

*Full Length Research Paper*

# Exploring the Therapeutic Benefits of *Curcuma longa* in Streptozotocin-Induced Diabetes in Rats

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Accepted 18 November, 2024

There is increasing evidence that complications related to diabetes are associated with increased oxidative stress. *Curcuma longa* has several biological properties, including antioxidant activity. The protective effect of *Curcuma longa* on streptozotocin (STZ)-induced oxidative stress in various tissues of rats was studied. Adult male albino Wister rats (8 weeks), weighing 195 to 225 g was made diabetic by injecting STZ (65 mg/kg body weight) intraperitoneally. During the whole experimental period, animals were fed with a balanced commercial chow and water ad libitum. Diabetic rats given either water or ethanolic extracts of the active material "curcumin" gained by crushing *Curcuma longa* rhizomes (80 mg/kg body weight) in aqueous suspension daily using an intragastric tube for a period of seven weeks. After this period the levels of oxidative stress parameters and activity of antioxidant enzymes were determined in various tissues. STZ-induced hyperglycemia resulted in increased glucose level, glycosylated haemoglobin in red blood cells and other tissues and altered antioxidant enzyme activities such as AST and ALT. These elevated blood parameters and enzymatic activities induced by hyperglycemia were significantly restored to near normal by oral administration of curcumin once daily for 7 weeks, as compared to untreated rats. There was a significant elevation in the level of liver and kidney malondialdehyde (MDA), while the activities of antioxidant enzymes superoxide dismutase and catalase (SOD and CAT) were significantly decreased in STZ rats which also restored to normal after curcumin treatment. The results obtained indicated that ethanolic extract has more potent protective action than water extract against all hyperglycemic parameters. These biochemical observations showing that feeding curcumin to the diabetic rats controlled oxidative stress by inhibiting the increase in TBARS and protein carbonyls and reversing altered antioxidant enzyme activities without altering the hyperglycemic state in most of the tissues. Curcumin appear to be beneficial in preventing diabetes-induced oxidative stress in rats despite unaltered hyperglycemic status.

**Keywords:** Diabetes mellitus; Streptozotocin; *Curcuma longa*; Therapeutic effects; Rats.

## INTRODUCTION

Hyperglycemia causes the autoxidation of glucose, glycation of proteins, and the activation of polyol metabolism. These changes accelerate generation of reactive oxygen species (ROS) and increases in oxidative chemical modification of lipids, DNA, and proteins in various tissues. Oxidative stress may play an important role in the development of complications in

diabetes such as lens cataracts, nephropathy, and neuropathy. Glycation reactions, especially Maillard reactions, occur in vivo as well as in vitro and are associated with the chronic complications of diabetes mellitus and aging and age-related diseases by increases in oxidative chemical modification of lipids, DNA, and proteins. Diabetes mellitus (type 2) is associated with

increased oxidative stress (McColl *et al.*, 1997). Free radicals are continually produced in the body as the result of normal metabolic processes and interaction with environmental stimuli. Under physiological conditions, a wide range of antioxidant defenses protects against adverse effects of free radical production in vivo (Halliwell and Gutteridge, 1989). Oxidative stress results from an imbalance between radical production and reduced activity of antioxidant defenses or both these phenomena. Hyperglycemia causes release of tissue damaging reactive oxygen species (ROS) balance between radical production and protective antioxidant defense (Signorini *et al.*, 2002; Halliwell and Gutteridge, 1990). It has been proposed that streptozotocin (STZ) acts as a diabetogenic agent owing to its ability to destroy pancreatic  $\beta$ -cells, possibly by a free radical mechanism (Halliwell and Gutteridge, 1994; Simmons, 1984).

The level of lipid peroxidation in cell is controlled by various cellular defense mechanisms consisting of enzymatic and nonenzymatic scavenger systems, the levels of which are altered in diabetes (Wohaieb and Godin, 1987). Moreover, disturbances of

antioxidant defense systems in diabetes were shown: alteration in antioxidant enzyme (Strain, 1991), impaired glutathione metabolism (Mc Lennan *et al.*, 1991) and decreased ascorbic acid (Jennings *et al.*, 1987).

In recent years, considerable focus has been given to an intensive search for novel type of antioxidants from numerous plant materials (Srivastava *et al.*, 1993). Management of diabetes without any side effects is still a challenge to the medical system. There is an increasing demand by patients to use the natural product with antidiabetic activity, because insulin and oral hypoglycemic drugs possess undesirable side effects (Kameswara Rao and Appa Rao, 2001). Plants with antidiabetic activities provide useful sources for the development of drugs in the treatment of diabetes mellitus. Phytochemicals isolated from plant source are used for the prevention and treatment of cancer, heart disease, diabetes and high blood pressure etc. (Mary *et al.*, 2002).

Curcumin (diferuloylmethane) is a naturally occurring yellow pigment isolated from the rhizomes of the plant *Curcuma longa* (Linn) found in south Asia (Lodha and Baggha, 2000) and is a potent antioxidant agent and free radical scavenger (Fujisawa *et al.*, 2004). Along with being an inhibitor of lipid peroxidation (Sreejayan and Rao, 1994), it is also an inhibitor of nitric oxide synthase (NOS) overexpression (Pan *et al.*, 2000) and of nuclear factor kappa B activation (Weber *et al.*, 2006). The efficacy of curcumin has been widely observed in reducing various diabetic secondary complications such as diabetic nephropathy/renal lesions (Sharma *et al.*, 2006), retinopathy (Kowluru and Kanwar, 2007), wound healing (Panchatcharam *et al.*, 2006), and reduction of

advanced glycation end products (Sajithal *et al.*, 1998). Its potential as a hypoglycemic agent has also been studied in animals (Pari and Murugan, 2005; Hussain, 2002) and humans (Srinivasan, 1972) with conflicting results. Furthermore, although many aspects of curcumin-induced cytoprotection are studied, its efficacy in protecting against streptozotocin-induced free radical-mediated damage has not been demonstrated so far. We hypothesized that curcumin may protect cells against streptozotocin-induced oxidative stress and resulting tissue damage and organ dysfunction. Logically, curcumin would impart some protection against oxidative damage to different cells, but it would be of interest to investigate the mode of curcumin-induced cytoprotection. In this study, the protective action of curcumin on streptozotocin-induced diabetes mellitus in rats was studied.

## MATERIAL AND METHODS

### Animals

Eight week male albino Wister rats weighing (195- 225g) were used in this study. The animals were obtained from the animal experimental unit of Faculty of Agriculture, Alexandria University, Egypt. The rats were housed in well-aerated individual cages and maintained in a temperature-controlled room ( $27 \pm 2^\circ \text{C}$ ) and humidity 45-56% with 12 h light: 12 h dark cycle for one week before and during the experiments. Animals were provided with standard commercial chow and water *ad libitum*. The care and use of all experimental animals complied with relevant animal welfare laws. Streptozotocin, all reagents and solvents used in this study were purchased from Sigma-Aldrich Corp., St Luis, MO, USA but Curcumin powder is a naturally occurring yellow pigment isolated from the rhizomes of the plant *Curcuma longa* which obtained from the local market at Alexandria, Egypt. Type 2 diabetes mellitus was induced in overnight fasted rats by a single intraperitoneal injection (i.p.) of 65 mg/kg body weight Streptozotocin "STZ" (Masiello *et al.*, 1998). STZ was dissolved in citrate buffer (pH 4.5). Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection. The animals with blood glucose concentration more than 200 mg/dl will be used for the study.

### Preparation of curcumin extract

The dried powder was defatted with petroleum ether (100 g in 200 ml ether). The defatted material was extracted with 95% ethanol and then vacuum dried. One part of powder was extracted in boiling water and then filtered

and vacuum dried.

## Experimental design

In the experiment, a total of 40 rats (30 diabetic surviving rats, 10 normal rats) were used. The rats were divided into four groups of 10 each. The experimental period was seven weeks beginning after the induction of STZ diabetes. Group I: normal untreated rats. Group II: diabetic control rats (STZ group). Group III and IV: were diabetic rats given either aqueous or ethanolic extracts of curcumin (80 mg/kg body weight) in aqueous suspension daily using an intragastric tube (Arun and Nalini, 2002) for seven weeks. At the end of experimental period, the rats were deprived of food overnight and blood was collected in a tube containing potassium oxalate and sodium fluoride for the estimation of blood glucose, haemoglobin and glycosylated haemoglobin. Plasma was separated for the assay of insulin. The liver and kidney were also dissected out and were divided into two parts. The first was kept at  $-20^{\circ}\text{C}$  in ice-cold containers for biochemical analysis, while the second part was used for histopathological studies.

## Serum biochemical assay

Serum enzymes aspartate aminotransferase (AST) and serum glutamate pyruvate transaminase (ALT) were determined according to (Reitman and Frankel, 1957).

## Estimation of MDA, SOD, CAT in liver and kidney tissues

Liver and kidney samples were dissected out and washed immediately with ice cold saline to remove as much blood as possible. Each tested tissue homogenates (5% w/v) were prepared in cold 50mM potassium phosphate buffer (pH 7.4) using glass homogenizer in ice. The cell debris was removed by centrifugation at 5000 rpm for 15 at  $40^{\circ}\text{C}$  using refrigerated centrifuge. The supernatant was used for the estimation of malondialdehyde (MDA) (Yagi and Rastogi, 1979), superoxide dismutase (SOD) (Kakkar *et al.*, 1972) and catalase (CAT) (Smna, 1972) levels.

## Statistical analysis

Statistical analysis was performed on a PC using SPSS, V.13, (special package for social sciences). Data are presented as arithmetic mean  $\pm$  S.D., The difference among means has been analyzed by one way ANOVA followed by student *t* test. A value of  $P < 0.05$  was

considered as statistically significant.

## RESULTS

The results of protective effect of water or ethanol extracts of curcumin on streptozotocin-induced diabetic rats (STZ) are shown in Table 1. In the STZ group, serum AST and ALT were significantly increased as compared to control group ( $p < 0.001$ ). The elevated activities of serum AST and ALT were significantly reduced in the animal groups treated with either water or ethanolic extracts. Treatment with ethanolic extract showed significantly more activity ( $P < 0.001$ ) than with water extract. Thus, the ethanol extract treated group was superior to the water extract. Results obtained revealed an increase in the level of liver and kidney MDA in STZ rats compared to control group. Treatment with extracts significantly prevented this raise in levels. The activities of SOD and CAT were significantly reduced in the STZ group, while they were significantly elevated near the normal values in the groups pretreated with either extracts. Ethanolic extract has been shown to be more protective than water extract.

The levels of blood glucose, total haemoglobin, glycosylated haemoglobin and plasma insulin of different experimental groups were shown in Figure 1. There was a significant elevation in blood glucose level, whereas plasma insulin levels decreased significantly in diabetic rats (STZ groups), compared with normal rats. Administration of water or ethanolic curcumin extracts tended to bring blood glucose and plasma insulin towards normal. The diabetic control rats showed a significant decrease in the level of total haemoglobin and significant increase in the level of glycosylated haemoglobin. No significant difference between liver and kidney parameters were found in all studied groups. Oral administration of water and ethanolic curcumin extracts to diabetic rats significantly restored total haemoglobin and glycosylated haemoglobin levels. The effect of ethanolic extract was more prominent when compared with water extract.

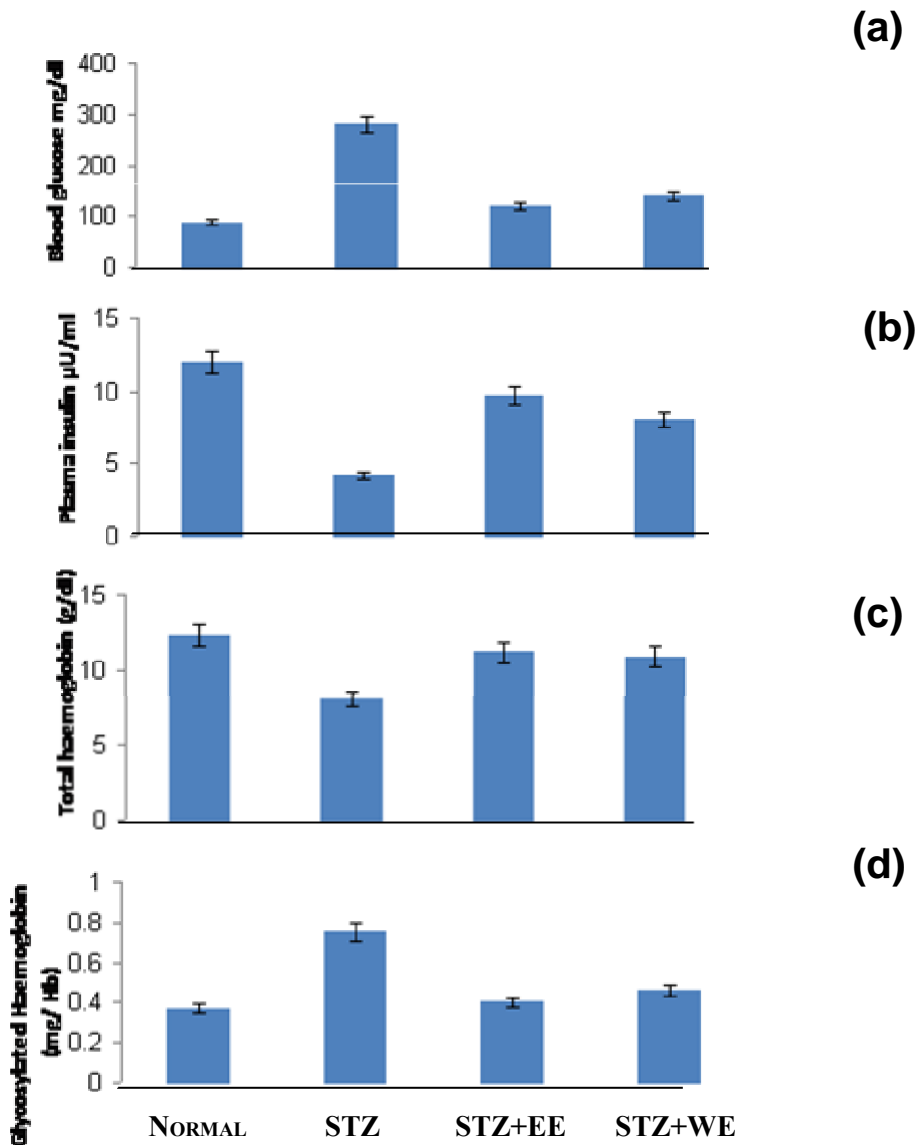
## DISCUSSION

Although many reports confirm the efficacy of *Curcuma longa* in cytoprotection of various cell lines against toxicity (Grandjean-Laquerriere *et al.*, 2002; Yadav *et al.*, 2005; Masamune *et al.*, 2006) few studies report the efficacy of curcumin in mitigating streptozotocin-induced damage to liver and kidney. Most diabetes related studies using curcumin show the efficacy of oral administration at various doses for reduction of secondary complications in streptozotocin-induced diabetic animals (Babu and Srinivasan, 1995; Nishizono *et al.*, 2000; Srinivasan *et*

**Table 1.** Antioxidant enzyme activities of liver and kidney of rat; superoxide dismutase (SOD), catalase (CAT), lipid peroxide product or Malendialdlyde (MDA) and serum aminotransferase enzymes (ALT and AST) of all studied groups (Mean  $\pm$  SD).

Animal group parameter	Normal control group		STZ group		WE Curcumin + STZ		EE Curcumin +STZ	
	Liver	Kidney	Liver	Kidney	Liver	Kidney	Liver	Kidney
Serum ALT(IU/ml)	37.9 $\pm$ 4.49	38.1 $\pm$ 4.44	78.8 $\pm$ 7.91	77.2 $\pm$ 8.88	46.8 $\pm$ 6.99	47.0 $\pm$ 7.09	40.9 $\pm$ 4.99	41.2 $\pm$ 4.67
P <sub>1</sub> Value	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001
P <sub>2</sub> Value	-	-	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.05	P $\leq$ 0.05
P <sub>3</sub> Value	-	-	-	-	-	-	P $\leq$ 0.05	P $\leq$ 0.05
Serum AST(IU/ml)	41.8 $\pm$ 4.55	42.1 $\pm$ 4.49	87.7 $\pm$ 8.01	86.2 $\pm$ 7.99	49.8 $\pm$ 6.69	50.1 $\pm$ 7.007	45.8 $\pm$ 4.72	44.9 $\pm$ 4.32
P <sub>1</sub> Value	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001
P <sub>2</sub> Value	-	-	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.05	P $\leq$ 0.05
P <sub>3</sub> Value	-	-	-	-	-	-	P $\leq$ 0.05	P $\leq$ 0.05
MDA (mmol/mg protein)	2.34 $\pm$ 0.16	2.36 $\pm$ 0.18	6.22 $\pm$ 0.55	6.29 $\pm$ 0.49	2.99 $\pm$ 0.23	3.02 $\pm$ 0.31	2.57 $\pm$ 0.32	2.62 $\pm$ 0.47
P <sub>1</sub> Value	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.001
P <sub>2</sub> Value	-	-	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.01	P $\leq$ 0.01
P <sub>3</sub> Value	-	-	-	-	-	-	P $\leq$ 0.05	P $\leq$ 0.05
SOD (MU/mg protein)	222.3 $\pm$ 14.1	225.1 $\pm$ 13.8	107.9 $\pm$ 21.7	111.2 $\pm$ 2704	214.3 $\pm$ 23.8	208.1 $\pm$ 27.7	188.7 $\pm$ 23.3	189.9 $\pm$ 24.
P <sub>1</sub> Value	-	-	P $\leq$ 0.001	P $\leq$ 0.001	N.S.	N.S.	P $\leq$ 0.001	P $\leq$ 0.001
P <sub>2</sub> Value	-	-	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.01	P $\leq$ 0.01
P <sub>3</sub> Value	-	-	-	-	-	-	P $\leq$ 0.01	P $\leq$ 0.01
CAT(n mol/min/mg protein)	9779.1 $\pm$ 122.1	9769.9 $\pm$ 142.1	2196.8 $\pm$ 139.1	2322.4 $\pm$ 144,8	8322.4 $\pm$ 144.7	8401.7 $\pm$ 137.7	4011.1 $\pm$ 177.6	4032.7 $\pm$ 146.4
P <sub>1</sub> Value	-	-	P $\leq$ 0.001	P $\leq$ 0.001	N.S.	N.S.	P $\leq$ 0.001	P $\leq$ 0.001
P <sub>2</sub> Value	-	-	-	-	P $\leq$ 0.001	P $\leq$ 0.001	P $\leq$ 0.01	P $\leq$ 0.01
P <sub>3</sub> Value	-	-	-	-	-	-	P $\leq$ 0.05	P $\leq$ 0.05

STZ: streptozotocin, WE: Water extract, EE: Ethanol extract, P1: comparison to normal control, P2: comparison to STZ group, P3: water E versus ethanol E, N.S.= not significant.



**Figure 1.** Effect of *Curcuma longa* on (a): The levels of blood glucose, (b): Plasma insulin, (c): Total haemoglobin and (d): Glycosylated haemoglobin in normal and experimental rats: STZ, Diabetic control; STZ+EE, Diabetic treated with ethanolic *Curcuma longa* extract; STZ+WE, Diabetic treated with water *Curcuma longa* extract. Values are given as means for 10 rats in each group  $\pm$  SD.

*al.*, 2003). However, almost no reports exist that show the prophylactic importance of curcumin as a diabetic protective agent. Our findings here contribute towards retention of type 2 diabetes which is the most prevalent and serious metabolic disease affecting people all over the world and cause secondary complications by scavenging free radicals that cause pathological changes and dysfunction of various organs.

Glycosylated haemoglobin was significantly increased in diabetic control rats and this increase is directly proportional to fasting blood glucose (Koenig *et al.*,

1976). Anemia is much more common disease in type 2 diabetic patients, contributing to the pathogenesis of diabetic complications. In the present study, the decreased concentration of haemoglobin indicates the anemia in STZ diabetic rats, in as much as during diabetes, the excess glucose transport in the blood reacts with haemoglobin to form glycosylated haemoglobin. Free radicals react with lipids and causes peroxidative changes that result in enhanced lipid peroxidation (Girotti, 1985). In our study, the lipid peroxidation markers (TBARS) were elevated in erythrocytes of diabetic rats as reported earlier

(Zhang and Swaan, 1999). The increase in lipid peroxidation might be a reflection of decrease in enzymatic and nonenzymatic antioxidants of defense systems.

Serum AST and ALT activities were used as a marker of tissue damage. Diabetes mellitus by STZ produces an experimental damage due to its toxic metabolite (Zhang and Swaan, 1999). The toxic metabolite free radical is produced by cytochrome p450 which further reacts with oxygen to produce trichloromethyl peroxy radicals. These radicals bind covalently with the macromolecule and cause peroxidative degradation of lipid membranes of the liver and kidney. The reduction of AST and ALT activities by the extracts is an indication of repair of tissue damage induced by diabetes complications. This is in agreement with Rekka *et al.* (1992), who found that serum transaminases returned to normal activities with the healing of tissue parenchyma and regeneration of hepatocytes and renal tissues. The ethanolic extract induced suppression of increased ALT and AST activities. Thus, administration of ethanolic or aqueous extracts of curcumin revealed protective activity against the toxic metabolites of diabetes, which is also supported by histological studies.

Treatment with curcumin brought back lipid peroxidation markers to near normal levels, which could be as a result of improved glycemic control and antioxidants status. We have reported that curcumin has significant glucose reducing property in STZ diabetic rats. Increased lipid peroxidation under diabetic conditions can be due to increased oxidative stress in the cell as a result of depletion of antioxidant scavenger systems. Associated with the changes in lipid peroxidation the diabetic tissues showed decreased activities of key antioxidants SOD and CAT and increase MDA which play an important role in scavenging the toxic intermediate of incomplete oxidation. SOD and CAT are the two major scavenging enzymes that remove toxic free radicals in vivo. Previous studies have reported that the activity of SOD is low in diabetes mellitus (Feillet- Coudray *et al.*, 1999). A decrease in the activity of these antioxidants can lead to an excess availability of superoxide anion  $O_2^{\bullet-}$  (free radical anion) and hydrogen peroxide in biological systems, which intern generate hydroxyl radicals, resulting in initiation and propagation of lipid peroxidation (Kumuhekar and Katyane, 1992). The result of increased activities of SOD and CAT suggest that curcumin contains a free radical scavenging activity, which could exert a beneficial effect against pathological alterations caused by the presence of  $O_2^{\bullet-}$  and  $OH^{\bullet}$ . The increased activity of SOD accelerates dismutaion of  $O_2^{\bullet-}$  to hydrogen peroxide ( $H_2O_2$ ) which is removed by CAT (Aebi, 1984). This action could involve mechanisms related to scavenging activity of curcumin. Lipid peroxidation is accelerated when free radicals are formed as the results of losing a hydrogen atom from the double

bond in the structure of unsaturated fatty acids. The free radical scavenging activity of water or ethanolic extracts of curcumin was evaluated.

Scavenging of free radicals is one of the major antioxidation mechanisms to inhibit the chain reaction of lipid peroxidation. Reduced lipid peroxidation was revealed by a significant decrease in MDA level in groups pretreated with water or ethanol extracts, simultaneously with a significant elevation in SOD and CAT activities. The present study revealed that SOD and CAT activities decreased in STZ animals, which may be due to altered antioxidant status. This is in accordance with results that indicated a decreased CAT in STZ animals may be due to the utilization of antioxidant enzymes in the removal of released  $H_2O_2$  released (Blum and Fridovich, 1985; Cerutti *et al.*, 1994). SOD and CAT activities increased significantly in the treated group versus the untreated animals.

In conclusion, the present investigation shows that curcumin extracts of *Curcuma longa* possesses antioxidant effect that may contribute to its protective action against lipid peroxidation and enhancing effect on cellular antioxidant defense. This activity contributes to the protection against oxidative damage in STZ induced diabetes. Further study will be carried out to identify the types of phenolic compounds present and to test for antitumor activity.

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