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Unveiling the Antidiabetic Potential: Quantitative Estimation and In Vitro Evaluation of *Cascabela thevetia Linn*

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Abstract

This study investigates the phytochemical composition and antidiabetic potential of various extracts from *Cascabela Thevetia* L. leaves. Phytochemical analysis revealed significant concentrations of phenols, flavonoids, alkaloids, tannins, saponins, and carbohydrates, with the ethanol extract showing particularly high levels of phenols (217.5±4.88 mg/g), flavonoids (76.49±4.10 mg/g), and alkaloids (18.61±3.64 mg/g). These compounds are known for their antioxidant, anti-inflammatory, and glucose-lowering activities, which are crucial for managing diabetes. The study also evaluated the glucose adsorption capacity of the extracts, revealing that the ethanol extract effectively reduced the availability of free glucose for intestinal absorption, thus managing postprandial hyperglycemia. This capacity was proportional to the molar concentration of glucose, highlighting the extract's efficacy at both low and high concentrations. The presence of soluble and insoluble fibers in the ethanol extract further enhances its glucose adsorption capability. The combined presence of phenolic compounds, flavonoids, alkaloids, and saponins in the ethanol extract suggests a multifaceted mechanism for its antidiabetic effects. These findings provide a strong foundation for future research, including animal and human trials, to validate the antidiabetic efficacy and safety of these extracts, and to explore the biochemical pathways involved. Overall, the study suggests that *Cascabela Thevetia* L. leaf extracts, particularly the ethanol extract, could be developed into effective natural treatments for diabetes, offering a complementary approach to conventional pharmacotherapy with potentially fewer side effects.

Keywords

Flavonides, antidiabetics, *Cascabela thevetia* L, secondary metabolites

1. Introduction

Diabetes Mellitus is becoming increasingly prevalent worldwide, driven largely by changing lifestyles and the rise in obesity. Modern sedentary habits, combined with high-calorie diets, contribute significantly to the global diabetes epidemic. As people adopt fewer active lifestyles and consume more processed foods, the incidence of diabetes rises correspondingly. This chronic condition is associated with severe long-term complications, including retinopathy, neuropathy, and angiopathy (Hinault et al., 2023, Patel et al., 2024a). These complications can lead to blindness, nerve damage (Patel et al., 2024b), and cardiovascular diseases, severely impacting individuals' quality of life and increasing healthcare costs. Diabetes Mellitus is ranked seventh among the leading causes of mortality globally and third when considering fatal complications. The disease affects approximately 171 million people worldwide, and despite the widespread use of daily medications to manage it, the situation remains challenging. Plants are frequently

prescribed for their hypoglycemic properties, and research has identified around 800 plant species with these effects. The use of medicinal plants in diabetes management dates back centuries, with many cultures relying on herbal remedies to control blood sugar levels. These plants offer a natural alternative to synthetic drugs, often with fewer side effects and lower costs. The interest in plant-based treatments has grown due to these benefits, as well as their accessibility in various regions (Jung et al., 200). Diabetes Mellitus, a complex metabolic disorder characterized by chronic hyperglycemia, poses a significant global health burden. Despite advancements in pharmacotherapy, there is still a need for novel therapeutic agents that offer enhanced efficacy and fewer side effects. In this context, natural products derived from medicinal plants have gained considerable attention as potential antidiabetic agents (Kasabri et al., 2011). Medicinal herbs with antidiabetic properties are commonly used as dietary supplements to regulate blood sugar levels and prevent chronic complications associated with diabetes. These herbs are often rich in antioxidants, which play a crucial role in combating oxidative stress and inflammation (Patel et a., 2022a), both of which are linked to diabetes and its complications (Gururani et al., 2023). The incidence of hypoglycemia has increased in recent years, paralleling the rise in diabetes, high blood pressure, and cardiovascular illnesses. Antioxidants in medicinal herbs are essential in addressing various health issues, as they help to neutralize free radicals and protect the body's cells from damage (Jubilee et al., 2024). Numerous herbal remedies have shown promising effects in lowering blood sugar levels and alleviating other diabetes-related complications (Kasabri et al., 2011, Pandey et al., 2023). For instance, herbs such as bitter melon, fenugreek, and ginseng have been extensively studied for their antidiabetic properties, demonstrating significant potential in managing diabetes and improving overall health.

Cascabela thevetia, commonly known as yellow oleander, is a perennial shrub belonging to the Apocynaceae family. Indigenous to tropical and subtropical regions, this plant boasts a rich history of traditional medicinal use across various cultures. The yellow oleander has been used in treatments ranging from heart ailments to skin diseases. Of particular interest in recent years are the leaves of *Cascabela thevetia*, which have brought attention for their purported antidiabetic properties (Cox-Georgian et al., 2019). The leaves contain a variety of bioactive compounds that are believed to contribute to their medicinal effects, making them a promising subject for scientific investigation. The current study focuses on two main objectives: first, to analyze the

phytochemical composition of *Cascabela thevetia* leaves, and second, to evaluate their in vitro antidiabetic activity. Phytochemical analysis is essential as it reveals the diverse array of bioactive compounds within the plant, such as alkaloids, flavonoids, glycosides, and saponins, which may be responsible for its therapeutic effects. Understanding the specific compounds present can help in identifying those that are most effective in exerting antidiabetic actions. In addition to phytochemical profiling, the study employs in vitro assays to assess the antidiabetic potential of the plant extracts. These assays are designed to test how the compounds within the leaves affect glucose metabolism and insulin sensitivity, which are crucial aspects of diabetes management. Through these preliminary tests, researchers we aim to gather evidence on the efficacy of *Cascabela thevetia* in modulating blood sugar levels and improving insulin response. The insights gained from this study could pave the way for the development of new pharmacotherapeutic agents derived from plant sources. Such agents may offer several advantages over conventional treatments, including fewer side effects and greater sustainability. In turn, these developments could provide safer and more effective treatment options for individuals living with diabetes, potentially improving their quality of life and reducing the burden of the disease on healthcare systems worldwide.

2. MATERIALS AND METHODS

2.1. Collection and Authentication

Leaves of the *Cascabela thevetia* L. Were collected from verified source. The leaves were shade-dried for approximately two weeks at room temperature and produced into a coarse powder stored in an airtight container free from moisture for future work. The plant was identified and authenticated by Dr. S. Shweta, Assistant Professor and Dr. Ashwini Kumar Dixit, Professor in Guru Ghasidas Vishwavidyalaya via letter of reference no. Bot/GGV/2023/111.

2.2. Preparation of leaves Extract

To extract the powdered leaves of *Cascabela thevetia*, which had been sun-dried, methanol and ethanol solvents were employed. Initially, 25 g of leaf powder were immersed in 250 milliliters of pure methanol and ethanol, maintaining a 1:10 (w/v) ratio. This mixture was subjected to orbital shaking at 140 rpm for three hours in a conical flask and then allowed to soak for four days at room temperature. After the soaking period, the mixture underwent three rounds of filtration using cotton cloth and Whatman No. 1 filter paper to remove the undesirable dry portions of the powder.

The solvent in the filtrate was then evaporated to obtain the desired extract (Bhoyer 2021; Baravalia et al., 2009). Finally, the extracted material was reintroduced to the corresponding solvent used in its preparation.

2.3. Quantitative Estimation of the Secondary Metabolites

2.3.1. Estimation of Total Phenols

To prepare the sample, 0.5 to 1 g of the material was weighed and thoroughly grounded, then mixed with ten times its volume of 80% ethanol. The resulting homogenate was centrifuged at 10,000 rpm for 20 minutes. The supernatant was collected, and the residue was re-extracted with five times the volume of 80% ethanol. Following another round of centrifugation, the supernatant was collected again and evaporated to dryness. The residue was then dissolved in 5 mL of distilled water. Portions of the sample, ranging from 0.2 to 2.0 mL, were pipetted into separate test tubes, and the volume in each tube was brought up to 3 mL by adding distilled water. Each tube received 0.5 mL of Folin's reagent, and after 3 minutes, 2 mL of a 20% sodium bicarbonate solution was added. The contents of the test tubes were thoroughly mixed, then cooled, and immersed in boiling water for one minute. The resulting color was measured at 650 nm (Malik et al., 1986).

2.3.2. Estimation of Total Flavonoids

The leaf extracts of the plant were obtained using ethyl acetate. These extracts were then filtered, dried over anhydrous sodium sulphate, and concentrated to a concentration of 1g/mL in a boiling water bath. Subsequently, the extracts were diluted with ethyl acetate to create a 0.01g/mL solution for testing purposes. Approximately 10 mL of this solution was transferred into a 25 mL volumetric flask. To this, 1 mL of 2% aluminium chloride was added, and the mixture was brought to volume using methanol and acetic acid. The solution was then left to stand for 30 minutes. During this time, the absorbance was measured at 390 nm, with a blank sample included for reference. A calibration curve, ranging from 1 to 10 μg/mL, was created using quercetin as the standard (Kadifkova Panovska et al., 2005).

2.3.3. Estimation of Total Alkaloids

The alcoholic extracts of the leaf sample were treated with 0.1N HCl and an aqueous acidified layer. This mixture was then separated using chloroform in a separating funnel. After discarding the chloroform layer, the pH of the remaining aqueous layer was made alkaline with ammonium

hydroxide and partitioned again with chloroform in a separating funnel. The chloroform layer was then evaporated, while the aqueous layer was discarded. The resulting material, presumed to contain the total alkaloids, was confirmed using Dragendorff's reagent (Ferguson, 2020).

2.3.4. Estimation of total tannins

With slight modifications, the Folin-Ciocalteu method was utilized to determine the total tannin concentration in *Cascabela thevetia* leaves. A 2-milliliter tube was filled with 1.5 mL of deionized water, 50 µL of Folin-Ciocalteu phenol reagent, and 50 µL of plant extract. After allowing the mixture to sit for eight minutes, 50 µL of a 35% sodium carbonate solution was added. The mixture was shaken well and then left to stand at room temperature in the dark for 20 minutes. Standard tannic acid solutions (250, 500, 750, and 1000 µg/mL) were prepared as references. The absorbance of the samples and standard solutions was measured using a UV/Visible spectrophotometer (SHIMADZU, UV-1800, Japan) at 700 nm, compared to a blank containing 50 µL of Folin-Ciocalteu phenol reagent, 1.5 mL of deionized water, and 50 µL of 35% sodium carbonate. The total tannin content (TTC) was calculated in triplicate using the equation $Y = 0.0054x + 0.0252$ with $R^2 = 0.9937$. The total tannin amount was expressed as mg/g dry weight (DW) (Rodrigues et al., 2014).

2.3.5. Estimation of total carbohydrates (Phenol–Sulphuric acid method)

0.5 grams of plant material was extracted with 80% ethanol. The resulting extract was dissolved in 10 mL of water. Different aliquots were prepared, and the final volume of each was adjusted to 1 mL with water. To each aliquot, 5 mL of 96% concentrated H2SO4 was added, followed by shaking and incubation for 40 minutes at room temperature. Then, 1 mL of 5% phenol was added to each tube, and the absorbance was measured at 490 nm. A standard curve was created using different concentrations of 25% glucose (Krishnaveni et al., 2014).

2.3.6. Estimation of saponins

10 g of the sample were combined with 100 mL of 20% aqueous ethanol. This mixture was maintained at 55°C for four hours using a water bath shaker. The filtrate was extracted using the same process. The combined extract, totaling 40 mL, was concentrated using a water bath at 90°C. The concentrated extract was then transferred into a separating funnel, and 10 mL of diethyl ether were added. After vigorous shaking, the ether layer was discarded, and the aqueous layer was

retained. This procedure was repeated once. Next, n-butanol was added to the aqueous layer. The entire mixture was washed twice with 10 mL of 5% aqueous NaCl in a separating funnel. The upper portion was then kept and heated in a water bath until vaporization. Finally, the remaining material was dried to a consistent weight in an oven (Edeoga et al., 2005).

2.4. In Vitro Antidiabetic Studies

2.4.1. Determination of Glucose Adsorption Capacity

The ethanolic leaf extract of *Cascabela thevetia* L. was mixed with various concentrations of glucose solution (5 mM, 10 mM, 20 mM, 50 mM, and 100 mM), vortexed, and the initial glucose concentration was measured. After incubation in a shaker water bath at 37°C for 6 hours, the solution was centrifuged at 4000g for 20 minutes. The amount of glucose remaining in the supernatant was determined using the Folin and Wu method (Ahmed Faiyaz et al., 2011). The glucose bound by the extract was estimated using the following formula:

$$Glucose\ bound\ (nm) = \frac{G1 - G6}{weight\ of\ the\ sample\ (mg)} \times volume\ of\ the\ solution\ (mL)$$

Where, G1 represents glucose concentration of the original solution, G6 represents glucose concentration after 6hrs and volume of solution = 25 mL.

3. Results

3.1. Quantitative Estimation of the Secondary Metabolites

3.1.1. Total Phenolics Content

Phenols are widely found secondary metabolites in plants, encompassing a diverse array of biologically active compounds known for their biochemical roles such as antioxidants and potential antidiabetic properties (Jain et al., 2019). According to Table 1 and Figure 1, the phenolic content in leaf extracts is recorded as 217.5±4.88 mg/g for ethanol extract, 209.9±5.30 mg/g for water extract, and 207.8±2.98 mg/g for methanol extract. Phenolics are renowned for their ability to scavenge free radicals, thereby enhancing their antioxidant capabilities (Zeb, 2020).

3.1.2. Total Flavonoid content

Flavonoids belong to a class of polyphenolic compounds renowned for their diverse biological properties, including scavenging of hydroxyl radicals, superoxide anion radicals, and lipid peroxyl

radicals. These properties underscore their role in promoting health and preventing disorders associated with oxidative damage to membranes, proteins, and DNA (Dias et al., 2021; Kim et al., 2020). Additionally, flavonoids are recognized for their ability to inhibit hydrolytic and oxidative enzymes, as well as their anti-inflammatory activity.

Table 1: Quantitative analysis of important organic constituents in various extracts of *Cascabela Thevetia. L*

S. No.	Organic Constituents	Solvents		
		Methanol	**Ethanol**	**Aqueous**
1	Phenols (mg/g)	207.8±2.98	217.5±4.88	209.9±5.30
2	Flavonoids (mg/g)	51.66±1.77	76.49±4.10	51.14±3.30
3	Alkaloids (mg/g)	17.09±2.34	18.61±3.64	11.57±1.44
4	Tannins (mg/g)	0.13±0.01	0.12±0.01	0.17±0.03
5	Carbohydrates (mg/g)	0.10±0.01	0.09±0.01	0.22±0.03
6	Saponins (mg/g)	0.30±0.01	0.32±0.01	0.25±0.08

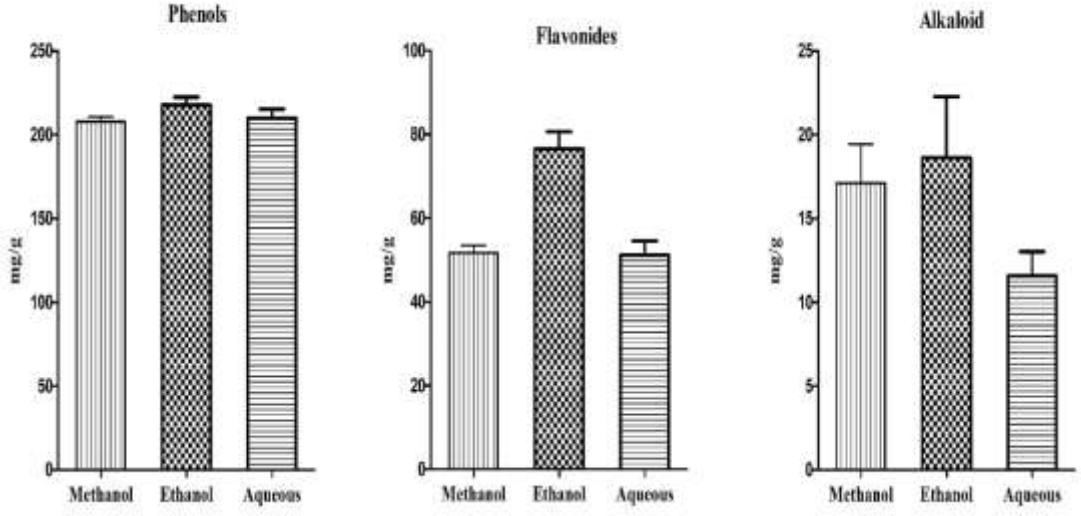

Figure 1: Quantitative analysis of Phenols, Flavonoids, and Alkaloids in leaves of *Cascabela thevetia.* Values are expressed as Mean ± SE (n=3).

The ethanol extract shows the highest concentration of total flavonoids at 76.49±4.10 mg/g, followed by the water extract at 51.14±3.30 mg/g, and the methanol extract at 51.66±1.77 mg/g as shown in Table 1 and Figure 1. Flavonoids play a crucial role in combating free radicals that can damage human cells (Mondal and Rahaman, 2020). Epidemiological studies consistently highlight a strong association between high dietary intake of flavonoids and a reduced risk of cardiovascular disease and diabetes. These compounds are well-documented for their antioxidant, anti-inflammatory, and potential antidiabetic effects, and have even been investigated for their chemo preventive properties in human cancer therapy (Javed et al., 2021).

3.1.3. Total Alkaloid Content

Alkaloids represent a diverse class of secondary metabolites found in plants, characterized by varying structures, types, biosynthesis pathways, and pharmacological actions (Velu et al., 2018). The methanol extract shows the highest concentration of alkaloids at 17.09±2.34 mg/g, followed by the ethanol extract at 18.61±3.64 mg/g, water extract at 11.57±1.44 mg/g, ethyl acetate extract at 7.65±1.27 mg/g, and chloroform extract at 6.55±1.52 mg/g as shown in Table 1 and Figure 1. These results highlight the notable presence of alkaloids in the extracts, particularly in the ethanol extract, which may possess free radical scavenging and potential anti-diabetic activities (Gali and Bedjou, 2019).

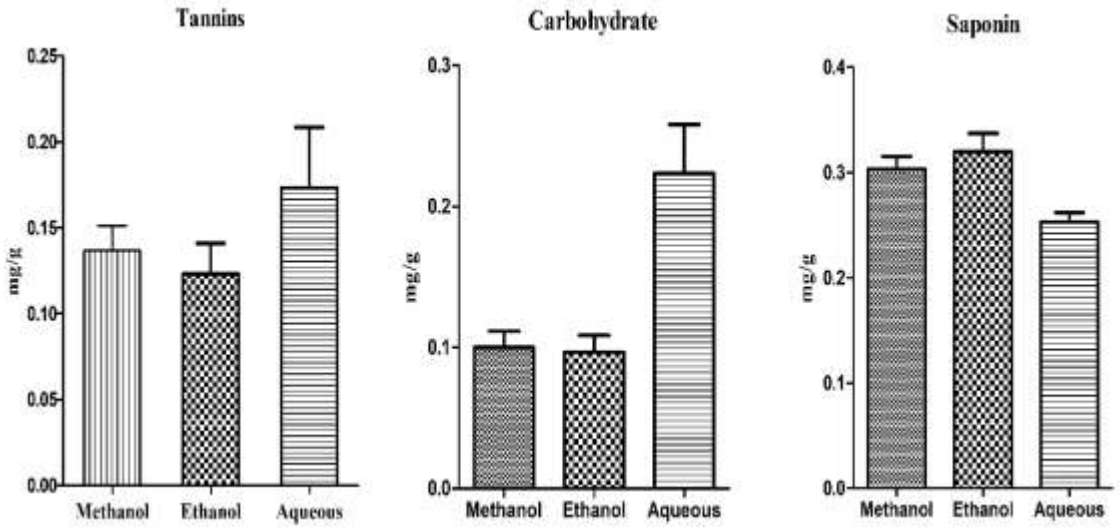

Figure 2: Quantitative analysis of Tannins, Carbohydrates, and Saponins in leaves of *Cascabela thevetia.* Values are expressed as Mean ± SE (n=3)

3.1.4. Tannin Content

Tannins are ubiquitous in almost all plants (Dai et al., 2020) and are known for their anthelminthic, antioxidant, antibacterial, and antiviral properties (Nicolas and Acero, 2019; Parham et al., 2020). The water extract exhibits the highest total tannin content at 0.17±0.03 mg/g, followed by the methanol extract at 0.13±0.01 mg/g, and the ethanol extract at 0.12±0.01 mg/g as shown in Table 1 and Figure 2. Herbs containing tannins are traditionally used for their astringent properties and in the treatment of intestinal diseases, showcasing their antibacterial effects (Bittner Fialová et al., 2021). Furthermore, research has demonstrated significant cancer-preventive activities associated with tannins (Jebali et al., 2022).

3.1.5. Carbohydrate Content

The approximate total carbohydrate content of the leaf extracts was determined as follows: water extract contained 0.10±0.01 mg/g, ethanol extract contained 0.09±0.01 mg/g, and methanol extract contained 0.09±0.02 mg/g (Table 1 and Figure 2). The extracts were prepared, and the Anthrone procedure was used for quantitative determination of carbohydrates.

3.1.6. Saponin Content

Saponins are secondary plant compounds characterized by a low molecular weight and composed of a tetracyclic steroidal or pentacyclic triterpenoid aglycone with one or more sugar chains (El

Aziz et al., 2019). The ethanol extract exhibits the highest saponin content at 0.32±0.01 mg/g, followed by the methanol extract at 0.30±0.01 mg/g, and the water extract at 0.27±0.08 mg/g as shown in Table 1 and Figure 2. Saponins are associated with a range of properties, including pesticidal, insecticidal, and molluscicidal activities, allelopathic effects, and both positive and negative impacts on human health. They also serve as Phyto protectants, defending plants from microbes and herbivores (Cosson et al., 2021, Kumawat et al., 2024). The quantitative analysis of phytoconstituents in various extracts from *Cascabela thevetia* leaves indicates that these extracts could potentially be utilized as sources of antioxidants and for the treatment and prevention of various medical conditions.

3.2. In vitro assay

3.2.1. Glucose Adsorption Capacity

Glucose adsorption is the physical process by which glucose molecules adhere to a solid surface (Dong et al., 2020). This process reduces the amount of free glucose in the solution, thereby decreasing glucose diffusion and uptake into the bloodstream. Insoluble fiber, a key component of many plants, has been shown to possess significant glucose adsorption properties (Fofie et al., 2014).

Table 2: Effect of Ethanolic and Aqueous Leaves extracts of *Cascabela thevetia* L. on Glucose Adsorption

Treatment	**Concentration (mM/L)**				
	5	**10**	**20**	**50**	**100**
	Glucose adsorption (mM/L)				
CT-Et	8.46±0.65	12.25±0.45	30.87±0.35	52.75±0.56	97.66±0.62
***CT*-Aq**	4.22±0.62	8.42±0.76	22.55±0.55	39.51±0.72	74.24±0.45

Values are expressed as Mean ± SE (n=3)

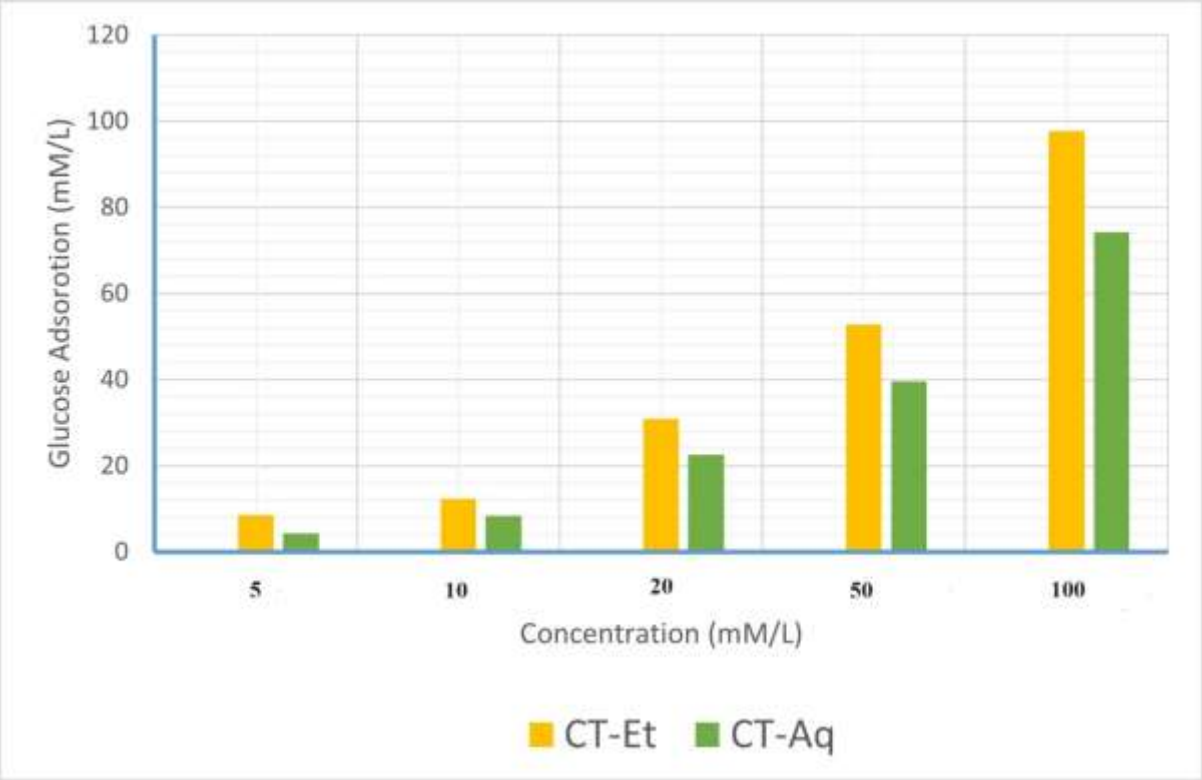

Figure 3. Effect of Ethanolic and Aqueous Leaves extracts of *Cascabela thevetia L.* on Glucose Adsorption. Values are expressed as Mean ± SE (n=3).

Table 2 and Figure 3 illustrate the glucose absorption capacity of CT-Et and CT-Aq, respectively. Both extracts demonstrated effective glucose binding, with the binding capacity being proportional to the molar concentration of glucose. CT-Et showed efficacy in adsorbing glucose at both low and high concentrations (5 and 100 mmol/L). Among the extracts tested, CT-Et exhibited the highest activity, likely due to the presence of soluble and insoluble components and fibers in *Cascabela thevetia* L. As glucose concentration increased, more glucose molecules were adsorbed, reducing the amount available for absorption across the intestinal lumen. This mechanism helps blunt postprandial hyperglycemia (Merino).

4. Discussion

The present study provides a comprehensive analysis of the phytochemical composition and antidiabetic potential of various extracts from *Cascabela thevetia* L. leaves. The detailed examination of these extracts has revealed crucial insights into their biochemical properties and therapeutic applications. The phytochemical screening indicated a rich presence of phenols,

flavonoids, alkaloids, tannins, saponins, and carbohydrates in the leaf extracts, with the ethanol extract, in particular, displaying the highest concentrations of several key constituents. The ethanol extract contained the highest phenolic content (217.5±4.88 mg/g), which is significant due to phenols' well-documented antioxidant and antidiabetic properties. These compounds can scavenge free radicals and contribute to overall antioxidant action, making them crucial in managing oxidative stress associated with diabetes (Zeb, 2020). Flavonoids were present at 76.49±4.10 mg/g in the ethanol extract, demonstrating a strong potential for free radical scavenging, anti-inflammatory, and antidiabetic activities. These properties align with previous studies highlighting the health benefits of flavonoid-rich diets, including reduced risks of cardiovascular disease and diabetes (Mondal and Rahaman, 2020; Javed et al., 2021). Furthermore, the methanol extract showed substantial alkaloid content (17.09±2.34 mg/g), closely followed by the ethanol extract (18.61±3.64 mg/g). Alkaloids are diverse secondary metabolites known for their pharmacological activities, including potential antidiabetic effects (Velu et al., 2018; Gali and Bedjou, 2019). These findings underscore the notable presence of alkaloids in the extracts, particularly in the ethanol extract, suggesting their potential in diabetes management. The glucose adsorption studies revealed that CT-Et (ethanol extract) had a significant capacity to bind glucose, effectively reducing the availability of free glucose for absorption in the intestines and thus helping manage postprandial hyperglycemia. This glucose-binding capacity was proportional to the molar concentration of glucose, indicating the ethanol extract's efficacy at both low and high concentrations (5 and 100 mmol/L). The presence of soluble and insoluble fibers in the ethanol extract likely enhances this glucose adsorption capacity, reducing glucose diffusion and uptake into the bloodstream. This mechanism is crucial for blunting postprandial hyperglycemia, a common issue in diabetic patients (Merino). The combination of high phenolic, flavonoid, and alkaloid contents in the ethanol extract suggests a multifaceted mechanism by which this extract can exert antidiabetic effects. The presence of these compounds is associated with antioxidant, anti-inflammatory, and glucose-lowering activities, making the ethanol extract a promising candidate for developing natural antidiabetic therapies. Additionally, the saponin content in the ethanol extract (0.32±0.01 mg/g) further supports its potential therapeutic efficacy. Saponins are known for their various health benefits, including antidiabetic properties, and their presence in significant amounts in the ethanol extract adds to its medicinal value (Cosson et al., 2021).

5. Conclusion

The study underscores the significant potential of *Cascabela thevetia* L. leaf extracts, particularly the ethanol extract, as sources of bioactive compounds with notable antidiabetic properties. The ethanol extract exhibited high concentrations of phenols, flavonoids, and alkaloids, compounds known for their antioxidant, anti-inflammatory, and glucose-lowering activities. The glucose adsorption capacity of the ethanol extract suggests its efficacy in managing postprandial hyperglycemia, a common concern in diabetic patients. Additionally, the presence of saponins further supports its therapeutic potential. These findings highlight the multifaceted mechanisms by which the ethanol extract can exert antidiabetic effects. Future research should focus on validating these findings through animal and human trials, exploring the precise biochemical pathways involved, and assessing the clinical applicability and safety of these extracts. The study provides a robust foundation for developing *Cascabela thevetia* L. leaf extracts into natural treatments for diabetes, offering a promising complementary approach to conventional pharmacotherapy with potentially fewer side effects.

Ethical approval

This declaration is not applicable.

Declaration of Competing Interest

The authors declare no conflict of interest.

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