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Exploration of Antidiabetic Properties of *Coriandrum sativum* in Animal Models and Cell Line Model

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ABSTRACT

The aim of the study was to evaluate the antidiabetic activity and antihyperglycemic potential of hydroalcoholic extract of coriander (*Coriandrum sativum* L.) leaves. The study was conducted using three different animal models: the Streptozotocin-induced diabetes model, the Alloxan-induced diabetes model, and the Glucose uptake assay. The study tested two different doses of the extract, 100 mg/kg body weight and 200 mg/kg body weight, to determine the most effective dose. In the Streptozotocin model, the 200 mg/kg dose was found to be more effective in reducing blood glucose levels compared to the 100 mg/kg dose. However, when compared to the standard drug, glibenclamide, both doses of the extract were less effective. In the Alloxan model, administration of glibenclamide and the extract at both doses significantly lowered blood glucose levels compared to the positive control group. The extract showed significant differences from the glibenclamide group only at the 200 mg/kg dose on day 14 of the treatment.

1. INTRODUCTION

Medicinal plants continue to be an important therapeutic aid for alleviating ailments of humankind. Over the last 2500 years, there have been very strong traditional systems of medicine such as Chinese, Ayurvedic, and the Unani, born and practiced, more in the eastern continent [1]. These traditions are still flourishing, since approximately 80% of the people in the developing countries rely on these systems of medicine for their primary health care needs. These plants contain substances that can be used for therapeutic purposes, of which are precursors for the synthesis of drugs [2]. A lot of research work has been carried out on some medicinal herbs and they have been found to have definite action on the nervous, circulatory, respiratory, digestive and urinary systems; as well as the sexual organs, the skin, vision, hearing and taste [3]. About 800 plant species have been reported to possess antidiabetic properties. Several plant species have been used for prevention or management of diabetes by the Native Americans, Chinese, South Americans and Asian Indians. The study showed that Asian and African continents have 56% and 17% share of the worldwide distribution of therapeutic herbal plants, respectively [4]. Biological actions of the plants are related to chemical composition that are rich in phenolics, alkaloids, flavonoids, terpenoids, coumarins, and glycosides usually show positive effects. On the other hand, many conventional drugs for treatment of diabetes, such as metformin are secretagogues which have a plant origin [5].

Diabetes is a chronic (long-lasting) health condition that affects how your body turns food into energy. Most of the food you eat is broken down into sugar (also called glucose) and released into your bloodstream [6]. When your blood sugar goes up, it signals your pancreas to release currently available therapy for diabetes includes insulin and various oral hypoglycemic agents such as sulfonylureas, metformin, glucosidase inhibitors, troglitazone, etc. But these are reported to produce serious adverse side effects such as liver problems, lactic acidosis and diarrhea [7]. It is currently affecting around 143 million people and the number of those affected is increasing day by day, by 2030 it is predicted to reach 366 million populations worldwide. The conventional drugs are used to treat diabetes by improving insulin sensitivity, increasing insulin production, and decreasing the amount of glucose in blood [8]. The adverse effect of drug treatment is not always satisfactory in maintaining normal levels of blood glucose and this view many medicinal plants have been provided a potential source of antidiabetic principle which are widely used for the treatment of diabetes mellitus in various traditional system of medicine worldwide and many of them are known to be effective against diabetes [9].

This research focuses on exploration of antidiabetic properties (as well as antihyperglycemic potentials) of *Coriandrum sativum* in animal models (Streptozotocin-induced diabetes model and Alloxan-induced diabetes model) at doses of 100 mg/kg b.w. and 200 mg/kg b.w. and cell line model (Glucose uptake assay in 3T3-L1 cell line). Also, the pharmacognostic characteristics, photochemical analysis, acute toxicity, and histology data were studied comprehensively.

2. MATERIALS AND METHODS

2.1. Chemicals

The reagents, consumables, solvents, and chemicals for this study were purchased via a local distributor from HiMedia® India Pvt. Ltd., Mumbai. Double distilled water was obtained through Borosil® system.

2.2. Instrumentation

All weighing were performed using Shimadzu® electronic balance (Model AUW220D, Kyoto, Japan). Microscopy was performed using trinocular microscope CosLab®HL-24(B) equipped with Scope Image 9.0 software for recording. The Glucose strips (One TouchTM) were obtained from the local pharmacy. Microscopy was performed using trinocular microscope CosLab®HL-24(B) equipped with Scope Image 9.0 software for recording.

2.3. Collection of plant material

The seeds of *Coriandrum sativum* were collected from local market at Bilaspur. The seeds were authenticated (No. Bot/GGV/2022/66) by Dr. Ashwini Kumar Dixit, Department of Botany, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India.

2.4. Preparation of extract

The collected seeds were dried in the shade for a specified period, and powdered suitably. The dried powder (100 g, divided into multiple smaller amounts) was subjected to continuous hot Soxhlet extraction with 50 mL distilled water and 50 mL alcohol (ethanol 90%) in equal ratio at a temperature of 55-65°C during 32 cycles. The solvent was removed under reduced pressure and con-trolled temperature using a rotary vacuum evaporator. The hydroalcoholic extract of *Coriandrum sativum* yield was found to be 9.74% w/w [10].

2.5. Pharmacognostic evaluations

2.5.1. Organoleptic properties

In organoleptic part, the color, shape, size, texture and fracture were studied suitably. The physiochemical parameters like a loss on drying (LOD) at 105°C, total ash content, acid insoluble ash, water soluble ash and alcohol soluble extractive value were determined as per methods given in Indian Pharmacopoeia (2010). The LOD determination is highly significant since any excess of water in plant materials will promote bacterial growth, the presence of molds and cause deterioration by hydrolytic activity. The total ash value serves as an indicator for determination of chalk powder, earthy silica materials lime or other earthy matter. Acid insoluble ash is used to detect excessive earthy materials, which has a varying amount of calcium oxalate crystals in the cells while water-soluble ash is used to detect the presence of material exhausted by water. Alcohol soluble extractive values are indicative of the presence of the adulterants, defective processing and poor quality of the drug. Powder characteristic studies like bulk density and tapped density were performed according to the procedures specified in USP Pharmacopoeia (2010) [11].

2.5.2. Histological properties

The transverse section (TS) of thorn was subjected to histological identifications under a trinocular microscope at 30x resolution. The section was stained with concentrated sulfuric acid and phloroglucinol. The powder microscopy was performed by duly staining with and observed using trinocular microscope at 10x resolution. All-important features were detected and recorded suitably [12].

2.6. Phytochemical screening

Phytochemical screening of extract was performed for the determination of sugars, alkaloids, glycosides, tannins, flavonoids, steroids, proteins, and terpenes as per the given standard test procedures as explained below [13].

2.6.1 Alkaloid

Hager's test: Saturated solution of picric acid was added to extract (10 mg/mL), the formation of yellow precipitate indicates the presence of alkaloids.

2.6.2 Flavonoid

Shinoda's test: Few magnesium turnings and concentrated HCl was added dropwise to extract (10 mg/mL), appearance of a pink scarlet or crimson red color after few minutes confirmed the presence of flavonoids.

2.6.3 Tannin

Gelatin test: To the extract (10 mg/mL), 1% gelatin solution containing 10% NaCl was added, formation of buff-colored precipitate resulted due to the presence of tannins.

2.6.4 Glycoside

Borntrager's test: The extract (10 mg/mL) was boiled with 1 mL of sulfuric acid in a test tube for 5 minutes and filtered while hot. The filtrate was cooled and shaken with an equal volume of dichloromethane. The lower layer of dichloromethane was separated and shaken with the half of its volume of dilute ammonia. A rose pink to red color was produced in the ammonia layer and indicated the presence of anthraquinone glycoside.

2.6.5 Cardiac Glycoside

Legal's test: To extract (10 mg/mL), pyridine and alkaline sodium nitroprusside solution were added. An appearance of blood red color signified the presence of cardiac glycoside, but no blood red color appeared reflecting complete absence of cardiac glycoside.

2.6.6 Saponin

Froth formation test: 2 mL of extract was taken in a test tube and shaken until a stable froth or foam was formed for 5 minutes (in presence of saponin), however, no foam was formed for 5 minutes indicating the absence of saponin in extract.

2.6.7 Carbohydrate

Fehling's test: 2 mL of extract was mixed with equal volumes of Fehling A and Fehling B in different tubes and boiled for few minutes. Both the contents were mixed as they attain nearly the boiling point. The appearance of brownish-red precipitate formation indicated the presence of carbohydrates.

2.6.8. Phenol

Ferric trichloride: The extract (10 mg/mL) was dissolved in water, and 8-10 drops of dilute ferric trichloride were added, the formation of bluish-black color indicated the presence of phenol.

2.6.9. Protein

Xanthoproteic test: To the extract (10 mg/mL), 1 mL of concentrated nitric acid was added and boiled to get a yellow precipitate, which after cooling, were added 2 mL of 40% sodium hydroxide solution, orange color appears (if protein is present). No orange color was formed with extract indicating absence of protein.

2.6.10. Sterol

Libermann-Burchard's test: The extract (10 mg/mL) was treated with 7-8 drops of acetic anhydride solution, boiled, and cooled further. Concentrated sulfuric acid (5-6 drops) was further added from the side of the test tube, where a brown ring was formed at the junction of both layers; and upper layer changed to green, which demonstrated the presence of steroids.

2.6.11. Diterpene

Copper acetate test: The extract (10 mg/mL) was treated with 3-4 drops of copper acetate solution, emerald, green color appeared (in presence of diterpene). In extract, no emerald, green color appeared, which confirmed the absence of diterpenes.

2.6.12. Triterpene

Salkowski's test: The extract (10 mg/mL) was treated with 5-6 drops of concentrated sulfuric acid, yellow color formation occurs in the lower layer (if triterpene is present), however no yellow color was formed describing absence of triterpene.

2.7 Animals

Swiss albino rat (average weight 170-260 g, aged 5-6 weeks) were utilized for screening the antidiabetic activity of coriander extract. After receiving approval from Department Ethical Committee, the animals were used from the animal house; kept in proper hygienic conditions, free access to water, fed standard rodent pellets, with 6 mice per cage enclosure and specified environment (24–25ºC temperature, humidity 50–60%, 12 hr light and dark).

2.8. Acute oral toxicity study

The acute oral toxicity study was conducted as per OECD guideline No. 423 for a period of 14 days. Albino rats of either sex were weighed and marked individually for proper observation purpose. They were then kept in Individual cages at room temperature, i.e., 22 ± 2 °C and 30% humidity. Food but not water was withdrawn from all animals overnight prior to AESO administration and 3-4 hours post administration. AESO was administered via oral route at doses of 5, 50, 300 and 2000 mg/kg in 2 mL of distilled water. 3 animals were used for each dosing level as recommended by guideline. Changes in skin, eyes, fur and mucous membrane colour were noted along with any sign of tremors, convulsions, salivation, diarrhea, lethargy and sleep etc. Changes in body weight were recorded before, during and at the end of study [14].

2.9. Anti-diabetic screening

2.9.1. *Streptozotocin-induced diabetic model*

The anti-diabetic study was performed according to the standard protocol. The rats demonstrating blood glucose level of range 60–75 mg/dl were initially selected. Streptozotocin solution (prepared by dissolving 100 mM citrate buffer of pH 4.5) was administered to the fasted male albino rats at a dose of 60 mg/kg body weight i. p. After the lapse of 48 hr, the blood glucose was monitored by commercial glucose strips. Only those rats were selected further which presented elevated levels (200–300 mg/dl) of blood glucose. On the 4th day, the blood glucose level was re-measured to authenticate the steady state hyperglycemia. The chosen animals were divided into 2 groups, each consisting of 6 rats. The first group (control) received only 1% gum acacia (carrier). The second group involved the standard drug (glibenclamide) for comparing the hypoglycemic activity. The successive groups were fed orally with *Coriandrum sativum* extract (100 mg/kg b.w. dose and 200 mg/kg b.w. dose in 1% gum acacia). The glucose profile of each rat was determined using the glucometer. Firstly, a sugar load of 5 g/kg was given to each animal orally and following that the test sample was administered after 30 min. The glucose lowering attribute of the analogs was scrutinized at time intervals of 0 hr, 1 hr, 3 hr, and 6 hr. The ability of *Coriandrum sativum* extract to reduce the blood glucose level was calculated according to the AUC method and expressed in percentage (%) [15].

2.9.2. *Alloxan-induced diabetic model*

Diabetes was induced in overnight fasted rats by intraperitoneal injection (IP) of alloxan monohydrate (150 mg/kg body weight), freshly prepared in normal saline. 20% dextrose solution (w/v) was administered after 6 h to prevent alloxan-induced hypoglycemia due to the massive release of insulin from pancreas. For the next 24 h, rats were maintained on 5% glucose in drinking water. After 72 h, blood glucose was checked by using digital glucometer. Animals with blood glucose greater than 200 mg/dL were selected and allowed to stabilize for 1 week before detailed experimentations [16].

2.9.3. *Glucose uptake assay*

The 3T3-L1 cell line is the best-characterized model of *in vivo* adipogenesis. The *in vitro* anti-diabetic activity of the synthesized compounds was evaluated by using 3T3-L1 cell line assay. Primarily, the cells were treated with dexamethasone (DM) and isobutylmethylxanthine (IBMX) and insulin which results in the adoption of a rounded phenotype and accumulation of lipids intracellularly begins to form lipid droplets. DM activates transcription factor CCAAT/enhancer-binding protein B whereas IBMX inhibits soluble cyclic nucleotide phosphodiesterases and results in an increased intracellular cAMP level, resulting in the activation of PPAR-g pathway. Insulin promotes adipocyte differentiation by activating PI3K and Akt activity. PPAR-γ is essential for the final phase of adipocyte differentiation and is the pharmacological target for glitazones class. The PPAR-g ligands stimulate the insulin-mediated glucose uptake in 3T3-L1 adipocytes. GLUT-1 levels are shown to increase while regulating the glucose levels in DMT2. For glucose uptake assay, the cells were seeded in a 96 well plate (5000 cells/well) in a complete medium (a-MEM + 10% Fetal Bovine Serum + 0.7% Penicillin-Streptomycin solution) and maintained at 5% CO_2 atmosphere. After 48 h (80% confluence), the medium was switched to a-MEM with 2% (v/v) FBS and was replaced after 2, 4 and 6 days of culture. The experiment was initiated on day 7 when myotube differentiation was complete. The cells were starved in serum free a-MEM for 2 h and then treated with samples and incubated for 24 h. Following treatment and incubation, the medium was aspirated and the cells were stimulated with 75 mL of 200 nM insulin prepared in KRPH from the stock of 1 mg/mL and incubated for 25 min. Plain KRPH buffer was added to the control wells. Pulsing was done by adding 15 uL of 0.06 mCi of radioactive solution for 10 min. The glucose uptake was terminated by washing the cells twice with 150 mL cold KRPH buffer. The cell-associated radioactivity was estimated by

lysing the cells with Microscint PSTM (60 mL/well) followed by liquid scintillation counting. The plate was read using a TOP Count reader (Perkin Elmer) [17].

2.10. Statistical analysis

All data are given as the mean minus the standard deviation of the mean ± SEM. One-way ANOVA and Dunnett's-test were used to assess all of the data. An ANOVA with post hoc Tukey's HSD test was used to compare mean values across groups. Repeated measure ANOVA was used to examine the tail immersion test findings (RM-ANOVA). The significance level was considered significant at $P < 0.05$. SPSS software v.17 (IBM Corporation, New York, USA) was employed for study.

3. RESULTS AND DISCUSSION

3.1. Pharmacognostic evaluations

The seeds were found to be pale ash to grey-brown color, 18 to 26 mm in dimension, globular shaped with a rough texture. The physicochemical studies showed that the loss on drying was found to be within pharmacopoeia specifications, *i.e.* 0.43%, which signifies that it has low water content and is merely free from any spoilage, browning, mold growth which the water causes specifically. The ash values (total, acid insoluble and water soluble) were found to be 15.13, 1.98 and 6.56 % w/w, respectively. The alcohol soluble extractive value was found to be 9.82, which implied that the bulk and tapped densities were found to be 0.156 and 0.273, respectively, which represents that the powder has a very fine capillary network with a large number of inter- and intra-particulate spaces and with high % compressibility index of 42.85. The physicochemical characteristics are given in table 1.

Table No. 1: Pharmacognostic Evaluation Of *Coriandrum Sativum*

Parameters	**Description**
Color	Pale ash to grey-brown
Shape	Globular
Size	18 – 26 mm
Texture	Rough
Loss on drying (105°C) (%)	0.43
Total ash content (% w/w)	15.13
Acid insoluble ash (% w/w)	1.98
Water soluble ash (% w/w)	6.56
Alcohol soluble extractive value	9.82
Bulk density	0.156
Tapped density	0.273
% Compressibility index	42.85

3.2. Histology

The transverse section of seeds displayed cork cambium, cortex, stone cells, starch grains and parenchymatous cells. Brick or polygonal cork cells, impregnated with layer and suberin were observed. The phloem cells were found to be mostly parenchymatous in nature. Prominent polygonal stone cells were found in thorns, which are sclerenchymatous cells that are modified to provide mechanical strength. The cortex was found to be composed of thick-walled rigid and strongly lignified cells, which were isodiametric or polyhedral in appearance. The presence of brown-reddish brown appearance is due to the presence of high tannin content in seed. Starch grains of variable sizes were detected. The thick walled parenchymatous cells were frequently observed in xylem portion of transverse section **(Figure 1)**.

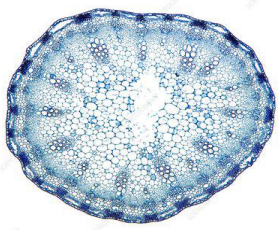

FIGURE NO. 1: TRANSVERSE SECTION OF *CORIANDRUM SATIVUM*

3.3. Phytochemical screening

Phytochemical screening of the extract revealed the presence of carbohydrates, tannins, flavonoids, alkaloids, sterols, phenol, and glycosides **(Table 3)**.

3.4. Acute oral toxicity study

The acute toxicity test using the Up and Down method at an oral limit doses of 175, 500, and 2000 mg/kg of the extract of *Coriandrum sativum* caused no death in the mice and rats. No lethal effects (inflammation, whirl, convulsions, unusual emaciation, respiratory depression, etc.) were noted throughout the short and long-term observation period. During the monitoring period, there was no change in food consumption or other behaviors.

3.5. Anti-diabetic activity

3.5.1. Streptozotocin-induced diabetes model

The perusal of data revealed that the hydroalcoholic extract of seeds of *Coriandrum sativum* decreased the blood glucose level statistically significant **(Table 2)** when compared with diabetic control. 200 mg/kg b.w. dose was found better than 100 mg/kg b.w., however, the standard Glibenclamide was better in comparison to both doses.

Table No. 2: Effects Of Hydroalcoholic Extract Of Coriander Seeds On Blood Sugar Level Using Streptozotocin-Induced Diabetes Model

Groups	**Blood glucose level in mg/dl**				
	1st day	**3rd day**	**7th day**	**11th day**	**14th day**
Control (normal saline; 0.9%)	89±2	91±4	100±18	105±16	79±12
Alloxan	239±18	263±16	290±46	461±141	585±14
Coriandrum sativum extract (100 mg/kg b.w.)	267±60	172±22	177±20	138±19	108±23
Coriandrum sativum extract (200 mg/kg b.w.)	304±46	188±7	159±16	134±5	107±12
Glibenclamide	298±42	188±15	156±7	146±15	97±39

TABLE NO. 3: Effects of hydroalcoholic extract of coriander seeds on blood sugar level using Alloxan-induced diabetes model

Groups	Blood glucose level in mg/dl			
	1st day	8th day	14th day	21st day
Control (normal saline; 0.9%)	113.83±4.79	115.67±1.02	115.50±1.56	118.50±1.15
Streptozotocin	368.33±5.05	373.50±1.76	367.33±3.22	375.33±4.46
Coriandrum sativum extract (100 mg/kg b.w.)	368.67±7.28	183.83±4.29	165.50±4.26	136.83±1.99
Coriandrum sativum extract (200 mg/kg b.w.)	361.83±14.72	180.50±3.07	157.83±5.28	128.67±2.40
Glibenclamide	374.67±5.06	161.33±2.21	124.67±1.80	104.50±3.12

3.5.2. Alloxan-induced diabetes model

Standard drug administration and extracts were performed for 14 days in hyperglycemic animals. Blood glucose level as a parameter was measured at days 3, 7, 10, and 14 treatments. Based on the blood glucose level measured during treatment, it could be seen that administration of glibenclamide and extraction at doses of 100 and 200 mg/kg b.w. could significantly lower blood glucose level compared with positive control group. The extract group at doses of 100 and 200 mg / kg b.w. did not show significant activity differences compared with the glibenclamide group on days 3, 7, and 11 **(Table 3)**. It was only on day 14, the extract at dose of 200 mg / kg bw group showed a significant difference compared to the glibenclamide group.

3.5.3. Glucose uptake assay

The hydroalcoholic extract of seeds of *Coriandrum sativum* showed 1.6 and 1.7 folds increase at concentration 50 mM and 100 mM, respectively when tested for glucose uptake

assay (3T3-L6 cell line). The reference standard Glibenclamide exhibited 1.9 folds increase of glucose over the control group at concentration of 50 mM whereas insulin exhibited 1.3 folds increase of glucose over the control group at concentration of 0.2 mM **(Table 4)**. It is evident from the *in vitro* glucose uptake activity testing that *Coriandrum sativum* at 100 mM concentration exhibits nearly similar potential to flush glucose in the cell lines as compared to the standard drug.

TABLE NO. 4: Effects of hydroalcoholic extract of coriander seeds on glucose uptake assay

Groups	**Glucose uptake assay**				
	Concentration (µM)	**Counts per minute (CPM)**	**STD**	**% CV**	**Fold increase over control**
Control (normal saline; 0.9%)	-	2044.3	206.8	10.1	1.0
Coriandrum sativum extract	50	3226.3	72.2	12.2	1.6
Coriandrum sativum extract	100	3399.3	487.7	14.3	1.7
Glibenclamide	50	4304.0	32.5	0.8	1.9
Insulin	0.2	3501.0	17.0	0.5	1.3

4. CONCLUSION

The hydroalcoholic extract of coriander (*Coriandrum sativum* L.) leaves was found to have antidiabetic and antihyperglycemic effects at doses of 100 mg/kg and 200 mg/kg in animal models, such as the Streptozotocin-induced diabetes model, Alloxan-induced diabetes model, and Glucose uptake assay. The extract was able to improve and regenerate the beta cells in the pancreas and inhibit the alpha-glucosidase enzyme in the small intestine, which is believed to be due to the presence of photochemical constituents, including carbohydrates, tannins, flavonoids, alkaloids, sterols, phenols, and glycosides.

Furthermore, the study found that the pharmacognostic characteristics and histology data of the extract provide new opportunities for the development of formulations for antidiabetic treatments. In addition, the toxicity study showed that the extract has a high level of safety in rats, which supports its potential for use as an antidiabetic treatment.

Overall, the results of this study highlight the potential of the hydroalcoholic extract of coriander leaves as a promising antidiabetic treatment, with additional benefits in terms of safety and formulation development.

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