize variability in treatment responses.

Fifth, the extract was not subjected to chromatographic characterization. Although total phenolic and flavonoid contents were measured, the concentrations of individual constituents and the reproducibility of their composition across extraction batches remain unknown.

Finally, mechanistic and longer-term metabolic assessments were limited. Circulating insulin, fructosamine, insulin sensitivity, and oxidative stress biomarkers were not evaluated. The study also did not establish the long-term safety of the extract or its effects in cats with naturally occurring diabetes mellitus. These limitations restrict conclusions regarding mechanisms of action, sustained metabolic benefits, and clinical applicability.

Implications for future research

The findings support further investigation of *P. foetida* extract as a candidate for experimental studies of

feline glucose regulation. Future investigations should incorporate randomized treatment allocation, appropriate controls, and sufficiently powered sample sizes. Dose-ranging studies are needed to establish the relationship between administered extract dose, body weight, metabolic response, and tolerability.

Standardized phytochemical profiling, including identification and quantification of individual constituents, would improve reproducibility and facilitate comparisons among preparations. Concurrent assessment of insulin secretion, insulin sensitivity, fructosamine, and oxidative stress biomarkers could help determine whether the observed metabolic changes are associated with specific physiological pathways.

Longer-term investigations should also assess safety, individual variability in response, and the persistence of metabolic effects after treatment discontinuation. Studies involving cats with naturally occurring diabetes mellitus would be necessary before any conclusions could be drawn regarding the extract's potential role in clinical disease management.

CONCLUSION

Ethanolic *P. foetida* leaf extract exhibited relatively weak *in vitro* antioxidant activity despite containing measurable amounts of phenolic and flavonoid compounds. In cats subjected to a mild dietary carbohydrate challenge, oral administration of the extract at 500 mg/cat/day for 4 weeks was associated with significant reductions in fasting blood glucose and $iAUC_{0–120}$ min compared with the untreated high-carbohydrate-diet phase. However, the glycemic response was less pronounced than that observed during glipizide treatment. Serum triglyceride concentrations were significantly lower during extract administration than during glipizide treatment, but neither triglyceride nor total cholesterol concentrations differed significantly between the extract and untreated high-carbohydrate-diet phases.

The findings provide preliminary evidence that *P. foetida* leaf extract may influence glucose regulation in cats experiencing mild diet-induced blood glucose elevation. However, the magnitude of the glycemic response was modest, and the experimental condition did not reproduce naturally occurring feline diabetes mellitus. Consequently, these results do not establish the extract as a treatment for feline diabetes or justify its substitution for established clinical management. The differences observed between treatment phases warrant further investigation before any nutritional or adjunctive application can be considered.

P. foetida leaf extract was associated with modest improvements in glycemic parameters during a mild dietary carbohydrate challenge, although its *in vitro* antioxidant activity was limited and its glucose-lowering response was smaller than that observed with glipizide. The findings support continued investigation of the extract's metabolic effects in cats but do not establish therapeutic efficacy, an optimal dosing regimen, or long-term safety. Randomized studies with standardized preparations and comprehensive metabolic assessments are necessary before its potential clinical application can be determined.

DATA AVAILABILITY

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

GENERATIVE AI DECLARATION

The authors declare that generative artificial intelligence (AI) tools were used solely to improve the language, grammar, and readability of the manuscript. All scientific content, data analyses, interpretation of results, and conclusions were developed and verified by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the published work.

AUTHORS' CONTRIBUTIONS

JA: Conceived and designed the study, performed phytochemical characterization, and conducted antioxidant activity analyses of the herbal extract. ET: Prepared and extracted the plant material, contributed to phytochemical characterization and antioxidant activity analyses, performed data analysis, and drafted the manuscript. RS: Designed the experimental protocol, supervised the animal study, collected blood samples, performed biochemical and antihyperglycemic analyses, coordinated data collection and research activities, and contributed to manuscript preparation. All authors interpreted the data, critically revised the manuscript for key intellectual content, and approved the final version for publication.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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