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Evaluation of Anti-hyperglycemic Effects of Sodom Apple (*Calotropis Procera*) Leaf in Diabetes Patients at General Hospital, Azare, Bauchi State, Nigeria.

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Abstract

Diabetes mellitus is a chronic metabolic disorder with increasing prevalence in Nigeria, traditional medicine, including Sodom apple (*Calotropis procera*) leaf, has been explored as an alternative treatment. This study was carried out at General Hospital, Azare, Bauchi State, Nigeria and Bioscience laboratory of Sa'adu Zungur University Bauchi State to see the anti-hypoglycemic effect of Sodom Apple leaf (*Colotropis procera*) and phytochemical screening of the leaf. The leaves sample of the plant was collected from Botanical garden of Sa'adu Zungur University Bauchi State. The phytochemical screening revealed and quantified the presence of phenolic compounds and flavonoids in a percentage of 29.1 and 2.8%, respectively. The leaves of *Colotropis procera* with length 13.5cm long was placed under the feet covered with soaks to generate heat for it to release the active compound for 8hrs per day up to 3days. Fasted blood sugar level test was conducted to see the effectiveness of the leaves at the 3rd day. Methanol and aqueous extracts were found to be highly effective in extracting a wide range of phytochemicals, including alkaloids, saponins, flavonoids, steroids, and terpenoids, with aqueous extracts offering a more diverse profile. Ethanol extracts selectively extracted specific compounds, such as steroids and terpenoids, albeit in smaller quantities. Phytochemical analysis revealed reducing sugars, phenols, and flavonoids, which contribute to the antioxidant properties of the extracts. In diabetic patients, treatment with *C. procera* leaf extracts significantly reduced fasting blood glucose levels across three groups, with Group 1 showing the most pronounced reduction (from 28.6 mmol/L to 10.0 mmol/L). Groups 2 and 3 also exhibited substantial decreases (from 27.3mmol/L to 12.0mmol/L and from 27.6 mmol/L to 11.6 mmol/L, respectively). These effects could be attributed to the bioactive compounds' abilities to enhance insulin secretion, improve glucose utilization, protect pancreatic β-cells from oxidative stress, and reduce inflammation. The findings suggest that *C. procera* leaf extract is a promising candidate for diabetes management due to its efficacy, affordability, and minimal side effects.

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1.0 Introduction

Diabetes mellitus is a disorder characterized by increased levels of blood glucose, consequence of impaired insulin production, insulin resistance or both. It is associated to long-term damage of eyes, liver, kidneys, nerves, blood vessels and it may cause degenerative diseases in central nervous system (Bhutada *et al*., 2011). When you think about detoxing, you probably think about detox diets, colon cleansing, or fasting. But, in recent years, detoxing through the feet has gained popularity. Proponents say foot detox therapy eliminates toxins from the body, increases energy, offers immune support, and improves overall health and well-being. Detoxing, short for detoxification is intended to eliminate or neutralize toxins throughout the body. Toxins are virtually everywhere, including in the foods we eat, the water we drink, the air we breathe, and common home products. There are approximately 85,000 chemicals regulated under the United States Toxic Substances Control Act (TSCA. Accessed Mar. 14, 2018), but the Environmental Protection Agency has only banned or restricted use of a handful of chemicals, including chlorofluorocarbons, asbestos, radon, lead, and hexavalent chromium. Unfortunately, many of these are persistent organic pollutants that stay in the environment long after their use is discontinued (TSCA. Accessed Mar. 14, 2018). Toxins are also removed through the body's natural elimination routes such as sweating, breathing, urinating, defecating, and during menses. Foot detoxes are intended to remove toxins and metals from the body by drawing them out through the feet. There are a variety of techniques for detoxing through the feet, including foot masks and scrubs, detox foot pads, acupressure, and ionic foot soaks(Global Healing Center; Foot Detox). A 2002 review on the health benefits of onions notes that they are indeed rich in sulfuric compounds. However, this is as far as the evidence to support the onion in sucks (Medical News Today 28 Nov 2017).

Plant compounds such as *triterpenes* (Wang *et al*., 2010), *xanthines* (Muruganandan *et al.,* 2005), flavonoids, tannins (Roy *et al.,* 2005), proteins (Ahmad, 2001), *lignans*, flavonol (Singhal and Kumar, 2009), among others, have been related to the improvement of hyperglycemia in diabetes. *Calotropis procera* (Aiton) W. T. Aiton, *Apocynaceae,* is a wild bush originated from Africa, India and Persia (Gomes *et al.,* 2006; Singhal and Kumar, 2009). In Brazil, it was introduced as an ornamental plant and in northeastern Brazil it is popularly known as cotton silk, silk flower, and "queimadeira" (Lima *et al.,* 2011). In addition, *C. procera* has biologically active substances such as flavonoids, cardioactive glycosides, triterpenoids, alkaloids, resins, anthocyanins, tannins, saponins and proteolytic enzymes (Shaker *et al.,* 2010). The latex of *C. procera* has been widely studied due to its antihyperglycaemic (Roy *et al.,* 2005), anti-inflammatory, gastroprotective (Tour and Talele, 2011), antinociceptive and selective cytotoxic effects (Teixeira *et al.,* 2011).

However, there is little information in the literature about the potential antidiabetic activity of secondary metabolites present in the leaves this species. Studies of Etuk and Mohammed (2009) using aqueous extract of *C. procera* demonstrated acute hypoglycemic activity in alloxan-diabetic rats. However, Rahmatullah *et al.,* (2010) evaluated acute hypoglycemic activity of methanolic extract of *C. procera* leaves in diabetic mices and observed no significant effects. In this way, the present study was designed to investigate the effects of the *C. procera* leaf under feet on biochemical blood parameters. Diabetes mellitus is a metabolism disorder characterized by inappropriate hyperglycemia (Ceriello, 2005), caused by a relative or absolute deficiency of insulin or by resistance to the action of insulin at the cellular level (Bakari and Narayan, 2003; Fasanmade *et al*, 2008). It is the most common endocrine disorder, affecting as many as 200 million people worldwide (Debra, 1991; Brown *et al*., 2003). The clinical consequences of the syndrome include blindness, heart and blood vessel disease, stroke, kidney failure, amputation and nerve damage and with up to 80% of death in people with diabetes caused by cardiovascular in the developed world (Cariello and Motz, 2004). *Colotropis procera* belongs to the family Aselepiadaceae with various nomenclatures as Sodom. The incidence of diabetes especially type 2 diabetes mellitus (T2DM) is rapidly growing in Bauchi state and Nigeria at large. There is scientific consensus that in recent years the condition of diabetes has grown dramatically into a global pandemic of alarming proportions World Health Organization (WHO, 2016). According to the International Diabetes Federation (IDF) Atlas 2015, estimates suggest that about 415 million adults worldwide have diabetes and were expected to rise to 642 million or more by 2040. Diabetes is an important cause of prolonged ill health and premature mortality, and 5 claims more lives per year than HIV(human immunodeficiency virus)-AIDS(acquired immunodeficiency syndrome) with nearly 1 death every 10 seconds (Ahmed, 2002). Approximately 5.0 million people aged between 20 and 79 years died from diabetes in 2015 and it accounted for 14.5% of global all-cause mortality among people in this age group International Diabetes Federation (IDF Atlas, 2015). Diabetes mellitus is no longer a disease of predominantly rich nations and thus most markedly developing countries are at the forefront of this epidemic World Health Organization (WHO*,* 2016). It is estimated that total global health

spending on diabetes accounted for USD 673 to 1,197 billion in 2015. Patients living with diabetes may need 2 to 3 three times the health-care resources compared to people without diabetes (IDF Atlas, 2015). Moreover, the prescribed mixed medications, hypoglycemic drugs and insulin therapy, for the treatment of diabetes have been reported to have adverse effects (Halimi *et al*., 2008). The continuous use of certain synthetic drugs has been reported to worsen heart disease, increase body weight, induce hypoglycemia and others diseases. (Hollander, 2007; Lau & Teoh, 2015).

Currently, there is growing interest in herbal remedies for diabetes mellitus due to the side effects associated with the oral hypoglycemic agents for the treatment of the disease and the higher cost of conventional drugs (Rao *et al*., 2010). Herbal drugs are prescribed due to their good effectiveness, fewer side effects in clinical 6 experiences, relatively low costs and easier accessibility (Chawla *et al*., 2013). Moreover, herbal medicines are demanded due to culturally linked traditions and social acceptability in using them. Even though, several plant extracts have been claimed to have hypoglycemic activity but the toxicities of those extracts, active principles and mechanisms of action are generally not well known (Yeh, Eisenberg, Kaptchuk & Phillips, 2003). Therefore, there should be some mechanism to embrace the use of medicinal plants into the modern system so as to share knowledge from both traditional and modern medicine and as a means of searching drugs (Abdullahi, 2011).

To fight the global diabetes pandemic, an accessible cost-effective easily-compliant intervention that has high clinical efficacy and that is free of adverse side effects is mandatory. Therefore, this research is expected to identify and document medicinal plants (*C.procera)* leaf used in the treatment of diabetes and contribute the knowledge and clarification on the efficacy and toxicity of some of the commonly used plants in the treatment of diabetes. Moreover, profiling the levels of trace elements and the bioactive compounds in the plants would support the use of the plants. The results of this research can be used in the development of herbal drugs that could be used as an alternative in the public health practices of the society.

The purpose of this research is to specifically achieve the following objectives:

To evaluate the effect of Sodom apple (*C.procera*) leaf placed under the feet of diabetes patients in the study area.

To carryout proximate analysis on the Sodom apple (*C.procera*) leaf to identify the active chemical constituents present in *C.procera* leaf extract.

To determine the quantity of the active chemical constituents found in *C.procera* leaf extract.

2. 0 Materials and Methods

2.1 Ethical Consideration

Ethical approval was soughed and obtained from the Ministry of Health Bauchi State.

2.2 Study Design

The study design is a laboratory approach which is an instructional procedure for diagnosis. A consent form was given to the patients seeking their involvement in the clinical study. Random sampling technique was applied to patients with subjected signs and symptoms. Blood sample of the selected patients was diagnosed in the laboratory to detect the fasting Blood Sugar (FBS).

2.3 Sample collection

One hundred and eighty (180) diabetic patients were sampled from the hospital over the period of three months, and were randomly grouped into three groups. For each treatment group, fresh leaves of *Calotropis procera* were placed under the feet of 60 patients and covered with socks for an hour so as to generate heat.

2.3 Collection and Authentication of the plant materials

The leave of *C. procera* were collected and authenticated at the herbarium unit of Biological Sciences Department Sa'adu Zungur University Bauchi, The fresh leave were washed and air dried. After drying, the leave was grounded to fine powder using sterile electronic blender under laboratory condition and stored at room temperature for further analysis.

2.4 Preparation of Extract

Aqueous, methanol and ethanol extracts of *C. procera* were prepared separately. Fifty grams (50g) powder of the plant material was soaked in 500 ml each of distilled water, methanol and ethanol respectively. The flasks were kept at room temperature for 3 days with intermittent shaking at 150rpm after which filtration was done using Whatman filter paper. The methanol and ethanol extracts was evaporated at 60°C using rotary evaporator while the aqueous extract was evaporated at 70°C in water bath until dried extract samples were obtained. All the dried extract samples were dissolved in 30% DMSO separately to the final concentration of 200 mg/Ml as a stock concentration. Various concentrations of 100, 75, 50 and 25 mg/Ml were made from the stock concentration (Ali et al., 2017).

2.5 Phytochemical Analysis of Calotropis procera

2.5.1 Test for Alkaloids

About 2ml of extract was added to 2ml of 10% concentrated hydrochloric acid and then few drops of

Wagner's reagent was also added. If a reddish brown precipitate is seen, indicates the presence of alkaloids (Harborne, 1973).

2.5.2 Test for Tannins

About 2-3ml of extract was taken and placed in a test tube. Then 2ml of 5% ferric chloride were also added and shaken. Appearance of dark blue or greenish black precipitate indicates the presence of tannins (Harborne, 1988).

2.5.3. Test for Saponins

About 2ml of extract and 2ml of distilled water was added and shaken for few minutes, it result in the formation of 1cm layer of foam that last for some minutes indicates the presence of saponins. (Harborne, 1988; Wall *et al.,* 1954).

2.5.4. Test for Flavonoids

About 2ml of extract were taken and placed into a test tube. Then 1ml of 10% sodium hydroxide solution were also added and shaken. Emergence of intense yellow color implies the existence flavonoids (El-Olemyl *et al.,* 1994; Harborne, 1998).

2.5.5 Test for Steroids

About 2ml of an extract were taken followed by 2ml of chloroform 2ml of concentrated sulphuric acid was carefully added, the presence of a reddish-brown ring precipitate indicates the presence of steroids (Harbone, 1973).

2.5.6 Test for Glycosides

The Keller-Kiliani Test and Concentrate H_2SO_4 test was used to confirm the presence of Glycosides in the hexane extract. Keller-kiliani test: In 2ml of the plant extract, glacial acetic acid, one drop of 5% $FeCl_3$ and conc. H_2SO_4 was added. Reddish brown colour appears at junction of the two liquid layers and upper layer appears bluish green, confirming the presence of glycosides. However, in Conk H_2SO_4 Test: In 5ml plant extract, 2ml glacial acetic acid, one drop of 5% $FeCl_3$ and Conc. H_2SO_4 was added. Brown ring appears, indicating the presence of glycosides.

2.3 Statistical Analysis

The data acquired in this study were analysed using GraphPad Prism version 9, utilizing one-way analysis of variance (ANOVA) with post hoc Tukey's test. The results were illustrated graphically as mean ± standard deviation (SD). All experiments were conducted in triplicate, with $p < 0.05$ deemed statistically significant in both analyses.

3.0 Results and Discussion

Methanol and Aqueous Extracts: Both solvents seem to be the most effective in extracting a wide range of phytochemicals from *C. procera* leaves. Methanol seems to extract a diverse set of compounds like alkaloids, saponins, flavonoids, steroids, and terpenoids, while aqueous extracts include alkaloids, tannins, saponins, flavonoids, steroids, and terpenoids. This indicates that both methanol and water are good choices for obtaining bioactive compounds from *C. procera* leaves, with aqueous extracts potentially offering a more diverse array of phytochemicals.

Ethanol Extract: Ethanol appears to be less effective for extracting certain phytochemicals, particularly alkaloids, tannins, flavonoids, and glycosides. However, it does extract steroids and terpenoids, albeit in smaller quantities compared to methanol and aqueous extracts. Ethanol might be selective in extracting specific compounds that are more soluble in it, like certain steroids and terpenoids.

The phytochemical analysis of the hydroalcoholic extract of the leaves of *C. procera* showed the presence of reducing sugars, phenols and flavonoids. The latex of this species has been shown to contain cardinolides, lignans and flavanol glycosides that have been considered to contribute to its antioxidant properties (Mueen Ahmed et al., 2003). In the same way, Roy *et al.* (2005) reported that the dry latex (100 and 400 mg/kg) has anti-hyperglycemic and antioxidant effects against alloxan-induced diabetes in rats. Indeed the role of oxidative stress and altered antioxidant level in the pathogenesis of diabetic complications is well established (Maxwell *et al.,* 1997). Persistent hyperglycemia leads to increased production of free radicals through glucose autooxidation and protein glycation (Zhang and Tan, 2000).

Lima *et al.* (2012) have shown that the hidroalcoholic extract from the leaves from *Persea americana*, which is also rich in phenolic compounds, also presented anti-hyperglycemic effect in STZ-induced diabetes.

All three groups show relatively high initial fasting blood glucose concentrations, with values ranging from approximately **27.6 mmol/L** and **32.8 mmol/L** before and after treatment. There is a noticeable reduction in fasting blood glucose levels across all three groups after 3 days of treatment with *C. procera* leaf treatment. This indicates that the leaf extract has a positive effect on lowering blood glucose levels in diabetic patients.

Group 1 shows a reduction from an average of 28.6 mmol/L (before treatment) to around 10.0 mmol/L (after treatment), with the lowest recorded value being 10.0 mmol/L. This significant decrease indicates that *C. procera* has a strong effect on lowering blood glucose in this group.

Group 2 starts at 27.3 mmol/L (before treatment) and decreases to about 12.0 mmol/L by the end of the treatment. The reduction is also substantial, though not as pronounced as Group 1.

Group 3 shows a similar trend, with blood glucose levels decreasing from 27.6 mmol/L (before treatment) to around 11.6 mmol/L after treatment.

Considering the wide use of this herb in folk therapeutics for the treatment of diabetes, the present study was conducted to investigate the antihyperglycaemic activity of *C. procera* leaf under feet in diabetic patients. Nowadays, herbal drugs are gaining popularity in the treatment of diabetes and its complications due to their efficacy, low incidence of side effects and low cost (Valiathan, 1998).

Potential for Diabetes Management: Given the significant reduction in blood glucose levels across all groups, *C. procera* leaf extract could potentially serve as an alternative or complementary treatment for diabetes management, especially for individuals who have difficulty controlling their blood sugar through conventional methods.

Variability between Groups: There is some variability in the degree of blood glucose reduction between the groups, but overall, the trend is consistent: all groups experience a decrease in fasting blood glucose. This variability may be attributed to factors such as the dosage, individual patient response, or the specific method of administration of the leaf extract in each group.

The anti-hypoglycemic effect of *C. procera* may be attributed to: Phytochemical Properties: Presence of bioactive compounds like flavonoids, alkaloids, and tannins, which can enhance insulin secretion, improves glucose utilization, or inhibits glucose absorption. Antioxidant Activity: Protection of pancreatic β-cells from oxidative damage, thus enhancing insulin production. And anti-inflammatory Effects: Reduction of inflammation associated with diabetes, contributing to improved glucose regulation.

Table 1: Phytochemicals Present/Absent in *C. procera* leaf extract

Phytochemical constituents	Alkaloid	Tannins	Saponin	Flavonoid	Steroids	Glycosides
Solvent						
Ethanol	-	-	-	-	+	-
Methanol	+	-	+	+	+	-
Aqueous	+	+	+	+	+	+

Key: (+) presence of metabolite, (-) absence of metabolite

Key: (+) presence of metabolite, (-) absence of metabolite

Table 2: Mean values of effect of *Colotropis procera* leaf under feet on fasting blood glucose in diabetic patients before and after 3 days of treatment (Group 1). Fasting blood glucose conc. (mmolL^{-1})

Treatment group	Control before	Control after	Group 1
Control before and after treatment	27.6mmolL^{-1}	32.8 mmolL^{-1}	27.6mmolL^{-1} 32.8 mmolL^{-1}
			28.6±0.889^{a}
			28.5±0.889^{a}
			23.5±0.889^{bc}
			23.3±0.889^{bc}
			21.6±0.889^{c}
			18.2±1.257^{c}
			18.8±0.723^{c}
			18.1±0.889^{c}
			17.2±0.889^{cd}
			17.0±0.889^{cd}
			16.8±0.889^{cd}
			16.6±0.877^{cd}
			12.3±0.725^{d}
			12.0±0.873^{d}
			11.7±0.756^{d}
			11.4±1.245^{d}
			10.3±0.445^{de}
			10.0±0.878^{de}
			10.0±0.776^{de}
			10.0±1.209^{de}

Note: Mean values by different superscripts across rows are significant P<0.05 Duncan test

Table 3: Mean values of effect of *Colotropis procera* leaf under feet on fasting blood glucose in diabetic patients before and after 3 days of treatment June, 2024. (Group 2). Fasting blood glucose conc. (mmolL^{-1})

Treatment group	Control before	Control after	Group 2
Control before and after treatment	27.6mmolL^{-1}	32.8 mmolL^{-1}	27.3±1.092^{a}
			25.2±0.886^{a}
			23.1±1.253^{b}
			22.3±1.253^{b}
			22.8±0.886^{b}
			20.4±0.886^{bc}
			19.8±0.886^{c}
			19.5±0.776^{c}
			19.1±0.723^{c}
			18.9±0.917^{cd}

			18.8±0.886^{cd}
			18.8±0.886^{cd}
			18.2±0.886^{cd}
			18±0.886^{cd}
			17.6±0.886^{cd}
			16.7±1 1.253^{d}
			16.6±0.886^{d}
			16.2±0.1297^{d}
			16±0.886^{d}
			18.8±0.886^{cd}

Note: Mean followed by different superscripts across rows are significant p<0.05 using Duncan test

Table 4: Mean values of effect of *Colotropis procera* leaf under feet on fasting blood glucose in diabetic patients before and after 3 days of treatment July, 2024, (Group 3). Fasting blood glucose conc. (mmolL^{-1})

Treatment group	Control before	Control after	Group 3
Control before and after treatment	27.6mmolL^{-1}	32.8 mmolL^{-1}	28.9±0.776^{a}
			27.7±0.723^{a}
			27.3±1.253^{a}
			25.7±0.917^{b}
			25.5±1.253^{b}
			22.5±0.889^{b}
			22.4±0.889^{c}
			21.7±0.723^{c}
			21.3±1.165^{c}
			20.5±0.886^{c}
			19.1±01.297^{cd}
			18.8±0.889^{cd}
			18.6±1.253^{d}
			18.6±0.889^{d}
			17.3±0.886^{d}
			17.1±0.917^{d}
			16.2±0.889^{d}
			15.1±0.723^{d}
			12.8±0.748^{e}
			11.1±0.886^{e}

Note: Mean followed by different superscripts across rows are significant p<0.05 using Duncan test

5.0 Conclusion

The results from these studies suggest that *C. procera* leaf has a promising role in managing blood glucose levels in diabetic patients. The treatment is effective in lowering blood glucose levels across all three groups, with the most significant reductions seen in Group 1. However, further research, including clinical trials with larger sample sizes and longer treatment durations, would be needed to better understand the efficacy, optimal dosage, and mechanisms behind *C. procera's* antidiabetic effects.

It is recommended that further research should be carried out in other part of the plant, the plants species and their parts to optimally extract and purify the bioactive principles responsible for inhibiting the growth of the said diabetes mellitus and formulating them into appropriate dosage for the treatment of diabetes diseases involving such organisms.

Declarations

Ethics approval and consent to participate

Obtained from Ministry of Health

Consent for publication

All authors have read and consented to the submission of the manuscript.

Availability of data and material

Not Applicable.

Competing interests

All authors declare no competing interests.

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