Efficacy of *Lepidium Sativum* to act as an anti-diabetic agent

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ABSTRACT

Objective: *Lepidium sativum*, commonly known as *chandrashoor* in India, has been used in the Indian traditional medicine system for the treatment of various diseases. The present study was undertaken to investigate the hypoglycemic effect of *Lepidium sativum* in normal and streptozotocin-induced diabetic rats.

Materials and methods: Thirty (30) adult male Wistar rats weighing 157±51g were randomly assigned to five groups of six rats each as Normal control, Diabetic control, Diabetics supplemented with *Lepidium sativum* extract, Diabetics treated with insulin, and Normal rats supplemented with *Lepidium sativum*. All rats were fed with a normal laboratory diet, nutrient rich pellets, and had free access to drinking water. The rats were injected with streptozotocin at a dose of 45 mg/kg body weight intraperitoneally to induce diabetes. The extracts were then given orally to different groups of rats at a dose of 20mg/kg body weight for 16 days. Thereafter, the rats were sacrificed, and blood samples collected by cardiac puncture were used for the determination of Glucose, Creatinine, Alkaline Phosphatase, Cholesterol, Malondialdehyde level, % DPPH, and FRAP content.

Results: Administration of lepidium extract showed a significant reduction in glucose, creatinine, and alkaline phosphatase levels. Elevated cholesterol level was restored approximately to normal; a significant decrease in malondialdehyde levels was also observed compared to diabetic controls.

Conclusion: *Lepidium sativum* extract shows efficacy in the prevention and management of diabetes mellitus and its related complications.

Keywords: *Lepidium sativum*, diabetes, insulin, streptozotocin, oxidative stress, cholesterol

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both [1]. DM is characterized by hyperglycemia, which usually culminates in several late complications: micro-vascular complications like retinopathy, nephropathy, and peripheral neuropathy; and an increased risk of cardiovascular disease [2].

The International Diabetes Federation [3] estimated the incidence of diabetes projection for the year 2015 to be 419 million adults and is expected to reach 642 million by 2040. Diabetes in all its forms imposes unacceptably high human, social and economic costs on countries at all income levels [4]. Modern and orthodox medicines, currently available for the management and treatment of diabetes mellitus, result in serious side effects such as hepatotoxicity, abdominal pain, flatulence, diarrhea, and hypoglycemia [5, 6]. Due to this fact, researchers are continuously trying to find antidiabetic agents with high efficacy and low side effects for the management and treatment of diabetes. The treatment of diabetes mellitus with insulin and sulphonylureas comes with the underlying consequence of hypoglycemic shock, which might result in fatality [7]. For the reasons stated above, the use of traditional medicine based on plants/plant products is very common in several parts of the world. The WHO has listed 21,000 plants [8] that are used for medicinal purposes around the world, and there are about 800 plants that have been reported to show antidiabetic potential [9].

Lepidium sativum L. (LS) is a fast-growing, edible herb [10] of the Brassicaceae family [11]. The seeds have many biological activities and are used in folk remedies. The seeds are thermogenic, depurative, aphrodisiac, ophthalmic, diuretic, abortive, and contraceptive in nature [12, 13].

Lepidium sativum seeds are rich sources of phytochemicals including phenolic compounds, terpenoids, alkaloids, flavonoids, and organosulfur compounds. It also contains phytosterols and their derivatives, which are known to possess antioxidant potential, anti-cancer, anti-inflammatory, and cardioprotective activity [14-16]. The oil of the L. sativum seeds is rich in alpha linolenic acid, and contains an ideal ratio of omega-3 fatty acids and omega-6 fatty acids, which shows cardioprotective and chemopreventive effects [17-19].

Aqueous LS extract has been shown to exhibit hypoglycemic activity in diabetic rats [20]. The present study was carried out in order to evaluate the hypoglycemic effect of aqueous LS extract in normal and streptozotocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS

Plant Material and Preparation of Extract

Lepidium sativum L. seeds were collected from a local market of Allahabad, U.P., India. The seeds were then washed thoroughly under running tap water and then with distilled water; and shade dried and ground into powder. The aqueous extract was prepared in a standardized manner by boiling 1 g of dried powdered LS seeds in 100 ml of distilled water for 10 min. It was further left for 15 min to infuse, then cooled and filtered. The filtrate was lyophilized and the desired dose (milligram of lyophilized aqueous LS extract per kilogram of body weight) was then prepared and re-constituted in 10 ml of distilled water per kilogram of body weight just before oral administration. The aqueous extract dose was 20 mg/kg of body weight daily by oral administration [20].

Experimental Design

The experiment was carried out on 30 male Wistar rats (4 ± 0.5 months old) with an average body weight of 157 ± 51g. They were housed in a temperature-controlled facility (25 ± 5 °C) with a 12 h light–dark cycle for at least 1 week. All rats were fed with a normal laboratory diet, nutrient rich pellets containing total energy as fat, protein and carbohydrates, and had free access to drinking water. After the stabilization period of one week, the rats were randomly divided into five groups, containing six animals in each group. *Group I: Normal* Control (NC) receiving no treatment/supplementation; *Group II:* Diabetic control: rats were injected a single dose of streptozotocin intraperitoneally. *Group III:* Diabetic-induced rats were administered insulin. *Group IV*: Diabetic-induced rats were administered LS extract via gavage technique (oral route) at 20 mg/kg of body weight/day for 16 days. *Group V:* Normal rats were given only LS extract for 16 consecutive days.

Diabetes was induced by intraperitoneal injection of streptozotocin dissolved in 0.1M cold sodium citrate buffer, pH 4.5, at a dose of 45mg/kg of body weight. After 96 hours, diabetes was confirmed by the determination of fasting blood glucose level with the help of a glucometer (Glucocare TM ultima). Rats with blood glucose of 241-275 mg/dL were considered diabetic and included in the study. All treatments were carried out up to 16 days. Animals from the first group were simultaneously administered water until 16 days.

Biochemical Assays

After the end of the treatment period, the rats were sacrificed under light anesthesia. Blood samples were collected by cardiac puncture into 10 units / ml heparin rinsed anticoagulant syringes, and then red blood cells were pelleted by centrifugation at 800 *g* for

10 min at 4°C. After the removal of plasma (immediately frozen at -80°C until use for biochemical assays), buffy coat, and the upper 15% of packed red blood cells (PRBCs), the RBCs were washed twice with cold phosphate buffered saline (PBS) (0.9% NaCl and 10 mmolL^{-1} Na$_2$HPO$_4$; pH 7.4) and then used for the experiment.

Lipid profile (ALP, Cholesterol) and creatinine were measured using reagent kits from Erba Diagnostics, Mannheim, Germany. Blood glucose values were determined using an Accu-Check Active Glucometer (Roche Diagnostics, Mannheim, Germany). Plasma lipid peroxidation (MDA) was measured according to the method of Esterbauerand Cheeseman [21], with a slight modification. The total antioxidant potential of the plasma was determined using a modification of the ferric reducing ability of plasma (FRAP) assay, as reported by Benzie and Strain [22].

Statistical Analysis

All values are expressed as mean ±SD. Statistical analysis was conducted using Student's *t*-test and the Mann-Whitney *U* test by usingPRISM version 5.01 software. A level of p<0.05 was considered statistically significant.

RESULTS

In this study, the anti-hyperglycemic effect of *Lepidium sativum* (LS) aqueous extract was investigated using streptozotocin-induced diabetic rats.

After 16 days of oral administration of aqueous LS extracts, significant reduction in blood glucose levels was observed in the streptozotocin-induced diabetic rats. Blood glucose was significantly elevated ($P < 0.05$) in diabetic rats compared with normal control rats (Figure 1). In diabetic rats, oral administration of aqueous LS extract (20 mg/kg of body weight) lowered blood glucose significantly ($P < 0.05$).

Cholesterol level was found to be increased significantly ($P < 0.05$) in diabetic rats compared with the normal control rats. A significant decrease was observed after the administration of LS extract in diabetic rats (Figure 2).

In the present study, the creatinine level increased significantly (p< 0.05) in diabetic rats when compared with the normal control rats. Oral administration of aqueous extract of LS offered a significant decrease in the creatinine level compared with diabetic rats (Figure 3).

Alkaline phosphatase was shown to be present in all body tissues with higher amounts in the liver, bile ducts, and bone. Elevation of alkaline phosphatase in diabetic conditions is an intrinsic feature of diabetes [23], which corroborates the findings of this work. The induction of diabetes with streptozotocin leads to the elevation of alkaline phosphatase in the diabetic group rats. Treatment of rats in the diabetic group with LS significantly decreased alkaline phosphatase (p<0.05) when compared with rats of the diabetic group (Figure 4).
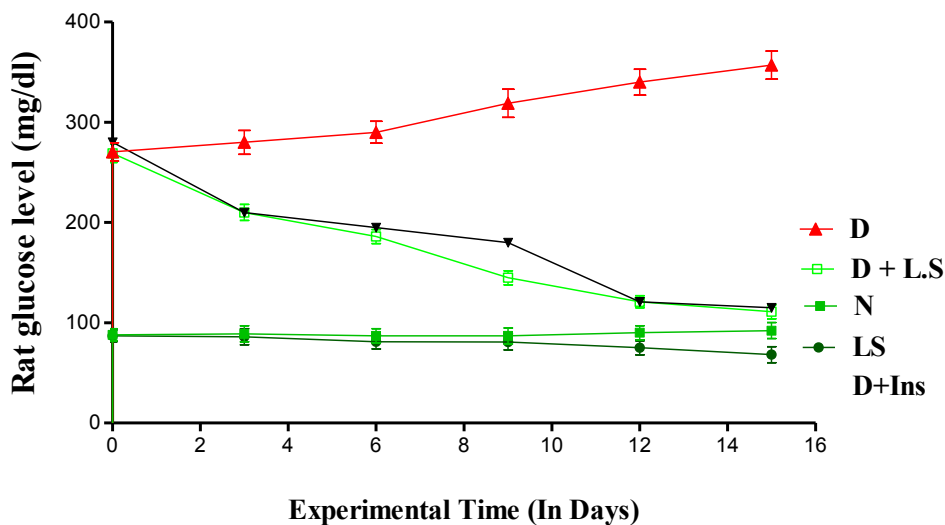

Figure 1. Effect of aqueous extract of *Lepidium sativum* on blood glucose levels of STZ - induced diabetic rats
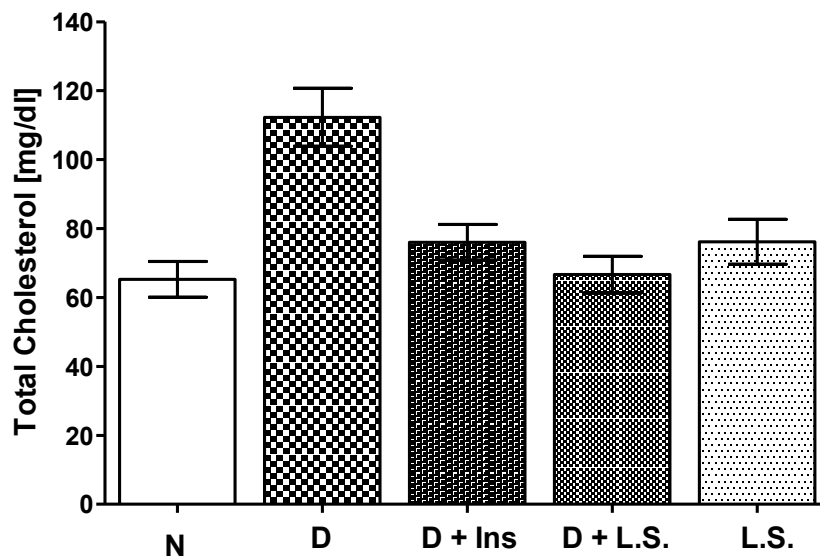
Figure 2. Effect of aqueous extract of *Lepidium sativum* supplementation on plasma cholesterol levels of STZ - induced diabetic rats
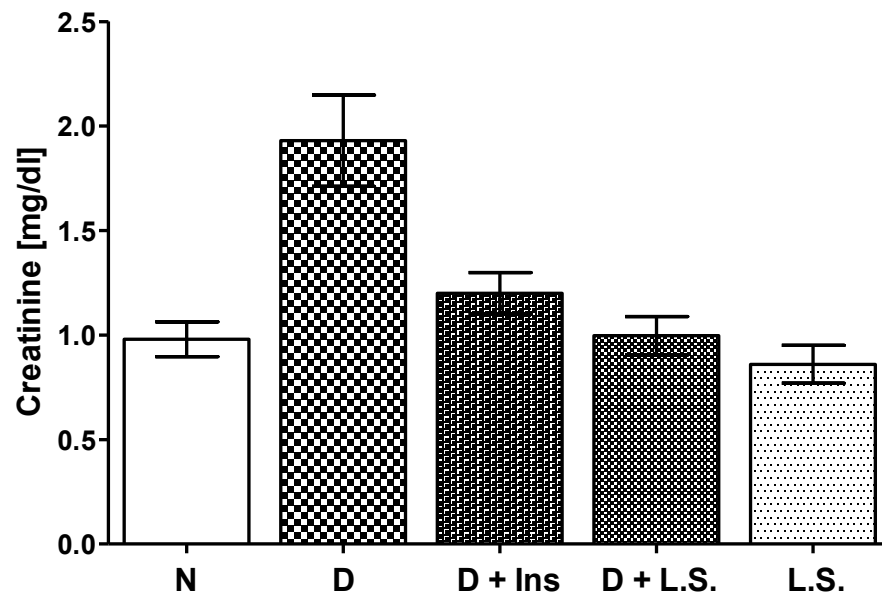

Figure 3. Effect of aqueous extract of *Lepidium sativum* supplementation on plasma creatinine levels of STZ - induced diabetic rats
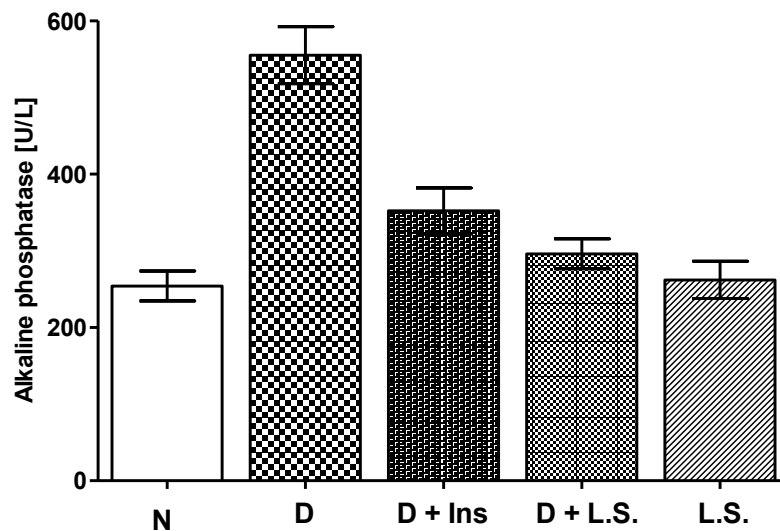
Figure 4. Effect of aqueous extract of *Lepidium sativum* supplementation on plasma alkaline phosphatase levels of STZ - induced diabetic rats

In the present study, it was observed that mean value of lipid peroxide (MDA) and DPPH% was significantly increased in the diabetic group compared with the control, which significantly decreased with the administration of aqueous LS extract (Figures 5 and 7).
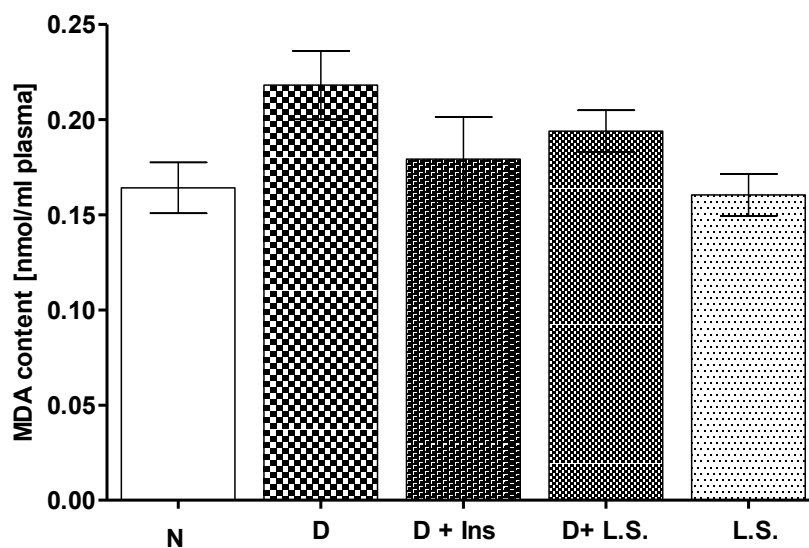

Figure 5. Effect of aqueous extract of *Lepidium sativum* supplementation on MDA levels of STZ - induced diabetic rats

Figure 6 depicts a significant decrease in FRAP levels in the diabetic group compared with the controls. Oral administration of *Lepidium sativum* extract restored the FRAP level in the diabetic group close to normal.
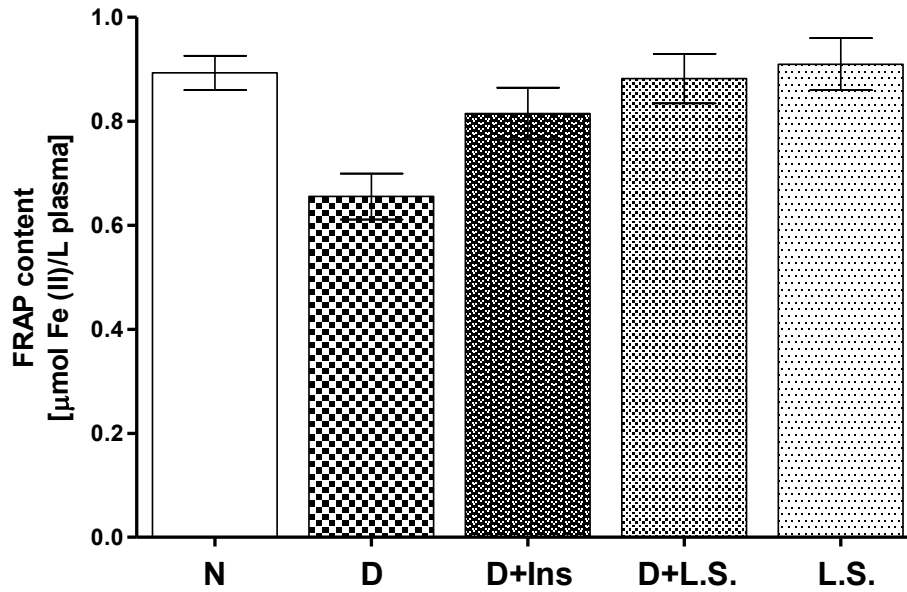
Figure 6. Effect of aqueous extract of *Lepidium sativum* supplementation on FRAP levels of STZ - induced diabetic rats
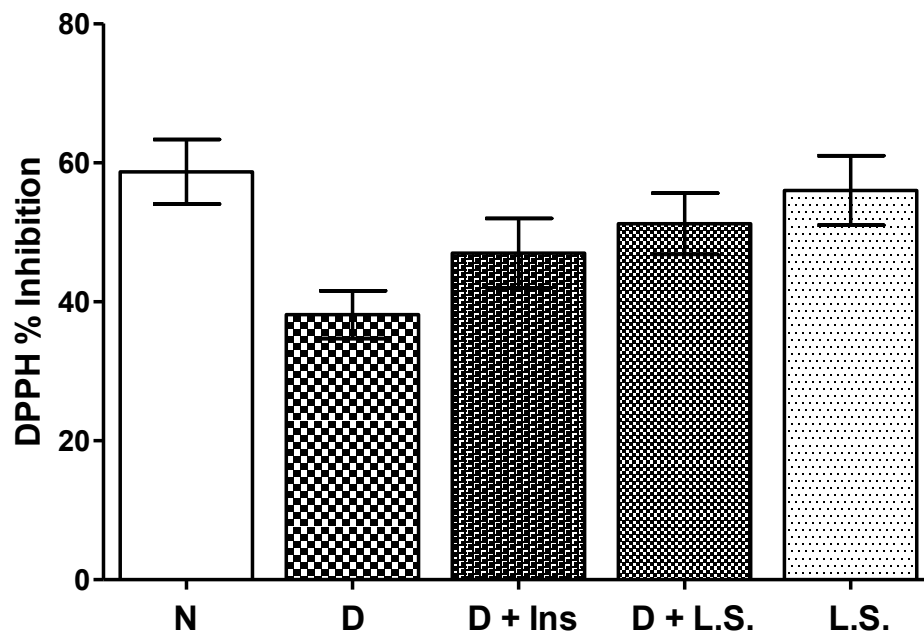

Figure 7. Effect of aqueous extract of *Lepidium sativum* supplementation on DPPH % inhibition of STZ - induced diabetic rats

DISCUSSION

Insulin and sulphonylureas, are used most commonly for the treatment of diabetes, which may increase the risk of hypoglycemia and lead to fatal consequences. Hence, there is a need to search for safer and more effective alternatives [7].

The decrease in blood sugar levels after *Lepidium sativum* administration may be due to the presence of linolenic acids. The presence of oleic acids

(30.6 wt %) and linolenic acids (29.3 wt %) had been reported in LS oil [23]. LS seed oil contains high concentrations of tocopherols. However, the primary phytosterols reported in LS are sitosterol, campesterol, and avenasterol [24]. The glucose lowering action might also be the result of LS extract stimulating the surviving β-cells of islets of Langerhans to release more insulin [25]. Flavonoids and glycosides have been demonstrated to be able to act and stimulate pancreatic β-cells to secrete insulin and enhance glucose metabolism [26].

Flavonoids, coumarins, sulphur glycosides, triterpenes, sterols, and various imidazole alkaloids are some of the phytochemicals present in LS [27]; with lepidine and semilepidine being the major alkaloids [28]. These alkaloids have been demonstrated to possess hypoglycemic activity [29-31]. Aqueous LS extract has been reported to affect glucose homeostasis by inhibiting endogenous glucose production in the liver [32], inhibiting renal glucose reabsorption through the alteration of renal glucose transporter (SLGT1) expression in the kidneys [33], increasing both glucose uptake [34] and glucose intracellular metabolism [35, 36] in the muscle and adipose tissues. Finally, the inhibition of intestinal glucose absorption could also be involved in this observed hypoglycemic activity of LS [37].

Lipid profile results are in agreement with the results obtained by [38], who reported that the lipid profile of hypercholesterolemic animals was significantly higher than control rats for total lipid, total cholesterol, triglyceride, LDL-C and VLDL-C, while only HDL-C was significantly lower in hypercholesterolemic rats than in control rats [24]. Serum cholesterol and triglyceride levels are also strongly related to the degree of diabetic control in rats. The increased total cholesterol, triglyceride and LDL-cholesterol levels observed in diabetic rats may be the result of impaired liver function caused by damage done by STZ, which acts either directly or indirectly by enhancing the serum glucose level [39].

Yadav et al, [40] showed that protective and curative treatment of ethanolic extract of LS seeds with cisplatin significantly reduced the level of urea and creatinine that indicates an increased glomerular filtration rate (GFR). Indeed, in people with diabetes, GFR is usually less than half of normal [41]. The increased urea and creatinine levels suggest the reduction of the glomerular filtration rate [42].

STZ treatments play a significant role in the alteration of liver functions, because the activity of aspartate aminotransferase (AST) and alanine transaminase (ALT) was significantly higher than those of normal values [43]. In diabetic rats, the activity of serum ALP was significantly increased by 72.31% from normal levels; therefore, the increase in the activity of ALP in serum is mainly due to the leakage of these

enzymes from the liver cytosol into the blood stream [44], which is an indication of the hepatotoxic effect of streptozotocin. Administration of LS extract to diabetic rats in this study significantly reduced ALP activity towards normal values.

Sakran et al. [45] observed a reduction in paracetamol-induced hepatotoxicity in male rats and found that 5,6-dimethoxy-2', 3'-methylenedioxy-7-C-β-d-gluco-pyranosyl isoflavone, isolated from the seeds of *Lepidium sativum* L. was effective in reducing the damage and toxicity effects on liver cells with a significant improvement of total antioxidant capacity and normalizing the levels of liver enzymes GSH, SOD, GPX, GST and CAT compared with the control group.

The reducing capacity of *Lepidium sativum* seed extracts can be used as a significant indicator of its potential antioxidant activity [46]. The result reveals that *Lepidium sativum* is a rich source for phyto-constituents like phenolic compounds, vitamin E, and terpenoids, and can be used as a potent antioxidant and antilipidemic agent [47].

Diabetic complications develop with increased activity of free radical-induced lipid peroxidation and accumulation of lipid peroxidation products. Free radicals react with polyunsaturated fatty acids (PUFA) to form peroxides, thus degrading lipids and releasing malondialdehyde (MDA), which is a stable product of lipid peroxidation, and measured as an index of lipid peroxidation.

Measuring total plasma antioxidant capacity using the FRAP method is a guide to knowing the antioxidant status, which is often low in diabetics. The biological system has a natural mechanism to counteract the effect of reactive oxygen species (ROS) thereby preventing oxidative damage to body cells. Oxidative stress in diabetes coexists with a reduction in antioxidant power [48]. The natural antioxidant defense mechanism of the biological system includes the enzymes catalase, glutathione peroxidase, superoxide dismutase; biomolecules like albumin and ferritin; and some other molecules such as ascorbic acid, β carotene, GSH, uric acid, and bilirubin. The total endogenous antioxidants and ones consumed from food sources give the total antioxidant capacity of the biological system. FRAP gives the total antioxidant capacity in the biological system and is a good indicator of the body's ability to protect itself from ROS [49]. This experimental work indicates that FRAP values in the diabetic control group was significantly lower compared with the normal control group. The administration of LS extract increased FRAP values, as noticed in the treated groups. This might be as a result of LS extract containing β carotene and ascorbic acid, which might have contributed to the total antioxidant capacity as given by FRAP.

Al-Sheddi et al. (2016) [50] observed that *Lepidium sativum* extract (LSE) at 25 µg/ml

concentration significantly inhibited the induction of ROS generation (45%) and lipid peroxidation (56%), and increased the mitochondrial membrane potential (55%) and GSH levels (46%). The study suggests the cytoprotective and antioxidative effects of LSE against H_2O_2-induced toxicity in HepG2.

CONCLUSION

By means of regulating the plasma redox balance, *Lepidium sativum* seeds have been observed to reduce the complications of diabetes developed due to oxidative stress/ free radical accumulation. LS seed extract has also been found effective in regulating blood glucose, plasma creatinine, and plasma alkaline phosphatase levels, thereby showing improved renal function and depicting hepatoprotective potential in LS. Maintaining the lipid profile in the normal range and reducing the increased levels of plasma MDA showed the anti-lipid peroxidation and cardioprotective action of LS. Our findings provide a scientific validation of the use of *Lepidium sativum* as an adjunct therapy in diabetes.

Conflicts of interest
Authors declare no conflicts of interest.

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