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Biomarkers of Diabetes Associated Oxidative Stress in Liver and Pancreas of Diabetic Mice after Administration of *Lepidium Sativum* Seed Extract

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Abstract: Many phyto constituents like alkaloid, steroid, riboflavin, saponine have been recommended in the alterative system of medicine for the diabetes mellitus. Current research is now directed towards finding naturally occurring anti diabetic properties from plant origin. *Lepidium sativum* is an important herbal plant and its leaves and seeds have been used in various ailments and as a health tonic. The purpose of this study was to examine the anti-lipofuscinogenic activity of *Lepidium sativum* seed extract (LSE). For present study adult albino male mice (*Mus musculus* L) were divided into three group's viz. i. Control Group: male mice were given intraperitoneal injection of 0.5ml citrate buffer pH 4.5. ii. Diabetic Group- Mice were fed high fat diet (HFD) for two weeks and then injected with multi low dose of STZ (40mg/kg body weight) intraperitoneally (IP); in citrate buffer; pH 4.5. iii. Recovery group- Diabetic mice were given LSE (at a dose 200mg/kg body wt., dissolved in 0.5ml distilled water) orally for 28 days. After completion of treatment body weight, pancreas and liver weight, level of oxidative stress marker i.e. lipid peroxidation and fluorescence was studied. Result showed decrease in body weight and gland weight in diabetic group and increase in recovery group. The end product of lipid peroxidation malondialdehyde (MDA) and fluorescence product were elevated in diabetic group and after LSE administration the both the parameters reduced significantly. The results showed an anti-lipofuscinogenic activity of *Lepidium sativum* seed extract.

Keywords: *Lepidium sativum* seed extract (LSE), oxidative stress, lipid peroxidation, fluorescence product, diabetes mellitus.

I. INTRODUCTION

In diabetes mellitus [DM], chronic hyperglycemia produces oxidative stress which promotes continuous production of free radicals and plays an important role in the onset and progression of the disease. Oxidative stress is a state of imbalance between generation of reactive oxygen species and levels of antioxidant defense system [1]. Cross linked product of oxidation damage are resistant to digestion by lysosomal enzymes. Lysosomes become unable to digest the phagocytosed material resulting into lipofuscinogenesis [2][3][4]. Lipofuscinogenesis often observed in post mitotic cells of different animals [5][6]. Lipofuscin granules are of autofluorescent material which accumulates progressively with age in secondary lysosomes and linked with hydrolytic activity within lysosomes [7][8][9][10][11]. In aging, mitochondria become enlarged, engulfed by lysosomes and contributes to formation of lipofuscin granules [12]. So, to protect the body against damage caused by reactive oxygen species antioxidant system play an important role [13]. The endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are responsible for the detoxification of deleterious oxygen radicals [14]. Streptozotocin is often used to induce diabetes mellitus in experimental animals through its toxic effects on pancreatic β cells. STZ-induced diabetes mellitus is associated with the generation of reactive oxygen species (ROS) causing oxidative damage [15]. Diabetics and experimental models exhibit high oxidative stress due to persistent and chronic hyperglycemia, which thereby depletes the activity of antioxidative defense system [16]. Thiobarbituric acid reactive substances (TBARS) are commonly measured as a direct marker of oxidative stress; they are formed from breakdown products during the oxidation of unsaturated fatty acids by ROS attack. Levels of TBARS are increased in diabetic patients [17][18][19][20]. Under diabetic conditions, ROS are produced *via* glucose autooxidation [21] and also *via* nonenzymatic protein glycation, which in turn catalyze lipid peroxidation in various tissues [22][23]. The activity of antioxidant enzymes in pancreas is low relative to in other tissues making it particularly vulnerable to oxygen radical attack [24]. The modern therapy for DM, including insulin injection and other oral hypoglycemic agents such as biguanides, sulphonylureas, alpha-glycosidase inhibitors, control the blood glucose level as long as they are regularly administered and they may also produce a number of undesirable effect [25]. Hence there is a need to search for newer anti-diabetic agents that have high therapeutic efficacy

with minimum side effects [26]. Recently, drug formulation from natural herbs, for treatment of diabetes mellitus drugs and other diseases, attracted the attention of many researchers [27]. *Lepidium sativum* is a fast growing herbaceous plant belonging to the family brassicaceae. It is well distributed in the Egypt and South West Asia and cultivated in India [28]. *Lepidium sativum* is a medicinally important plant, the seed of which has been used in traditional medicine for the treatment of bronchitis, asthma and cough [29]. Due to excellent medicinal values, seeds are of interest in phytochemicals and pharmacological research. Therefore this study was carried out to evaluate the antihyperglycemic and anti-lipofuscinogenic activity of ethanolic extracts of *Lepidium sativum* seeds on high fat diet/ streptozotocin in induced diabetic mice.

II. MATERIALS AND METHODS

A. Chemicals

STZ was purchased from Sigma-Aldrich Company (India). The other experimental chemicals used were of analytical grade and were purchased from Hi Media (Mumbai, India).

B. Preparation of *Lepidium sativum* Seed extract

Lepidium sativum seeds were collected from the local market of Kolhapur and dried seeds were cleaned and ground into fine powder using a grinding machine. Extraction was carried out by the soxhlet method. Ethanol was used for extraction for six hrs. The extract was filtered and evaporated to dryness under reduced pressure at 60°C by a rotary evaporator. Extract was placed in dark bottle and stored at -8°C until further analysis.

C. Experimental Animal

Male albino mice (*Mus Musculus L.*) were used for the present study. They were housed in departmental animal house (1825/PO/EReBi/S/15/CPCSEA) under standard laboratory 12:12 h L: D cycle light, 21±2°C temperature and 55±5% relative humidity. They had free access to standard rodent pelleted diet (Nutrivet Life Sciences, Pune), and water ad libitum. All these animals were maintained and treated as per the directions of the Institutional Animal Ethical Committee (IAEC) and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

D. Experimental design and development of HFD/STZ model of type 2 diabetes:

In this experiment 18 mice were used. They were divided into three groups of 6 animals each.

- 1) *Control group*: Mice were fed standard diet throughout the experiment and injected with 0.5 ml citrate buffer intraperitoneally (IP), pH 4.5.
- 2) *Diabetic group (HFD/STZ group)*: Mice were fed HFD (40% fat as a percentage of total kcal) for two weeks and then injected with multi low dose of STZ (40mg/kg body wt) intraperitoneally (IP); in citrate buffer; pH 4.5 for five consecutive days [30].
- 3) *Recovery group (HFD/STZ+LSE group)*: Diabetic mice were given LSE (200mg/kg body wt., dissolved in 0.5ml distilled water) orally for 28 days.

After 28 days of treatment, the mice were fasted overnight. The body weight and blood glucose levels were measured. Then the mice were sacrificed by cervical dislocation. Liver and pancreas were dissected out, weighted and used for biochemical analysis.

E. Biochemical analysis

- 1) *Liver glycogen assay*: Hepatic glycogen content was estimated by Morris method (1948) [31]. The glycogen in the tissue is converted to glucose which reacts with anthron gives green colour. The green color developed was read at 640 nm.
- 2) *Lipid peroxidation assay*: Lipid peroxidation level was determined by Thiobarbituric Acid (TBA) reaction according to Wills (1966) method [32]. Tissue homogenate (2mg/ml) were prepared in chilled mortar and pestle using 75mM potassium phosphate buffer pH 7.0. Malondialdehyde (MDA) is the end product of fatty acid peroxidation, reacts with TBA gives pink colored complex which has maximum absorbance at 532 nm. The concentration of MDA was expressed as nmol MDA/mg wet tissue.
- 3) *Fluorescence product assay*: Fluorescence product was measured by Dillard and Tappel method (1971) [33]. The fluorescence was measured by using quinine sulphate as a standard by using photofluorometer. The lipofuscin granules from liver and pancreas were extracted using chloroform: Methanol mixture (2:1 v/v).

F. Statistical Analysis

All values were expressed as mean ±SD. Statistical analysis was carried out by one-way ANOVA, Turkey's HSD test

III. RESULTS

Table No-1: Effect *Lepidium sativum* seed extract (LSE) on body weight (gm), Liver and Pancreas weight of HFD/STZ induced diabetic mice. Values are mean \pm S.D. (Numbers in parenthesis denotes number of animals).

Sr No.	Group(6)	Weight of animal (gm)	Statistical Significant	Weight of Liver (gm)	Statistical Significant	Weight of Pancreas (mg)	Statistical Significant
1	Control	40.37 \pm 2.1938	1:2 P<0.01	2.242 \pm 0.128141	1:2 P<0.01	0.247 \pm 0.010569	1:2P<0.01
2	Diabetic	29.574 \pm 1.0696	2:3 P<0.01	1.578 \pm 0.105214	2:3 P<0.01	0.163 \pm 0.015205	2:3 P<0.01
3	Recovery	34.32 \pm 2.3012	1:3 P<0.01	2.098 \pm 0.091214	1:3 P<0.01	0.209 \pm 0.009182	1:3 P<0.01
P<0.01=Significant							

Table 2.Effect of *Lepidium sativum* seed extract (LSE) on blood glucose (in mg/dl) and glycogen content (in mg/100mg tissue) of HFD/STZ induced diabetic mice. Values are mean \pm S.D (Numbers in parenthesis denotes number of animals).

Sr No.	Group(6)	Blood glucose (mg/dl)	Statistical Significant	Glycogen content (in mg/100mg tissue)	Statistical Significant
1	Control	103.8 \pm 6.8702	1:2 P<0.01 2:3 P<0.01 1:3 P<0.01	4.5 \pm 0.3953	1:2 P<0.01 2:3 P<0.01 1:3 P>0.5
2	Diabetic	275.6 \pm 20.9476		2.65 \pm 0.2404	
3	Recovery	133.6 \pm 8.6487		4.025 \pm 0.3469	
P<0.01=Significant, P>0.5= Non significant					

Table 3.Effect of *Lepidium sativum* seed extract (LSE) on total lipid peroxidation in Liver and Pancreas of HFD/STZ induced diabetic mice. (Lipid peroxidation in n mol MDA /mgwet tissue). Values are mean \pm S.D (Numbers in parenthesis denotes number of animals).

Sr. No	Group (6)	Total lipid peroxidation in Liver	Statistical Significant	Total lipid peroxidation in Pancreas	Statistical Significant
1	Control	16.4996 \pm 4.9053	1:2 P<0.01 2:3 P<0.01 1:3 P<0.01	12.3454 \pm 3.4515	1:2 P<0.01 2:3 P<0.01 1:3 P>0.5
2	Diabetic	57.6918 \pm 9.1219		40.384 \pm 5.769	
3	Recovery	33.6918 \pm 5.9481		8.0764 \pm 1.6818	
P<0.01=Significant, P>0.5= Non significant					

Table 4. Effect of *Lepidium sativum* seed extract (LSE) on fluorescence product in Liver and Pancreas of HFD/STZ induced diabetic mice. (fluorescence product in $\mu\text{g}/\text{mg}$ tissue). Values are mean \pm S.D (Numbers in parenthesis denotes number of animals).

Sr. No	Group(6)	Total fluorescence product in Liver	Statistical Significant	Total fluorescence product in Pancreas	Statistical Significant
1	Control	0.003921 \pm 0.002773	1 : 2 P<.01 2 : 3 P<.05 1 : 3 P<.05	0.003921 \pm 0.001387	1:2 P<.01 2:3 P<.01 1:3 P<.01
2	Diabetic	0.019607 \pm 0.0031		0.015294 \pm 0.002557	
3	Recovery	0.012548 \pm 0.002236		0.006274 \pm 0.001641	
P<0.01=Significant, P<0.05= almost significant					

Table 1 shows the body weight and gland weight of experimental groups. The diabetic mice exhibited a significant loss of bodyweight as well as liver and pancreatic weight as compared to control group (1:2,P<0. 01). Oral administration of LSE for 28 days caused significant improvement in body weight and gland weight in recovery group (2:3,P<0.01). Blood glucose level in diabetic group was significantly increased than the control group (1:2,P<0. 01). Decreased blood glucose level was observed in recovery group after LSE treatment for 28days (Table 2).The glycogen content in liver was significantly decreased in diabetic group as compared to control group (1:2,P<.01), while it was significantly increased in recovery group as compared to diabetic group (2:3, P<0. 01) (Table 2).The total lipid peroxidation i.e. level of MDA and fluorescence product in liver as well as pancreas was increased in diabetic group as compared to control and increase was highly significant (1:2, P < 0.01), while it was decreased significantly in recovery group as compared to diabetic group. (2:3, P<0. 01) (Table 3 and 4).

IV. DISCUSSION

Pharmacological activities of *Lepidium sativum* seed in animal models, in a diabetes study have been poorly documented. Therefore, the present study was carried out to investigate the antidiabetic and anti-lipofuscinogenic activities of the seed extract of *L. sativum* to ratify their traditional use as a treatment for diabetes.

In Diabetes there is a constant high blood glucose level and it can cause of weight loss in body. This may be because of insufficient amounts of insulin secreted by the beta cells. When there isn't enough insulin around, glucose stays in blood and can't get into the cells to be used for energy. The body needs fuel from somewhere, so in the absence of glucose, it starts to burn muscle and fat proteins. This mechanism of muscle wasting can be attributed to be the main reason of weight loss in diabetics [34].It was found that diabetic mice significantly (P<0.01) lose their body weight as compared to control group at the end of the study period. However, in recovery group treatment with LSE showed significant (P<0.01) gain in body weight suggesting that LSE may normalize energy metabolism in tissues particularly in liver. These findings agreed with the results of Abirami and Kowsalya (2013) [35].Also, our study after administration of the LSE to diabetic mice for 28 days revealed the antidiabetic activity of the extract by reducing blood glucose level. This clearly indicates LSE may be protecting β cells from oxidative stress and promote surviving and regeneration of β cells, leads into increase in insulin secretions. These finding was supported by our previous histopathological study [36]. The liver is sensitive to insulin in modulating glucose metabolism, and thus, can be severely affected during diabetes. Insulin stimulates the activity of glycogen synthase and inhibits glycogen phosphorylase, which causes glycogenesis. In this study, a significant reduction in the glycogen content was observed in the liver of the diabetic mice. LSE treatment to diabetic mice significantly elevated hepatic glycogen contents. The decrease in hepatic glycogen content in diabetes is probably due to lack of insulin in the diabetic state that result in the inactivation of glycogen synthase enzyme and activation of glycogen phosphorylase. The significant increase in the liver glycogen content in recovery groups may be because of reactivation of glycogen synthase enzyme. Hence, another important way to control diabetic conditions is improvement of enzymes needed for glycogenesis of the individual. Hyperglycemia results in continue production of free radical through various biochemical reactions. Free radicals may also be formed via the autoxidation of unsaturated lipids in plasma and membrane lipids. The free radical produced may react with polyunsaturated fatty acids in cell membranes leading to lipid peroxidation and results in increased production of free radicals[37].The increased lipid peroxidation in the diabetic animals may be due to the observed remarkable increase in the

concentration of TBARS and hydroperoxides (lipid peroxidative markers) in the liver, pancreas of diabetic rats [38]. Malondialdehyde (MDA) is formed in extensive membrane lipid peroxidation. It is digested by lysosomes. The free radicals also bring about damage to lysosomes and lysosomal enzymes, making them inefficient which turn into residual bodies known as lipofuscin granules [39][40]. The lipofuscin granules are auto fluorescent they lead to increase in fluorescence product also. In the present study, elevated MDA and fluorescence product was observed in both tissue i.e. liver and pancreas. And the levels of both oxidative stress markers were significantly lower after oral administration of LSE. The above result suggests that the ethanolic extract of LSE may exert anti-lipofuscinogenic activity and protect the tissues from lipid peroxidation.

V. CONCLUSION

The above results indicated that *Lepidium sativum* seed (LSE) extract protect hepatocytes and β cells against ROS mediated destruction by reducing lipid peroxidation and fluorescence level in tissue and minimizing hyperglycemia which could be due to release of insulin from remnant or recovered β -cells or sensitizing the insulin receptor. It concludes that *Lepidium sativum* seed extract are having anti peroxidative property.

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