Antioxidant, Antihyperglycemic, and Antihyperlipidemic Effects of *Coriandrum sativum* Leaf and Stem in Alloxan-Induced Diabetic Rats

S. Sreelatha and R. Inbavalli

Abstract: In India's indigenous system of medicine, *Coriandrum sativum* (CS), commonly used as a food ingredient, is claimed to be useful for various ailments. To establish its utility in diabetes mellitus, the present study evaluated the antidiabetic and antioxidant effects of CS in alloxan-induced diabetic rats. The extracts were shown to contain bioactive compounds including phenolics, flavonoids, steroids, and tannins. The extracts of CS in alloxan-induced diabetic rats were found to significantly lower blood glucose levels. Antidiabetic activity of the CS extracts was compared with the clinically available drug glibenclamide. The levels of serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol were lower in the extract-treated group and high-density lipoprotein cholesterol was higher than the diabetic control rats. The extracts of CS exhibited strong scavenging effect on 2, 2-diphenyl-2-picrylhydrazyl free radical and inhibition of lipid peroxidation. The free radical scavenging effect of the extracts was comparable with that of the reference antioxidants. Furthermore, it also showed an improved antioxidant potential as evidenced by decreased lipid peroxidation and a significant increase in the activity of various antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase in the liver of diabetic rats. These results indicate that the extracts could protect liver function and exhibited hypoglycemic, hypolipidemic, and antioxidant efficacies in the diabetic rats. These results support the use of this plant extract to manage diabetes mellitus.

Keywords: alloxan, antioxidant ability, *Coriandrum sativum*, hypoglycemic effect, hypolipidemic effect

Practical Applications: The leaves and stem of this plant *Coriandrum sativum* if used in cuisine would be a remedy for diabetes.

Introduction

Diabetes mellitus is a chronic metabolic disorder caused by an absolute or relative lack of insulin (Paul Zimmet and others 2001). It is associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism. Hyperglycemia and hyperlipidemia are the major causes of morbidity and mortality of diabetes (Taskinen 2002). The number of diabetic patients is rapidly increasing; however the control of diabetes with fewer side effects is a challenge. There is an increasing demand by patients to use natural products with antidiabetic activity, due to the obvious side effects associated with the use of insulin and oral hypoglycemic agents (Anila and Vijiyalakshmi 2002). Nowadays, synthetic agents and insulin used effectively for the treatment of diabetes have prominent side effects, such as hypoglycemia, drug-resistance, dropsy, and weight gain (Tahrani and others 2010). Increased free radical generation and oxidative stress play an important role in pathogenesis of diabetes and its late complications. The efficiency of antioxidant mechanism is altered in diabetes. Antioxidants thus play a major role in protecting the human body against oxidative damage. Some herbal medicines are good source of antioxidants (Oberley 1988). Hence traditional plant medicines are used throughout the world for treating diabetes.

Coriandrum sativum (CS) also called as "cilantro" is a well-known plant derived from the traditional system of medicine in India and a native of the Mediterranean region. There are 2 distinct species with distinct morphological types. Only *C. sativum L.* is cultivated widely in the tropics. India has the prime position in the cultivation and production of Coriander (Sharma and Sharma 2004). The seeds contain an essential oil "linalool" a monoterpenoid and the leaves contain substantial amounts of caffeic acid, ferulic acid, gallic acid, and chlorogenic acid (Bajpai and others 2005). The seeds and aerial parts of the plant are extensively used in traditional system of medicine for various ailments like spasm (Kurian 2003), rheumatism, neuralgia, gastric complaint (Khare 2004), bronchitis, diarrhea, dysentery, gout, dyspepsia, and giddiness (Varier 1994). The plant is known to possess antibacterial, antifungal (Fujita 2004), free radical scavenging, and lipid per oxidation activities (Lal and others 2004). The effect of coriander seeds (*Coriandrum sativum*) on carbohydrate metabolism was also studied in rats fed with high fat cholesterol diets (Chitra and Leelamma 1999).

It has also been reported that the leaves of CS possess phytochemical constituents (Bhaskarachary, 1995) and the polyphenolic-rich fractions from CS lowered the levels of lipid

MS 20120027 Submitted 1/6/2012, Accepted 3/24/2012. *Author Inbavalli is with School of Life Science, Bharathidasan Univ., Palkalaiperur, Tiruchirappalli, Tamil Nadu, India. Author Sreelatha is with Faculty of Science, NUS, Singapore and Dept. of Chemistry & Biosciences, SASTRA Univ., Tirumalaisamudram, Thanjavur, Tamil Nadu, India. Direct inquiries to author Sreelatha (E-mail: sree_latha04@yahoo.com).*

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peroxides in H_2O_2-treated lymphocytes (Hashim and others 2005). It has been shown that both seeds and leaves from coriander have radical scavenging properties and the effects are more potent in extracts from leaves than in seeds (Wangensteen and others 2004). Since, coriander leaves and stem are one of the commonly used spices in the cuisine which will increase the content of antioxidants, we made an attempt to evaluate the traditional claim. But no detailed investigations have been carried out on the antioxidant and hypoglycemic effects of the leaf and stem extract. This observation has motivated the investigation of the antidiabetic activity, and the phytochemical constituents responsible, of the leaf and stem extract of CS in alloxan-induced diabetic rats.

Materials and Methods

Reagents

Glucose assay kit, Folin-Ciocalteu's (FC) phenol reagent were obtained from Sigma Diagnostics Pvt. Ltd., India. Trolox, 2,2-diphenyl-2-picrylhydrazyl (DPPH), and hydrogen peroxide were purchased from Sigma-Aldrich Co., St. Louis, MO., USA.

Plant material and extraction

The fresh leaves and stems of CS were collected from the Horticultural Research Institute, Coimbatore, Tamil Nadu, India and authenticated by Botanical Survey of India, Coimbatore, Tamil Nadu, India where a voucher specimen (No: 907) has been deposited. Coriander leaves and stem (450 g) were finely chopped before extraction with aqueous ethanol (80%) for 24 h (Petra and others 1999). After the removal of the solvent in vacuo, the crude extract (18 g) was suspended in distilled water and extracted with 150 mL portions of ethyl acetate until the extracts were nearly colorless. Solvents were removed in vacuo, and the yield of 6.5 g and 4.4 g, respectively, were obtained.

Total phenolic, flavonoid contents, and total antioxidant activity

The total phenolic content was determined by the FC method (Slinkard and Singleton 1977) and expressed as grams of gallic acid equivalents per 100 g plant extract. Distilled water was mixed with a dimethyl sulfoxide solution of the test compound. Then, 200 μL of FC reagent was added. After 5 min, 600 μL of 20% sodium carbonate solution was added and the solutions were mixed again. The solutions were left at room temperature for 2 h. Then the absorption of the developed blue color was determined at 765 nm, using a Shimadzu-UV1800-spectrophotometer (Shimadzu, Kyoto, Japan). On estimating the levels of phenolic compounds in each fraction, the ethyl acetate fraction was found to have higher phenolic content. Flavonoids were extracted and estimated by the method where (Chang and others 2002) an aliquot of the extract was pipetted out and evaporated to dryness. 4.0 mL of vanillin reagent was added and heated for 15 min in a boiling water bath. The standard was also treated in the same manner. The optical density was read at 340 nm. The values are expressed as mg flavonoids/g leaf. The total antioxidant activity (AOA) of the leaf extracts was determined by using autoxidation of beta-carotene and linoleic acid coupled reaction method (Mitsuda and others 1996) and expressed as percentage of inhibition, relative to control.

DPPH scavenging activity

The free radical scavenging activity of the extract was measured in terms of hydrogen donating or radical scavenging ability using the stable free radical DPPH (Blois 2002). One milliliter solution of the extract in methanol was added to 0.5 mL of 0.15 mM DPPH solution in methanol. The contents were mixed vigorously and allowed to stand at 20 °C for 30 min. The absorbance was read at 517 nm. IC_{50} value (the concentration required to scavenge 50% DPPH free radicals) was calculated. The capacity to scavenge the DPPH radical was calculated using the following equation:

DPPH scavenging effect (%) = $[(A_0 \_ A1/A_0) \_ 100]$, where A_0 was the absorbance of the control reaction and A1 the absorbance in the presence of the sample.

Animal and experimental design

Wistar Albino rats (150–180 g) of both genders were used for the study. The animals were housed under standard conditions (25 °C, 12 h light, and 12 h dark cycle) and fed with standardized pelleted feed (TANUVAS) and clean drinking water *ad libitum*. All the protocols were performed in accordance with the Institutional Animal Ethical Committee (IAEC) as per the directions of the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). After an acclimatization period of 1 wk they were used for the study.

Different groups of healthy adult albino rats were treated with graded doses of the CS extract (100, 250, 500, and 750 mg, per os [p.o]). Group I was maintained as control. Groups II to V received the CS leaf and stem extract as 2 sets. They were observed continuously for 2 h for any gross behavioral changes and death, if any, and then intermittently for the next 6 h, and then again at 24 h after dosing with CS extracts.

Healthy adult albino rats were divided into 5 groups of 6 animals each. Group I served as the control and received saline. Group II served as the diabetic control. Group III to Group V are the alloxan-treated rats followed with the treatment schedule, respectively. Group III and Group IV were treated orally using an intragastric tube with 200 mg/kg/day of CS leaf and stem extract, respectively, and Group V received the standard drug Glibenclamide (5mg/kg/day, p.o). Treatment continued for 7 consecutive days.

Table 1–Phenolics, flavonoids, scavenging activity, and total antioxidant activity in CS extracts.

Sample	Total phenols (GAE/100 g)	Total flavonoids (QE/100 g)	DPPH scavenging activity (IC_{50} (μg/mL)	Total antioxidant activity (%)
Leaf extract	25.23 ± 2.17 *	19.15 ± 2.33*	25.32 ± 0.54*	64.56 ± 0.51*
Stem extract	15.14 ± 1.62	18.41 ± 2.85	20.36 ± 0.63	55.36 ± 0.28

Values are means of triplicates ± standard deviation. *$P < 0.01$ as compared to stem extract.
Total phenolics expressed as g gallic acid equivalents (GAE/100 g) plant material. Total flavonoids expressed as g quercetin equivalents (QE/100 g) plant material.

Table 2–Effect of CS extracts on blood glucose level.

Groups	Blood glucose mg/dL	Urinary glucose
Control	84.27 ± 0.14#	–
Diabetic control	256.47 ± 1.61	+++
Alloxan + leaf extract (200 mg/kg)	109.74 ± 1.39*	+
Alloxan + stem extract (200 mg/kg)	124.40 ± 1.66*	+
Alloxan + glibenclamide (5 mg/kg)	105.31 ± 1.12*	+

Values are means ± SD; $n = 6$. Diabetic control was compared with the vehicle control and extract-treated groups were compared with the diabetic control. # $P < 0.01$, *$P < 0.01$ compared with diabetic control.

Induction of diabetes

Rats were made diabetic by a single intraperitoneal injection of alloxan monohydrate (150 mg/kg) (Aruna and others 1999) in 0.2 mL saline. Alloxan was first weighed individually for each animal and then solubilized in 0.2 mL saline. Rats with effective and permanent elevated plasma glucose levels > 140 mg/kg were selected for the experimental study.

Determination of blood glucose

Blood samples were collected by the retro-orbital plexus puncture method from control and experimental animals and blood glucose levels were determined by the glucose oxidase method.

Determination of biochemical parameters

The rats were fasted overnight, and blood samples were collected from the eye pit of all rats under ether anesthesia. The blood samples were used for the measurement of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) levels by an automatic biochemical analyzer. The animals were killed while still under ether anesthesia and the liver was removed immediately, weighed and washed using chilled saline solution. The liver was homogenized in 4 volumes of Tris-HCL buffer (pH 7.4) .The homogenate was centrifuged at 4000× *g* for 20 min at 4 °C. The protein concentration in liver was determined by the Bradford method using bovine serum albumin as standard (Bradford 1976). The levels of superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), and glutathione peroxidase (GSH-px) were measured using commercial enzyme kits in the liver homogenate.

Statistical analysis

All the parameters studied were subjected to statistical treatment using Sigma Stat statistical package (Version 3.1). All the values are expressed as mean ± SD ($n = 6$) where "n" represents the number of samples. One-way Anova, followed by *post hoc* analysis using Fischer's least significant difference test, was adopted to all the parameters under study to test the level of statistical significance. The difference was considered significant if $P < 0.05$.

Results and Discussion

The present study for the first time reports the hypoglycemic and antidiabetic effect of CS leaf and stem extracts. Administration of CS extracts showed marked hypoglycemic, hypolipidemic, and antioxidant effects *in vivo.*

Total phenolics, flavonoids composition, and total antioxidant activity

Phyto chemical analysis of the extracts revealed the presence of polyphenols. The content of the phenolic compound was calculated as milligram gallic acid equivalents per gram tissue. The leaf extract had the highest phenolic content followed by the stem extract (Table 1). Highest AOA was observed in the leaf extract than the stem extract and it was compared with the positive control α-tocopherol. Since polyphenols are responsible for the AOA, the obtained amount of total polyphenols in the extracts suggested that the leaf extract possess a high AOA.

DPPH scavenging activity

DPPH has been used widely for the determination of primary AOA of herbal extracts. The amount of sample needed to decrease the initial DPPH concentration by 50% is a parameter widely used to measure AOA. The scavenging effects of leaf and stem extract on the DPPH radical are shown in Table 1. CS extracts significantly reduced DPPH radicals. In comparison, the positive control, Trolox® had an IC_{50} of 18.14 ± 0.32 μg/mL. The DPPH scavenging ability of the extract may be attributed to its hydrogen donating ability and the leaf extract showed significant scavenging activity.

Effect of CS extracts on blood glucose

The acute oral toxicity study of CS revealed no mortality up to 750 mg/kg body weight. There were no changes in behavioral activities such as restlessness, respiratory distress, diarrhea, convulsions, and coma of the animals which received CS extract of either leaf or stem at any dose. The hypoglycemic effect of the ethyl acetate extract of CS leaf and stem on the blood glucose levels of diabetic rats is shown in Table 2. Administration of alloxan (150 mg/kg, i.p.) led to the elevation of blood glucose levels, which was maintained over a period of 2 wk. At the end of the study

Table 3–Effect of CS extracts on serum lipids.

Treatment	TG mg/dL	HDL mg/dL	VLDL mg/dL	LDL mg/dL	Total cholesterol mg/dL
Control	118.15 ± 5.03	38.6 ± 1.83#	16.43 ± 1.006#	41.9 ± 4.37#	120.53 ± 7.21#
Diabetic control	260.8 ± 9.51	24.56 ± 4.9	29.76 ± 1.9	226.4 ± 6.79	276.3 ± 4.49
Alloxan + leaf extract (200 mg/kg)	128.9 ± 0.1*	61.92 ± 4.72*	17.24 ± 1.39	105.64 ± 2.40*	158.9 ± 5.63*
Alloxan + stem extract (200 mg/kg)	114.7 ± 6.95*	67.27 ± 3.90*	25.78 ± 1.02	101.71 ± 3.45	196.4 ± 4.01*
Alloxan + glibenclamide (5 mg/kg)	92.58 ± 6.7	68.82 ± 2.79*	20.92 ± 1.34	104.20 ± 2.66*	176.64 ± 6.79*

Values are means ± SD; $n = 6$. Diabetic control was compared with the vehicle control and extract-treated groups were compared with the diabetic control. #$P < 0.01$, *$P < 0.01$ compared with diabetic control.

Table 4–Effect of CS extracts on antioxidant parameters in liver tissue.

Groups	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)	GPx (U/mg protein)
Control	6.23 ± 0.23#	46.23 ± 0.14#	28.41 ± 0.21	26.23 ± 0.24#
Diabetic control	11.60 ± 0.46	39.60 ± 0.43	10.61 ± 0.29	19.60 ± 0.63
Alloxan + leaf extract (200 mg/kg)	7.22 ± 0.35*	43.22 ± 0.36*	24.51 ± 0.32*	23.22 ± 0.66*
Alloxan + stem extract (200 mg/kg)	8.23 ± 0.24*	42.23 ± 0.27*	27.15 ± 0.42*	22.23 ± 0.37*
Alloxan + glibenclamide (5 mg/kg)	6.86 ± 0.27	46.86 ± 0.29	27.91 ± 0.24*	25.86 ± 0.27

Values are means ± SD; $n = 6$. SOD = amount of enzyme that causes 50% reduction in NBT oxidation; CAT = micromoles of hydrogen peroxide decomposed per minute; GPx = μg of glutathione consumed/min.
Diabetic control was compared with the vehicle control and extract-treated groups were compared with the diabetic control.#$P < 0.01$, *$P < 0.01$ compared with diabetic control.

the leaf extract showed a significant ($P < 0.001$) reduction in the blood glucose comparable with that of glibenclamide (5 mg/kg)-treated groups. It was suggested that the regeneration of β-cells following destruction by alloxan might be the primary cause for the antidiabetic activity of the extracts.

Alloxan is widely used to induce experimental diabetes in animals. Alloxan establishes a redox cycle with the formation of superoxide radicals and undergoes dismutation to hydrogen peroxide with the formation of hydroxyl radicals. Evidence suggests that the diabetogenic capacity of alloxan may depend on its ability to damage β-cells and induce oxidative stress. The action of reactive oxygen species (ROS) with a simultaneous massive increase in cytosolic calcium concentration causes the rapid destruction of β-cells (Szkudelski 2001). Administration of the CS leaf and stem extracts significantly reversed the damage associated with alloxan-induced diabetes. Therefore, according to the results obtained, the hypoglycemic effect of CS extracts may be due to restoration of insulin response. It was reported that the seeds of CS was shown to decrease the glucose level and demonstrated hypoglycemic action (Gray and others 1999).The results are further *similar* to that of glibenclamide and it is also observed with other plant extracts (Kesari and others 2005). The results also revealed a defined role of leaf and stem extract of CS suppressing blood glucose in normal and diabetic rats. From the above results it can be concluded that CS leaf and stem extract exhibited a hypoglycemic effect which may be due to its phytoconstituents, especially phenolics for the observed effects and implied that CS extracts might control the development of diabetes.

Effect of CS extracts on blood lipids

In alloxan diabetic rats, there was a significant ($P < 0.001$) increase in TC, TG, LDL, and VLDL cholesterol and a significant decrease in HDL cholesterol ratio in serum compared to that of normal control. The standard antidiabetic drugs as well as the plant extracts used in the experimental study significantly decreased the levels of cholesterol, TG, LDL, and VLDL cholesterol as shown in Table 3. Taken together, the results seem to suggest that the treatment with CS extracts could be beneficial for the treatment of the hyperglycemia and the related hyperlipidemia.

In addition to its hypoglycemic effect, CS extracts were also able to alter the levels of lipid metabolites including TC, TG, HDL, and LDL cholesterol levels in diabetic rats suggesting a remarkable hypolipidemic effect. The levels of serum lipids are usually raised in diabetes mellitus and such an elevation represents a risk factor for coronary heart disease (Sakatani and others 2005). The increase of blood glucose is accompanied by a rise in TC, LDL, TG, and a fall in HDL (Sharma and others 2003). Therefore, the increase in the level of serum lipids in alloxan-induced rats and a decrease in serum lipids in the CS extracts-treated rats was also observed. These findings indicate that the extracts might be beneficial to diabetic patients with atherosclerosis, since an elevated HDL level is associated with a reduced risk of the development of atherosclerosis in diabetes mellitus (Vasan and others 2003). Thus this result suggested that CS extracts would be helpful to the prevention of diabetic complications through improving dyslipidemia.

Effect of CS extracts on enzymic activities

The effects of CS extracts on the levels of MDA, SOD, and GSH-px are shown in Table 4. The results showed that the level of MDA was significantly increased in alloxan-treated rats, while the activities of SOD, CAT, and GSH-px were decreased compared with the control group. The standard antidiabetic drugs as well as the plant extracts used in the experimental study significantly decreased the levels of MDA and elevated the levels of SOD, CAT and GSH-px.

Studies have shown that there is a close relationship between the increase in free radicals, blood glucose, and lipid peroxidation. Free radicals can diffuse intracellularly and result in mitochondrial enzyme damage, DNA breaks, impair cellular function, and contribute to the pathophysiology of diabetes (Ceriello 2000). Oxygen free radicals exert their cytotoxic effects on membrane phospholipids resulting in the formation of MDA. Intracellular concentration of ROS is a consequence of both their production and their removal by various antioxidants. The major components of antioxidant system, namely, SOD, CAT, and glutathione peroxidase (GPx), work in concert to detoxify free radicals. SOD and GSH are the scavenger of free radicals, and have important effects on the control of oxidation reactions in the body (Ananthan and others 2004). According to the results, the levels of SOD, CAT, and GSH-px were increased and the concentration of MDA was decreased after the CS extract treatment, suggesting that the extracts have effective antioxidative properties and could scavenge excess free radicals. The observed increase of free radical scavenging activity suggests that CS extracts have an efficient protective mechanism in response to ROS which may help to regenerate β-cells and protect pancreatic islets against cytotoxic effects of alloxan. The AOA of CS leaf and stem extract responsible for preventing the deleterious effects of oxidative stress was also disclosed in our recent study (Sreelatha and Padma 2009). Many studies have also reported the hypoglycemic effect of flavonoids in diabetic animal models (Jayaprakasam and others 2005). Recent studies on the antioxidant properties of flavonoids reveal their stimulatory action on antioxidant enzymes (Nagata and others 1999). It is also reported that ferulic acid, quercetin, and kaempferol exert beneficial effects on hyperglycemia of diabetic animals (Fang and others 2008). Also the leaves of CS contain substantial amounts of caffeic acid, ferulic acid, gallic acid, chlorogenic acid, kaempferol, and quercetin (Bhaskarachary 1995; Bajpai and others 2005) which might contribute to the observed antihyperglycemic activity. Our data also suggest the presence of higher concentration of total phenolic and flavonoid contents in the leaf and stem extract which is consistent with the ability of the plant extract to promote insulin and reduce glucose level. Therefore, the analysis of total phenolic content of CS extracts in the present study shows that phenolics present in high concentrations are necessary to counteract with the radical generating system.

Further studies are needed to evaluate the actual therapeutic value of these extracts and several of these compounds are known to exert AOA.

Conclusion

Polyphenols, ascorbates, and flavonoids are known to be responsible for antioxidant and free radical scavenging potentials. The total AOA and the phenolic contents in the extracts contribute to the antidiabetic potential which suggests that both leaves and stem can be exploited as an important source of natural antioxidants with health protective potentials. The antidiabetic activities of the extracts of both leaves and stem could be explained, at least in part by the effect of antioxidants and the protective effect by the phenolics. In conclusion, the data obtained in this study point out that CS leaves and stem possess a significant antidiabetic effect, which seems to justify the traditional use of this food ingredient in folk

medicine and warrant further study as a promising drug for various oxidative stress disorders. The results also suggest that consumption of both leaf and stem can enhance the antioxidant properties in alloxan-induced diabetic rats, which promisingly support for the use of CS as an excellent food supplement in the treatment of diabetes.

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