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# Evaluation of Hypoglycemic Activity of Boswellia carterii and Cissus rotundifolia in Streptozotocin/Nicotinamide-Induced Diabetic Rats

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## ABSTRACT

**Objective:** To evaluate the hypoglycemic activity of *Boswellia carterii* and *Cissus rotundifolia* in rats compared to that of glibenclamide and metformin as common oral hypoglycemic drugs.

**Methods:** Thirty-six male Wistar rats, divided into six groups of six rats each, were assigned into diabetic and non-diabetic groups. Diabetes was induced in rats by single intraperitoneal administration of streptozotocin (65 mg/kg b.w.) and nicotinamide (110 mg/kg b.w.). The first two groups were normal and diabetic controls, whereas the other four diabetic groups were treated with water extracts of the medicinal plants; *B. carterii* (100 mg/kg b.w.) *and C. rotundifolia* (100 mg/kg b.w.), glibenclamide (5 mg/kg b.w.) and metformin (150 mg/kg b.w.). Body weight and serum glucose were measured on days 1, 7, 14, 21 and 28. Serum cholesterol and triglyceride levels were also measured.

**Results:** Treatment of diabetic rats with the water extracts of *B. carterii* and *C. rotundifolia* for four weeks resulted in a significant ($p<0.05$) increase in their body weights and a significant decrease in the levels of serum glucose, cholesterol and triglycerides. The effects of the two plant extracts were almost similar to those of glibenclamide and metformin.

**Conclusion:** Water extracts of *B. carterii* or *C. rotundifolia* have a hypoglycemic effect resembling those of glibenclamide and metformin, and these findings provide a pharmacological evidence for their anti-diabetic claims in folk medicine.

**Keywords:** *Boswellia carterii, Cissus rotundifolia,* Streptozotocin, Hypoglycemic activity

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## 1. Introduction

Diabetes mellitus (DM) is a common metabolic disease that affects the people of both developed and developing countries (1). According to the International Diabetes Federation (IDF), it is estimated that 230 million people in the world have diabetes. Additionally, the World Health Organization (WHO) estimates that this number will exceed 370 million by 2030 and considers the disease as the fifth leading cause of death in the world (1). DM may be caused by the abnormality of carbohydrate metabolism that is linked to low blood insulin level or insensitivity of target organs to insulin, leading to hyperglycemia (2).

Chronic hyperglycemia in diabetic patients leads to severe damage in body tissues, organ dysfunctions and finally irreversible failure of some vital organs, especially the eyes, kidneys, heart and blood vessels (3). DM is associated with many complications such as blindness, renal failure, cardiovascular diseases and limb amputations (2). Furthermore, it could be accompanied by dyslipidemia that may lead to cardiovascular disorders, which are major causes of morbidity and mortality among diabetic patients (3).

The pernicious effects of DM are mediated by the oxidative stress that is associated with high production of reactive oxygen species (ROS) and impaired antioxidant defense systems, which cause lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism (4).

Streptozotocin (STZ) is a toxic chemical to pancreatic β-cells that induces their rapid and irreversible necrosis. The resulted glucose auto-oxidation leads to extreme formation of free radicals in DM, disrupting the cell membrane functions and enhancing susceptibility to lipid peroxidation (5). Previous studies reported differences in the type and characteristics of diabetes according to the administered doses of STZ and nicotinamide (NA) as well as the experimental animal species used (6). NA was used in this study for its protective effect on β-cells against the diabetogenic effect of STZ and this may be due, in part, to an increase in the pool size of nicotinamide adenine dinucleotide in pancreatic β-cells, that leads to the partial destruction of these cells and the induction of type-2 DM (6).

Globally, DM has shadowed the spread of modern lifestyle and can be linked to an increasingly overweight and sedentary population, where about 90% of the cases are of the type-2 DM, paralleling the incidence of obesity (2). For people with type-1 DM, insulin replacement therapy from exogenous sources is necessary for saving lives (7). Although lifestyle modification is the first-line approach for early-stage diabetic patients, chemotherapeutic treatment of type-2 DM remains the major approach to successfully control hyperglycemia (8). Nevertheless, oral hypoglycemic drugs have prominent side effects and fail to significantly alter the course of diabetic complications (9).

Oral hypoglycemic drugs can act in various ways such as enhancing of pancreatic β-cells to release insulin, resisting glucose-increasing hormones, increasing the number and sensitivity of insulin receptors, increasing glycogenesis and promoting the tissue use of glucose (10). Other activities of these drugs include scavenging of free radicals, correcting the metabolic disorders of lipids and proteins and enhancing the microcirculation of the body (11). Most glucose-lowering drugs have side effects, including severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit,

digestive discomfort, headache and dizziness (12). The sulfonylureas and biguanides are the traditional treatment groups of choice for type-2 DM (7).

The WHO estimate that about 80% of the populations living in the developing countries rely almost exclusively on traditional medicine for their primary health cares (13, 14). However, only a minority of traditionally used medicinal plants have been evaluated for their chemical and pharmacological properties (15).

*Boswellia carterii* (Family: Burseraceae), commonly called olibanum, is one of the oldest aromatic materials used by mankind. It has been mainly used in traditional Chinese medicine to alleviate pain and inflammation (16). The extract of *B. carterii* contains potentially active triterpene acids such as boswellic acids and incensole acetate (17). The plant resin has been used for treating ulcerative colitis, chronic colitis, Crohn's disease and osteoarthritis due to its anti-inflammatory effects. In the folk medicine, *B. carterii* resin is prescribed either alone or in combination with other plants for diabetic patients (18). Historically, it has been used as incense in religious and cultural ceremonies, and it is now widely used as an adhesive agent and as an ingredient in cosmetic preparations (19).

*Cissus rotundifolia* is a climbing or prostrate shrub found throughout Africa, Egypt and the Arabian Peninsula, being used as a vegetable. It has minor economic importance as a medicinal plant (20, 21, 22). *C. rotundifolia* from Asia and Africa has shown anti-diabetic as well as anti-parasitic properties (23, 24). In Yemen, the boiled leaves of *C. rotundifolia* are eaten with meals as an appetizer and are also used as an antipyretic in the treatment of malaria and dengue fever (25). The present study aimed to evaluate the hypoglycemic activity of *B. carterii* and *C. rotundifolia* in rats compared to glibenclamide and metformin.

## 2. Methods

The experimental protocol of the present study was approved by the Ethics Committee of the University of Science and Technology, Sana'a, Yemen.

### *2.1. Materials and experimental animals*

STZ and NA were bought from Sigma-Aldrich Corporation (Germany), whereas Glibenclamide (Daonil®) and metformin (Glucophage®) were obtained from pharmacies in Sana'a, Yemen. Kits for the measurement of glucose, cholesterol and triglycerides (Química Clínica Aplicada S.A., Amposta, Spain) were bought from the local market. *B. carterii* resin and *C. rotundifolia* leaves were brought from the local market and identified in Aden University.

Thirty-six adult male Wistar rats (*Rattus norvegicus*) weighing between 240 and 300 g were brought from the Animal House of the Faculty of Science, Sana'a University. Rats were housed in well-ventilated cages (six rats each) and acclimatized to the laboratory conditions (12:12 h light/dark schedule with 25±2°C and 55–65% relative humidity). The rats were fed with the same food and water *ad libitum*.

### *2.2. Preparation of water extract of the plant species*

Fifty grams of the dry resin of *B. carterii* were boiled in 100 ml of distilled water for 10 min. After cooling to room temperature, it was filtered. The aqueous extract (25% w/v) was stored in a refrigerator till use (18). On the other hand, the aerial parts of *C. rotundifolia* were collected, immediately dried at 45°C, grounded into a moderately fine powder (800 g). The aqueous

extract (15% w/v) was prepared by adding 150 g of dried powder to 1000 ml of distilled water and heated to about 80°C for 30 min. (26).

### *2.3. Induction of DM*

DM was induced in overnight-fasted rats by a single intraperitoneal (IP) injection of a freshly buffered (0.1 mol/L citrate, pH 4.5) solution of STZ at a dosage of 65 mg/kg body weight (b.w.). NA (110 mg/kg b.w.) was dissolved in normal physiological saline (0.9% NaCl solution) and given to counter the hypoglycemic shock 15 min. before STZ administration. After 72 hours, rats with fasting blood glucose levels of >150 mg/dL were considered diabetic (8).

### *2.4. Study design*

The rats were randomly divided into six experimental groups of six rats each as follows: Group I (normal control): received IP citrate buffer solution (0.5 ml) and oral distilled water (0.5 ml) by oral gavage; Group II: (diabetic control) received IP STZ (65 mg/kg b.w.) and NA (110 mg/kg b.w.) (8); Group III: received STZ (65 mg/kg b.w.) and NA (110 mg/kg b.w.) and thereafter treated with *B. carterii* water extract (100 mg/kg b.w.) (18); Group IV: received STZ (65 mg/kg b.w.) and NA (110 mg/kg b.w.) and thereafter treated with *C. rotundifolia* water extract (100 mg/kg b.w.) (26); Group V: received STZ (65 mg/kg b.w.) and NA (110 mg\kg b.w.) and thereafter treated with glibenclamide (5 mg/kg b.w.) (14); Group VI: received STZ (65 mg/kg b.w.) and NA (110 mg/kg b.w.) and thereafter treated with metformin (150 mg/kg b.w.) (27).

Treatment with plant extracts and drugs was given daily for 4 weeks using oral gastric gavage. Throughout the experimental period, starting from the first day of extract administration to diabetic rats, the body weight and fasting blood glucose level were measured every 7th day. On the day 28 of extract administration, blood samples were collected from rats by cardiac puncture under mild ether anesthesia. Blood samples were left for 30 min. and centrifuged at 3000 rounds per min. for 20 min. to separate sera for biochemical analysis. Serum glucose, cholesterol and triglycerides were estimated by the enzymatic colorimetric method (28).

### *2.5. Statistical analysis*

Data were analyzed using the IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). All results were expressed as mean ± standard error (SE). Means of different groups were compared by one-way analysis of variance (ANOVA) test followed by the least significant difference (LSD) post hoc test for multiple comparisons. Statistical significance was considered at *p*-values < 0.05.

## 3. Results

### *3.1. Effects of plant extracts on body weight*

Table (1) shows that the mean body weights of rats in the diabetic control group were lower than those in other groups. STZ caused a significant weight loss of rats in the diabetic group compared to normal controls, whereas treatment of diabetic rats with plant extracts (*B. carterii* or *C. rotundifolia*) significantly ($p<0.05$) suppressed such a decrease in their mean body weights. No significant difference was observed in the mean body weight of diabetic rats after treatment with metformin compared to those treated with *C. rotundifolia*. On the other hand, glibenclamide caused a significant increase in the mean body weights of rats compared to the groups treated with plant extracts.

**Table 1.** Weekly body weight changes (gm) in rats treated with *B. carterii* and *C. rotundifolia* water extracts compared to controls and drug-treated groups during the experimental period of 28 days

| Group (*n*=6 each) | Body weight (mean±SE) | | | | |
|---|---|---|---|---|---|
| | Day 1 | Day 7 | Day 14 | Day 21 | Day 28 |
| **Normal control** | 272.17 ±1.58 | 279.33 ±1.54 | 286.83 ±2.41 | 294.00 ±2.63 | 301.00 ±3.00 |
| **Diabetic control** | 270.33 ±1.31 | 264.83 ±1.40 * | 258.00 ±1.75* | 251.67 ±1.8 * | 246.00 ±1.67* |
| ***B. carterii*** | 272.67 ±0.88 | 279.00 ±1.51# | 283.50 ±1.18 # | 287.67 ±1.86#@ | 292.33 ±1.43#@$ |
| ***C. rotundifolia*** | 273.33 ±2.17 | 276.67 ±2.17 #@ | 280.83 ±1.85 #@ | 284.83 ±1.87@ | 288.33 ±2.38 #@ |
| **Glibenclamide** | 273.50 ±1.54 | 283.17 ±2.37# | 288.17 ±2.75# | 296.50 ±2.47# | 307.00 ±2.48 # |
| **Metformin** | 273.33 ±3.69 | 276.83 ±3.40# | 280.00 ±3.32# | 282.33 ±3.84# | 284.50 ±4.17# |

Means with different symbols are significantly different at $p<0.05$; * significant compared to the normal control; #significant compared to the diabetic control; @ significant compared to the glibenclamide group; $ significant compared to the metformin group

## *3.2. Effects of plant extracts on glucose level*

Table (2) shows that rats in the diabetic control group showed a significant increase in the mean glucose levels from the first week until the end of the fourth week of treatment compared to other groups. The mean serum glucose levels of the diabetic groups treated with the plant extracts were significantly decreased compared to the diabetic control group. However, the decline in the mean glucose levels in extract-treated groups was lower than that in drug-treated groups.

## *3.3. Effects on cholesterol level*

Figure (1) shows that rats in the diabetic control group had a significant increase in their mean cholesterol levels compared to the normal control group. The rats treated with *B. carterii* extract showed a significant decrease in the mean cholesterol level compared to the diabetic control group while those treated with *C. rotundifolia* extract showed a non-significant decrease in their mean cholesterol levels. On the other hand, no significant changes in the mean cholesterol levels were observed in rats treated with *B. carterii* and *C. rotundifolia* compared to those treated with metformin and glibenclamide.

**Table 2.** Weekly glucose level (mg/dL) changes in rats treated with *B. carterii* and *C. rotundifolia* water extracts compared to controls and drug-treated groups during the experimental period of 28 days

| Group (*n*=6 each) | Body glucose level (mean±SE) | | | | |
|---|---|---|---|---|---|
| | Day 1 | Day 7 | Day 14 | Day 21 | Day 28 |
| **Normal control** | 83.17 ±2.63 | 82.17 ±2.20 | 86.33 ±2.50 | 88.83 ±1.96 | 85.67 ±2.76 |
| **Diabetic control** | 193.00 ±6.18* | 198.50 ±4.53* | 220.67 ±4.30* | 240.83 ±4.95* | 255.67 ±4.78* |
| ***B. carterii*** | 196.50 ±6.82 | 171.33 ±5.55#@$ | 157.67 ±4.59#@$ | 142.67 ±3.97#@$ | 125.50 ±5.18#@$ |
| ***C. rotundifolia*** | 203.33 ±4.61 | 179.17 ±5.27#@$ | 164.67 ±4.46#@$ | 150.17 ±3.97#@$ | 138.50 ±2.85#@$ |
| **Glibenclamide** | 193.00 ±5.62 | 150.83 ±4.62# | 126.17 ±2.95# | 105.67 ±2.20# | 92.00 ±2.80# |
| **Metformin** | 188.33 ±4.76 | 153.17 ±5.80# | 133.33 ±6.30# | 114.00 ±6.07# | 100.33 ±4.07# |

Means with different symbols are significantly different at p<0.05; * significant compared to the normal control; # significant compared to the diabetic control; @ significant compared to the glibenclamide group; $ significant compared to the metformin group

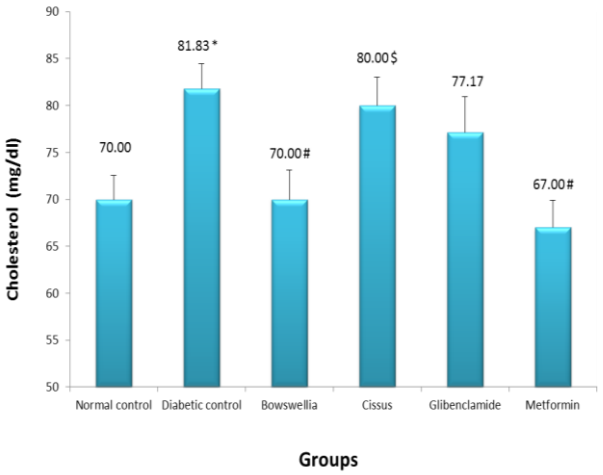


**Figure 1.** Effects of *Boswellia*, *Cissus*, glibenclamide and metformin on the mean cholesterol levels (mg/dL) in STZ/NA-induced diabetic rats**;** Means with different symbols are significantly different at $p<0.05$; * significant compared to the normal control; # significant compared to the diabetic control; @ significant compared to the glibenclamide group; $ significant compared to the metformin group

## *3.4. Effects on level of triglycerides*

Figure (2) shows that rats in the diabetic control group had a significant increase in their mean

triglycerides levels compared to the normal control group. The plant extracts (*B. carterii* or *C. rotundifolia*) significantly decreased the mean triglycerides levels in diabetic rats compared to the diabetic control. However, no significant changes were observed in the mean triglycerides levels in rats treated with *B. carterii* compared to those treated with metformin.

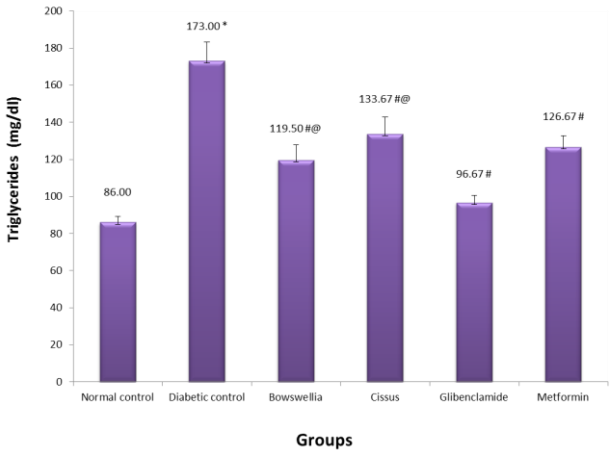


**Figure 2.** Effects of Boswellia, Cissus, glibenclamide and metformin on the mean triglycerides levels (mg/dL) in STZ/NA-induced diabetic rats; Means with different symbols are significantly different at $p < 0.05$.; * significant compared to the normal control; # significant compared to the diabetic control; @ significant compared to the glibenclamide group; $ significant compared to the metformin group

## 4. Discussion

DM is a metabolic disorder arising mainly due to the poor production of insulin by the pancreatic β-cells or their resistance to its action. Hyperglycemia in DM leads to serious complications in vital organs (3). In addition, poorly controlled hyperglycemia leads to the production of abnormally high levels of ROS, which could react with essential molecules, such as lipids, proteins and DNA, leading to histological and functional alterations (28, 29).

Less than 1% of an estimated number of 250,000 plant species have been screened pharmacologically, with only a small fraction of these for DM (30). A large proportion of the most commonly used drugs in modern medicine, such as atropine, digoxin and some antimalarials and anticancer drugs, have been derived from plant sources (12). In the present study, the aqueous extracts of *B. carterii* resin and *C. rotundifolia* leaves were investigated for their hypoglycemic activities in STZ/NA-induced diabetic rats.

STZ induces rapid and irreversible β-cell necrosis as a result of free radical generation, leading to a massive reduction in these insulin-secreting cells (29). Increased levels of ROS in β-cells may lead to DNA damage by oxidation, and therefore, to their destruction by necrosis (6). On the other hand, NA causes activation of the poly adenosine diphosphate-ribose synthase to repair the damaged DNA (31).

In the present study, reduced mean body weight in STZ/NA-induced diabetic rats might be attributed to the increased muscle wasting and degradation of structural proteins due to carbohydrate unavailability as an energy source (29). This finding agrees with previous observations that have also reported loss of body weight (5, 32). However, a significant increase towards normal body weight was observed in diabetic rats treated with *B. carterii* or *C. rotundifolia* extracts compared to diabetic controls. This improvement indicates the protective effect of these extracts against the degradation of structural proteins and may also be due to their direct lipid lowering activities or their indirect influence on various lipid regulation systems (33).

The hypoglycemic activities of plant extracts of *B. carterii* and *C. rotundifolia* in this study could be possibly due to the stimulation of insulin secretion from the remaining β-cells which, in turn, promotes tissue glucose utilization in diabetic rats either by enhancing its uptake and metabolism or by inhibiting hepatic gluconeogenesis (28). Moreover, the anti-oxidant activity

of *B. carterii* and *C. rotundifolia* may be one of the possible actions of their hypoglycemic activity. The antioxidant effects of different *Boswellia* and *Cissus* species have been reported by several researchers (27, 34). The hypoglycemic activity of *B. carterii* could be partly attributed to the presence of pentacyclic triterpene (boswellic acid derivatives) (35). In addition, the presence of triterpenes, glycosides, flavonoids, coumarins or saponins could be responsible for the hypoglycemic activity of C*. rotundifolia* (24). Being comparable to those of commonly marketed drugs used for treating type-2 DM, the anti-hyperglycemic effects of *B. carterii* and *C. rotundifolia* extracts in diabetic rats provide a pharmacological evidence for their folklore claim as anti-diabetic agents (18, 22, 33).

Hyperlipidemia in diabetic patients represents a risk factor for coronary heart diseases. The abnormally high levels of serum lipids are mainly due to the action of insulin that inhibits the actions of lipolytic hormones on the fat depots (28). Normally, insulin activates lipoprotein lipase, which hydrolyzes triglycerides. However, in DM, lipoprotein lipase is not activated as a result of insulin deficiency, resulting in hypertriglyceridemia and hypercholesterolemia (36).

In the present study, the altered serum lipid profile was disturbed in diabetic rats by the significant increase in cholesterol and triglycerides levels compared to normal controls. Treatment of diabetic rats with *B. carterii* and *C. rotundifolia* extracts significantly corrected the levels of cholesterol and triglycerides towards normal. This improvement may be partly attributed to the increase in insulin secretion that affects lipid metabolism and to the regeneration of β-cell as a result of the decrease in production of free radicals by lipid peroxidation (4, 37). Thus, the two plant extracts could be helpful in improving lipid metabolism that may, in turn, help to prevent diabetic complications such as coronary heart diseases and atherosclerosis (38). The present study revealed a similarity in the reduction of cholesterol levels between *B. carterii* and metformin from one side as well as between *C. rotundifolia* and glibenclamide from the other side. This may reflect the comparable actions of the plant extracts and the tested drugs (18, 22, 36).

The findings of the present study are in agreement with other previous studies, which reported that treatment with *B. carterii* led to a significant improvement in the decreased body weight, hyperglycemia, hypoinsulinemia, decreased liver glycogen caused by alloxan (18). Moreover, other studies on other *Boswellia* species reported the antiglycation and anti-oxidant activities of *B. sacra*, *B. serrata* and *B. glabra* in experimental diabetic rats (34, 39). In addition, the hypoglycemic activity of *C. rotundifolia* in the present study is in correlation with the findings by Onyechi et al. (1998) on healthy human subjects and Shukery (2012) on male rabbits (23, 40). Moreover, the anti-inflammatory and anti-oxidant activities of *C. rotundifolia* have been recently reported (24). Other studies reported the hypoglycemic and hypolipidemic activities of other species of the same genus *Cissus*, including *C. verticillata* and *C. quadragualis* (41, 42), supporting the hypoglycemic activity of *C. rotundifolia* in the present study.

## 5. Conclusions

Water extracts of *B. carterii* and *C. rotundifolia* are efficacious in lowering blood glucose in diabetes rats in a way resembling the actions of common anti-hyperglycemic drugs (glibenclamide and metformin). They also have anti-hyperlipidemic and anti-oxidant properties. Studies on standardization, characterization, ef-

ficacy, long-term side effects, toxicity and plant-drug interaction are recommended.

## Authors' contributions

AAA designed the study, supervised the work, analyzed data and contributed in editing and revising the manuscript, AMA performed experiments and wrote the initial draft of the manuscript. All authors approved the submission of the final draft.

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## Competing interests

The authors declare that they have no competing interests associated with this article.

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