

Hypoglycemic and Antioxidative Potential of *Coriandrum sativum* Seed Extract in Alloxan Induced Diabetic Rats.

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ABSTRACT

Diabetes, an endocrine disorder, causes hyperglycemia along with oxidative stress that leads to diabetes-related complications. Diabetic nephropathy is one of the complications related to oxidative stress. Antioxidants play a pivotal role to protect body organs against damage caused by free radical species like Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). Nowadays, drugs that are used to treat diabetes mellitus cause serious side effects, leading to the gaining popularity of alternative herbal medicine. This study aims to investigate antioxidant potential concerning kidney tissue and hypoglycemic effect of *Coriandrum sativum* seeds in alloxan induced diabetic rats. The rats were divided into Normal, Diabetic and Coriander seed crude methanolic extract treated groups. Diabetes was induced by administering Alloxan at a dose of 100 mg per kg body weight. Diabetic rats were treated with crude methanolic Coriander seed extract at a dose of 500mg/kg bodyweight for 30 days using gavage. Blood serum was used for Glucose estimation whereas Kidney tissues were collected and stored in Tris Buffer for antioxidant assay. Glucose and antioxidant assays were carried out using previously reported methods with slight modifications. The results showed a significant ($p < 0.05$) decrease in blood glucose level indicating its hypoglycemic effect. Besides, it caused a significant ($p < 0.05$) increase in Antioxidant enzymes and compounds of kidney tissue such as Superoxide Dismutase (SOD), Glutathione-S-transferase (GST), Glutathione Peroxidase (GPx), Catalase (CAT), Glutathione Reductase (GSSG Red) and Reduced Glutathione (GSH) as compared to the diabetic group. Thus, it indicates that the crude methanolic extract of *Coriandrum sativum* seeds has the potential to combat hyperglycemia and oxidative stress-induced diabetic complications.

KEY WORDS: DIABETES, HYPOGLYCEMIC, ANTIOXIDANT, CORIANDRUM SATIVUM, OXIDATIVE STRESS.

INTRODUCTION

Diabetes, being, an Endocrine disorder having many complications (Adeyemi et al., 2010). Oxidative stress has been reported to play a key role in the initiation and progression of diabetes mellitus along with its complications. Diabetes-induced Hyperglycemia increases oxidative stress, which may be due to either increased free radical species production or a decrease in antioxidant defenses (Giacco and Brownlee, 2010). Studies indicate that oxidative damage caused due to oxidative stress is an important factor related to diabetic nephropathy (Zhang

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and Sun, 2015). Diabetic nephropathy, a chronic disease, caused due to diabetes mellitus, if left untreated, leads to end-stage renal failure (Chen et al., 2015; Ghaderian et al., 2015; Magee et al., 2017). Hyperglycemia and Oxidative stress together play an important role in the progression of Diabetic Nephropathy (Rehman and Akash, 2017). Chronic hyperglycemia is the prime factor of diabetes mellitus complications that modulates metabolism by elevating the production of reactive oxygen species (Rosca et al., 2005). Moreover, it has been reported that Diabetes mellitus is linked to elevation in oxidative stress (Ighodaro, 2018 Prabhakar et al., 2020).

Antioxidant enzymes such as Superoxide dismutase (SOD), Catalase (CAT), Glutathione reductase (GSSG Red), Glutathione Peroxidase (GPx), Glutathione Transferase (GST) and other antioxidant molecules such as Reduced Glutathione (GSH) scavenges the free radicals and provide protection to cells against oxidative damage (Bahadir et al., 2016). The antioxidant can decrease the oxidation rate of other molecules; various studies have indicated that antioxidants have the ability to suppress the complications of diabetes (Ayala et al., 2014 Deepa et al., 2018). Previous works have proved the efficiency of plants in the regulation of oxidative stress related to diabetes mellitus (Taleb et al., 2009). *Coriandrum sativum* (Family Apiaceae) also known as Cilantro is one of the extensively used herbs as traditional medicine for gastrointestinal disorders etc. Several workers have reported that *C.sativum* has antioxidant (Wangenstein et al., 2004), antihyperglycemic (Eidi et al., 2009) and antihyperlipidemic (Chithra and Leelamma, 1999; Sreelatha and Inbavalli, 2012). In the present study, an attempt has been made to further assess the hypoglycemic and antioxidative effect of crude methanolic extract of *Coriandrum sativum* seeds with reference to the kidney in case of *Diabetes mellitus*.

MATERIAL AND METHODS

The Plant part was authenticated by Prof. S. R. Padmadeo, Former Head of Department of Botany, Patna University. The seeds of *C.sativum* were purchased from the local market during the harvesting season of the plant. Seeds of *C. sativum* were carefully washed with distilled water 3-6 times to remove dirt and other contaminating material. The plant materials were shade dried at ambient temperature and pressure until no moisture was left in it. The plant material was converted to fine powder using kitchen grinder followed by sieving with the help of muslin cloth to remove coarse particles. The powdered form of seeds of *C.sativum* respectively was stored in a well-labeled airtight container for further use. The methanolic crude extract of *C.sativum* was prepared using Soxhlet apparatus (Riviera, India). 100 grams of fine powder of plant material was weighed using a digital weighing machine (Wensar, India) and placed in the cellulose thimble using gloves. The thimble was carefully placed in the extraction chamber of the soxhlet apparatus while 500 ml of Methanol (100%) was placed in the boiling flask attached to the heating mantle.

The Soxhlet apparatus was run for 48 hours at 60°C to ensure that all phytochemicals in the plant material have dissolved in methanol (Nafisa et al., 2007).

After 48 hrs cycle, the methanolic extract was collected from the Soxhlet apparatus and was further filtered using Whatman filter paper to get rid of any solid particle. The methanolic extract was concentrated by Rotavapour (Popular, India) at 60 °C and reduced pressure to one-twentieth volume (5 ml). it was further lyophilized to get thick greenish brown coloured residue in case of *C. sativum* which were stored in a well-labeled vial at 4°C. Alloxan monohydrate used in this study was a product of Sigma Chemical Company, St Louis, MO, U.S.A. Glucose glucometer was a product of Dr. Morepen, Delhi, India. UV-Vis Spectrophotometer (Systronics, India) was used to analyse enzymes and molecules. All other chemicals and assay kits used were products of Sigma-Aldrich Inc. and Merck, Germany, respectively. Healthy Wistar male albino rats (100–150 g) were kept under well-ventilated standard environmental conditions (temperature 25±2 °C, relative humidity 50±5 %) with a 12 h light / dark cycle. Animals were allowed to acclimatize for 7 days before the commencement of the experiment. The experiments were designed and conducted as per the current ethical norms and guidelines approved by the Ministry of Social justices and Environment, Government of India (Nafisa et al., 2007).

The rats were fed on Laboratory prepared pellet having the composition suggested by Subcommittee on Laboratory animal nutrition, National Research Council, USA and water *ad libitum* to ensure proper growth and nourishment. The extra supplement that was given was carrot, sprouted Bengal gram and green gram. Alloxan monohydrate 100 mg/kg body weight dissolved in 0.9% sterilized NaCl solution of pH 7.0 was administered in the tail vein of rats to induce diabetes mellitus. After 48 hours, their fasting blood glucose levels were monitored using a glucometer by collecting blood from the tail artery of animals. Those rats having fasting glucose levels in the range of 250 and 400 mg/dl were considered diabetic and used for the experiment (Nafisa et al., 2007).

The pure breed rats were kept in new polypropylene cages and were categorized into the following groups:-Group I – Normal/Control., Group II – Alloxan treated Diabetic rat, Group III – Crude Methanolic Coriander seed Extract treated ratMethanolic crude *C. sativum* seed extract at a dose of 500mg/kg. body weight was prepared from the stock solution according to the weight of the rats by dissolving in olive oil. Oral administration of the desired herbal extract was made through oral gavages for 10, 20 and 30 days. For the present research work, blood samples were collected by tail clipping for fasting glucose estimation and after an interval of 10, 20, and 30 days rats were sacrificed for organ collection and preservation. For the entire research work, a tissue sample of the kidney for the antioxidant assay of different parameters was kept in Tris-buffer at -20 °C.

The kidney tissue was isolated, washed in 0.2 M Tris buffer solution, blotted dry and weighed. A 10% tissue homogenate was prepared in 0.2 M Tris buffer solution by a motor-driven Teflon pestle glass homogenizer. The tissue homogenate was centrifuged at 10,000 rpm for 20 min, to remove cell debris and then the supernatant was centrifuged at 15,000 rpm for 30 min. The supernatant obtained was used for various assays. The tissues collected at each interval were immediately processed and each tissue sample was analyzed separately (Rotruck et al., 1973).

Superoxide Dismutase (SOD) activity was measured by the method of Marklund and Marklund based on the inhibition of the auto-oxidation of pyrogallol (Marklund and Marklund, 1974). Catalase (CAT) activity was determined by measuring the rate of decomposition of H_2O_2 by the method of Claiborne, 1985. The Glutathione Peroxidase (GPx) activity was determined using H_2O_2 as a substrate according to the method of (Rotruck et al., 1973). Glutathione Peroxidase enzyme catalyzes the decomposition of H_2O_2 or other peroxides (-OH) with the simultaneous oxidation of GSH into GSSG (Rotruck et al., 1973). The tissue GSH content was estimated by the method of Beutler based on the development of a stable yellow colored complex, with 5,5'-dithio, bis-2, nitrobenzoic acid (DTNB) or Ellman's reagent (Beutler et al., 1967). The activity of GSH-R was measured by the oxidation of NADPH as described by Horn, 1963. The activity of GST was determined using 1-chloro 2,4-dinitrobenzene (CDNB) as substrate (Habig et al., 1974). Data were expressed as the Mean \pm SEM. For statistical analysis of the data, group means were compared by one-way analysis of variance (ANOVA) followed by Tukey and Duncan post hoc test for multiple comparisons using Graph Pad Prism 8 software. $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Diabetes is a disease, if not controlled in time can lead to a secondary pathological condition due to a rise in oxidative stress during the progress of the disease. In the present study, an attempt has been made to investigate the ameliorating impact of Coriander seed extract on diabetic nephropathy. Diabetes was induced with the help of alloxan, alloxan caused diabetes by the destruction of pancreatic Beta cells (Jelodar et al., 2007). Alloxan treated rats at a dose of 100 mg/kg body weight caused elevation in blood glucose up to 489% as compared to control leading to loss of weight and lethargic activity.

Nevertheless, when the crude -coriander methanolic extract at a dose of 500 mg/kg body weight were administered to diabetic rat caused a significant decline in blood glucose level up to -74% (Fig.1). Kajal and Singh, (2019) reported similar findings through their work on petroleum ether extract of *C. sativum* seeds (Radenkovic et al., 2016; Kajal and Singh, 2019). The antioxidant effects of crude coriander were studied in terms of antioxidant enzymes like SOD, Catalase, GPx,

GST and Glutathione Reductase along with antioxidant molecules like Reduced Glutathione (GSH) (Yasui and Baba, 2006; Kangralkar et al., 2010; Radenkovic et al., 2016).

The Superoxide Dismutase (SOD) belongs to the metalloenzyme group that forms defense against oxygen species (ROS) mediated injury by catalyzing the dismutation of superoxide anion free radical (O_2^-) into molecular oxygen and hydrogen peroxide (H_2O_2) thereby decreasing O_2^- concentration which harm cells (Yasui and Baba, 2006; Kangralkar et al., 2010; Radenkovic et al., 2016). In the diabetic rat group, SOD level considerably decreased (-84%), Nonetheless, Crude methanolic coriander seed extract treatment leads to a significant increase in enzyme activity (+100%) ($p < 0.005$) as compared to the diabetic group suggesting a decrease in oxidation stress and ROS level (Landis and Tower, 2005) (Table 1). Catalase and Glutathione Peroxidase are other significant antioxidant enzymes that help to overcome stress by the elimination of H_2O_2 (Bagri et al., 2009).

There was a marked decline in catalase activity up to 98% in the diabetic group as compared to normal, which may be due to inactivation by superoxide radical and Glycation of Enzyme (Bagri et al., 2009). However, on treatment with plant extract for 30 days, catalase activity augmented 15.46 times as compared to the diabetic group showing a recovering trend ($P < 0.05$) (Table 2), which may be due to the antioxidant potential of the plant. Similarly, GPx activity decreased substantially by 90% in the diabetic group. Reduced activity of GPx in the Diabetes group may be attributed to free radical induced inactivation and Glycation of the enzyme (Zhang and Tan, 2000; Rajasekaran et al., 2005).

Administration of crude methanolic *C. sativum* extract increased the activities of GPx by (+82%) on day 30 ($p < 0.05$) with respect to the diabetic group (Table 3), which is in agreement with the result of (Sreelatha and Inbavalli, 2012). GST is multifactorial enzymes that play a key role in the detoxification of electrophilic metabolites (Hayes et al., 2005). GST activity in alloxan induced diabetes group illustrated a two-fold decrease with respect to normal on day 30. However, on treatment with methanolic crude coriander seed extract, there was an elevation in enzyme activity by 1.42 fold from day 10 to day 30 showing the beneficial effect of the extract (Table 4), which is similar to the reports of Rai et al., 2010.

The decreased activity of GST noted in the diabetic group may be due to deactivation caused by ROS. This suggests that plant extract may assist in neutralizing ROS (Andalu and Vardacharlu, 2003; Sreelatha and Inbavalli, 2012). Glutathione reductase (GSSG red) another key antioxidant enzyme assists in regenerating reduced glutathione (GSH) from the oxidized form of Glutathione that is produced due to oxidation of GSH and therefore ratio of cellular GSH: GSSG is maintained (Dym and Eisenberg, 2001; Taleb et al., 2009; Sato et al., 2011).

Glutathione reductase activity followed the declining trend in the case of the diabetic rat group (-58%) but on treatment with crude seed extract of coriander, there was 43% increase in enzyme activity as compared to the diabetic group on day 30 (P<0.05) (Table 5), which is in consensus with the work of (Taleb et al., 2009). Reduced Glutathione, a tripeptide antioxidant that protects the cellular system from the deleterious effect and scavenging free radicals besides being acting as co-substrate for detoxification by glutathione peroxidases (Anantham et al., 2004; Nain et al., 2012). In the present study, the GSH level was reduced to -24% in the diabetic group as compared to Normal that suggests increased oxidative stress (Table 6). Treatment with crude coriander seed extract leads to 25% increase in GSH level in the diabetic rat (p<0.05) in contrary to the diabetic group without treatment, which is in congruence with the

findings of (Ozsoy et al., 2006; Hussien, 2008; Nain et al., 2012).

Figure 1: Effect of methanolic extract of crude coriander seeds on blood glucose

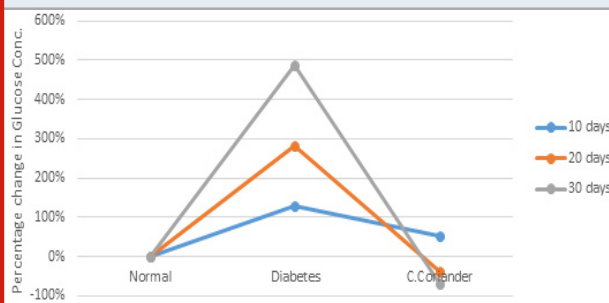


Table 1. Effect of Methanolic extract of crude Coriander seeds on SOD (U/ mg of protein) in Kidney Tissue

Days	Normal	Diabetes	C.Coriander
10 days	172.1567 ± 0.494821	130.3967 ± 0.471926*	4.243333 ± 0.024037*#
20 days	172.1567 ± 0.494821	97.06333 ± 0.087432*	7.256667 ± 0.016667*#
30 days	172.1567 ± 0.494821	27.59667 ± 0.800861*	55.30333 ± 0.104775*#

Values indicate mean ± SEM (n=3)

*p<0.05, compared with normal control values, # p<0.05, compared with Diabetic values

Table 2. Effect of Methanolic extract of crude Coriander seeds on Catalase (U/ mg of protein) in Kidney Tissue

Days	Normal	Diabetes	C.Coriander
10	413.7567 ± 57.7487	271.85 ± 1.66872	17.26 ± 0.355387#
20	413.7567 ± 57.7487	51.48 ± 0.931522	26.34667 ± 0.7349#
30	413.7567 ± 57.7487	8.703334 ± 0.275096	266.8567 ± 0.280496#

Values indicate mean ± SEM (n=3)

*p<0.05, compared with normal control values, # p<0.05, compared with Diabetic values

Table 3. Effect of Methanolic extract of crude Coriander seeds on GPx (U/ mg of protein) in Kidney Tissue

Days	Normal	Diabetes	C.Coriander
10 days	12.28667 ± 0.01453	4.26 ± 0.05*	1.233333 ± 0.082529*#
20 days	12.28667 ± 0.01453	2.093333 ± 0.027285*	1.94 ± 0.04*#
30 days	12.28667 ± 0.01453	1.23 ± 0.005773*	2.243333 ± 0.024037*#

Values indicate mean ± SEM (n=3)

*p<0.05, compared with normal control values, # p<0.05, compared with Diabetic values

Table 4. Effect of Methanolic extract of crude Coriander seeds on GST (U/ mg of protein) in Kidney Tissue

Days	Normal	Diabetes	C.Coriander
10 days	0.612667± 0.00491	0.481± 0.001155*	0.331± 0.001155*#
20 days	0.612667± 0.00491	0.462667± 0.00318*	0.749333± 0.001202*#
30 days	0.612667± 0.00491	0.311± 0.002309*	1.297± 0.006506*#

Values indicate mean ± SEM (n=3)

*p<0.05, compared with normal control values, # p<0.05, compared with Diabetic values

Table 5. Effect of Methanolic extract of crude Coriander seeds on Glutathione Reductase (U/ mg of protein) in Kidney Tissue.

Days	Normal	Diabetes	C.Coriander
10 days	0.774333± 0.001453	0.693± 0.003055*	0.202667± 0.000882*#
20 days	0.774333± 0.001453	0.462± 0.000577*	0.322± 0.000577*#
30 days	0.774333± 0.001453	0.323333± 0.001856*	0.463667± 0.001764*#

Values indicate mean ± SEM (n=3)

*p<0.05, compared with normal control values, # p<0.05, compared with Diabetic values

Table 6. Effect of Methanolic extract of crude Coriander seeds on GSH (U/ ml of sample homogenate) in Kidney Tissue

Days	Normal	Diabetes	C.Coriander
10 days	11.56967± 0.024333	10.21667± 0.006667*	5.241± 0.024*#
20 days	11.56967± 0.024333	9.613± 0.024*	5.966± 0.024*#
30 days	11.56967± 0.024333	8.767667± 0.041858*	10.94167± 0.041858*#

Values indicate mean ± SEM (n=3)

*p<0.05, compared with normal control values, # p<0.05, compared with Diabetic values

CONCLUSION

Diabetes mellitus shows its severity through complications that are caused by oxidative stress generated by ROS due to hyperglycemia leading to diabetic nephropathy. The study reveals that crude methanolic *Coriandrum sativum* seeds are effective in lowering blood glucose level and has the potential to alleviate diabetes mellitus related oxidative stress from organs such as the kidney. Thus, it can be concluded that it has both hypoglycemic and antioxidant potential. However, it needs further investigation to identify active components, as this study was performed in a small population group with limited resources.

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Conflict of Interest: The authors declare that there are no conflicts of interest regarding publication or any other activity related to this article.

Ethical Clearance Statement: The Current Research Work Was Ethically Approved by the Institutional Review Board (IRB) of the experiments were designed and conducted as per the current ethical norms and guidelines approved by the Ministry of Social justices and Environment, Government of India.

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