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EVALUATION OF ANTI-DIABETIC AND ANTI-HYPERLIPIDEMIC ACTIVITIES OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA* IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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Keywords:

Antidiabetic activity, *Origanum majorana*, Glibenclamide, Streptozotocin

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ABSTRACT: Diabetes mellitus or sugar diabetes is a condition that occurs when the body can't use glucose (a type of sugar) normally. It is a chronic disease associated with abnormally high levels of the glucose in the blood because of disturbances in carbohydrates, fat and proteins metabolism and it is due to one of two mechanisms that inadequate production of insulin (which is made by the pancreas and lower blood glucose), or inadequate sensitivity of cells to the action of insulin. This causes glucose levels in the blood to rise, increased urination, extreme thirst and unexplained weight loss. The prominent objective of this work was to find out the anti-diabetic and anti-hyperlipidemic activities of *Origanum majorana* ethanol leaf extract (100, 200, 400 mg/kg body weight) in streptozotocin (50 mg/kg b.w) induced diabetic rats. After oral administration of such extract the blood glucose levels were recorded at specific intervals. In consequence it was observe that extract was significantly diminished blood glucose level. Simultaneously the effect of the extract on diabetes induced hyperlipidemia was studied where it markedly decreased the elevated total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) level while increased the high density lipoprotein (HDL). The preliminary phytochemical screening revealed the presences of tannins, glycosides, terpenoids, saponins, flavonoids and alkaloids. The conclusion exhibited that ethanol extract shows antidiabetic activity compared to standard drug glibenclamide (4 mg/kg). The further *in-vivo* study, isolation of pure phytoconstituents should be investigated to discover the antidiabetic action and other needful effects.

INTRODUCTION: Diabetes is a group of diseases marked by high levels of blood glucose resulting from problems in how insulin is produced, how insulin works, or both.

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Diabetes affects many parts of the body and is associated with serious complications, such as heart disease, stroke, blindness, kidney failure, and lower-limb amputation [1, 2]. As of 2015, an estimated 415 million people had diabetes worldwide, 3 with type 2 DM making up about 90% of the cases [4, 5].

This represents 8.3% of the adult population, with equal rates in both women and men [6]. It has been estimated that Indian people are more genetically susceptible to diabetes accounting about 40 million and would reach up to 74 million by 2025 [7, 8].

Recent research has demonstrated that plant-based diets (especially whole, not processed foods) may successfully prevent diabetes and related complications [9, 10].

Adverse effect are more in allopathic drugs so herbal materials which are being used as traditional medicine for the treatment of diabetes are considered one of the good sources for discovery of new drugs [11, 12]. *Origanum majorana* or *Majorana hortensis* is known as Marwa in India, belonging to the mint family (Lamiaceae). Commonly known as Sweet marjoram. Marjoram has many uses with numerous health benefits [13]. Digestive benefits (Increasing the efficiency of digestion by increasing digestive enzymes and saliva, improving appetite, relieving nausea, eliminating flatulence, preventing intestinal infections, relieving diarrhea and constipation) [14, 15].

Marjoram is a great antiseptic, antibacterial, antifungal and antiviral agent and used in a variety of common illnesses (food poisoning, staph infection, tetanous infection in wounds, typhoid, malaria, influenza, common cold, mumps, measles) [16]. Another benefit of marjoram is the enhancement of the cardiovascular and circulatory system (Lowering the blood pressure, greatly reducing the risk of hypertension, preventing the build up of cholesterol).

Anti-inflammatory effects like (asthma, muscle spasms, sinus headaches, migraines, fever, body aches) [17, 18]. Topical application for (painful joints, sore muscles, sprains, back aches, toothaches). Emotional and neurological benefits like (relieving insomnia, reducing stress, calming anxiety, minimizing emotional reactions, increasing control of sexual desire) [19].

The herb contains important phytoconstituents like tannins, glycosides, terpenes, flavonoids, linalool and cavacrol. This study was aimed at investigating the effects of antidiabetic and antihyperlipidemic activities of ethanol leaf extract of the of *Origanum majorana* [20].

MATERIAL AND METHODS:

Plant Materials: The leaf of *Origanum majorana* was collected from the forest region of Bobbili, Vizianagaram (District), Andhra Pradesh, India. And they were identified and authenticated by Dr. Madhava Chetty, Department of Botany, S. V. University, Chittoor District Tirupati and leaves were deposited in the Herbarium of Department of Botany.

Preparation of Plant Extract: Leaves were washed thoroughly with sterile distilled water in order to remove any dirt or filthy particles present on the surface and were shade dried then made into fine powder. These powdered samples (100g/500 ml) in ethanol for 48 hours at 45 ºC. The Phytochemical constituents are extracted by using soxhlet apparatus. The extract was soaked and evaporated under pressure and concentrated at 50°C and the residue obtained was stored at 4 °C.

Preliminary Phytochemical Screening: *Majorana hortensis* is peculiarized with the aid of powerful, aromatic and amusing fragrance quality. Investigation on marjoram herb recorded the extremely existence of volatile oil as chief phyto constituents due to its fragrant character [21, 22]. Different qualitative phytochemical tests exhibited for the presence of flavonoids, tannins, glycosides, cardiac glycosides, sterols, terpenoids in ethanol extract of leaves of *Origanum majorana.*

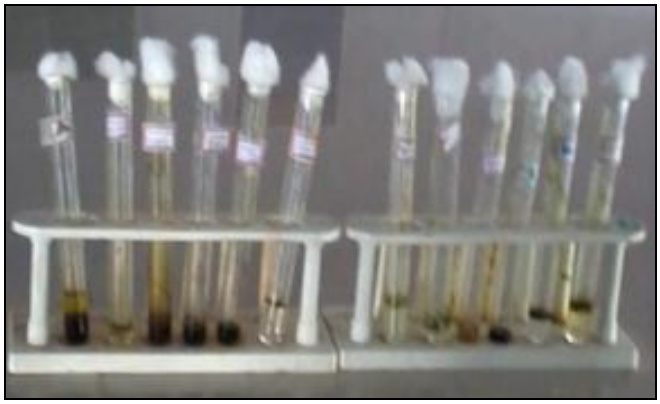

FIG. 1: QUALITATIVE PHYTOCHEMICAL TESTS

Experimental Animals: The animals used in experiment were procured from animal house of Nalla Narasimha Reddy Education Society's Group of Institution, from Pharmacy Department. Wistar rats of either sex weighing about 160 - 200 g were taken. Experimental protocols were approved by The Institutional Animal Ethic Committee (CPCSEA NO.-282/P0/Bt/S/2000). The animals were kept in polycarbonate cages and maintained under standard housing conditions of temperature (22 ± 20 ° C) and humidity (45 - 60%) with 12 h light - dark cycle. Animals were fed pellet diet with

supply of water *ad libitum* and normal saline. Animals were divided into five different groups as normol glycemic control, diabetic control, reference group, and test groups.

Acute Oral Toxicity Study: Acute oral toxicity studies of ethanol leaf extract of *Origanum majorana* was carried out as per the guidelines of Organization for Economic Co-operationand Development (OECD) no. 423. As per OECD guidelines minimum number of animals should be used (3 animals per dose) for experiment to obtain the information as acute toxicity of test dose. Overnight fasted rats were orally fed with plant extract at a dose level of 250, 500, 1000 and 2000 mg/kg body weight respectively. The animals were observed continuously for 2 hrs to investigate any sign of toxicity, occasionally for 4 hrs for their general behavior and after a period of 24 hrs, animals were observed for any sign of mortality till 7 days [23, 24].

Induction of Diabetes Experimentally: Wistar rats (160 - 200 gm) were fasted for 18 hours before the induction of diabetes with streptozotocin (STZ), for induction of type-1 diabetes mellitus. Animals (n=36) were injected intraperitoneal with 0.22 - 0.25ml of freshly prepared solution of STZ (50 mg/ml in 0.01 m citrate buffer, pH 4.5) at a final dose of 50 mg/kg body wt. The diabetic state was assessed in STZ-treated rats by measuring the non-fasting serum glucose concentration after 72 hours. Only rats with serum glucose levels greater than 200 - 250 mg/dl were selected and used in this experiment.

Experimental Design for Oral Glucose Tolerance Test (OGTT): In oral glucose tolerance test, animals of diabetic control group have shown significant elevation in blood glucose level through entire study when compare to normal animals. But treatment with standard drug glibenclamide and ethanol extract (100, 200, 400 mg/kg) of *Origanum majorana* Baill could able to reduce significantly (P<0.01) blood glucose level in therapeutic groups after 60 mins and 120 mins [25]. The results of OGTT have shown in (**Table 2**).

Streptozotocin-induced Diabetic Model: The animals were divided into six groups of six rats each. The ethanolic leaf extract was administered for 21 days. Group I served as normal control rats administered sodium carboxy methyl cellulose (SCMC) daily for 21 days; Group II diabetic control rats administered STZ (50mg/kg) with SCMC, Group III diabetic rats administered standard drug glibenclamide (4 mg/kg); Group IV diabetic rats administered *Origanum majorana* (100 mg/kg); Group V diabetic rats administered *Origanum majorana* (200 mg/kg). Group VI diabetic rats administered *Origanum majorana* (400 mg/kg). The fasting glucose levels were determined on days 1, 7, 14 and 21 of extract administration. During the experimental period, the blood glucose level, the lipid level and body weight of different group animals are estimated [26, 27].

Estimation of Biochemical Parameters: The biochemical parameters were determined on day 21 after the animals were sacrificed by cervical dislocation. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) were determined by the glucose oxidase method, using an auto-analyzer [28, 29].

Statistical Analysis: Results of estimation of biochemical and functional parameters have been reported as mean value ± SEM. The variation in a set of data has been estimated by performing one way analysis of variance (ANOVA). Individual comparisons of group mean values were done using Dunnet's test (Sigma start 3.5). P values <0.05, were considered statistically significant.

RESULTS:

Preliminary Phytochemical Screening: From qualitative tests it was identified the presence of many phytoconstituents such as tannins, alkaloids, saponins, flavonoids, terpenoids, and phenols from *Origanum majorana* ethanol leaf extract.

TABLE 1: PHYTOCHEMICAL SCREENING OF ETHANOL LEAF EXTRACT OF *ORIGANUM MAJORANA*

S. no.	Phytochemicals	Ethanol extract
1	Alkaloids	+
2	Flavonoids	+++
3	Saponins	+
4	Tannins	++
5	Pholbhatannins	-
6	Sterols	+
7	Resins	++
8	Glycosides	+++
9	Phenols	+
10	Anthraquinones	-
11	Terpinoids	+
12	Cardiacglycosides	++

Acute Oral Toxicity Study: The result of acute toxicity study on laboratory animals it was observed that ethanol leaf extract of *Origanum majorana* showed no lethality up to the dose of 2000 mg/kg body weight hence the animals were safe up to a maximum dose of 2000 mg/kg body weight.

Oral Glucose Tolerance Test (OGTT): At 90mins, 100 mg/kg and 200 mg/kg body weight of both tests extract treated rats produces significant reduction in plasma glucose level, while in disease control rats, plasma glucose level was increased after administration of ethanol leaf extracts of *Origanum majorana* shown in **Table 2**.

TABLE 2: EFFECT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA (EEOM)* (100, 200, 400 mg/kg, PO), ON ORAL GLUCOSE TOLERANCE TEST (OGTT) IN NORMAL AND STREPTOZOTOCIN INDUCED DIABETIC RATS

S. no.	Treatment of Dose (mg/kg)	Blood Glucose Level (mg/dl)				
		Fasting	30 mins	60 mins	90 mins	120 mins
I	Normal control (Normal Saline)	77.5 ± 0.63	80.5 ± 0.59	110.39 ±0.66	98.5± 0.71	93.25 ± 0.51
II	Disease control (STZ induced)	86 ± 0.88	116.45 ± 0.84	149.5 ± 0.72	143.8± 0.68	222.5 ± 0.47
III	Diabetes + Glibenclamide (4mg/kg)	83.5 ± 0.82	103.05 ± 1.02	98.08 ± 1.52	87.62± 1.05	81.25 ± 0.98
IV	Diabetes + EEOM (100mg/kg)	82.6 ± 0.71	87.9 ± 0.69	91.12 ± 1.01	86.55± 0.75	83.21 ± 0.73
V	Diabetes + EEOM (200mg/kg)	84.25 ± 0.62	90.0 5± 0.58	121.52± 0.63	113.25± 1.49	105.24 ±1.32
VI	Diabetes + EEOM (400mg/kg)	81.5 ± 0.58	97.6 ± 0.56	126.85± 0.72	122.62± 0.45	110.35± 0.31

Values are given as Mean ± SEM for n=6. Group II was compared with group I. Group III, IV, V and VI were compared with group II. Values are statistically significant at **p< 0.01

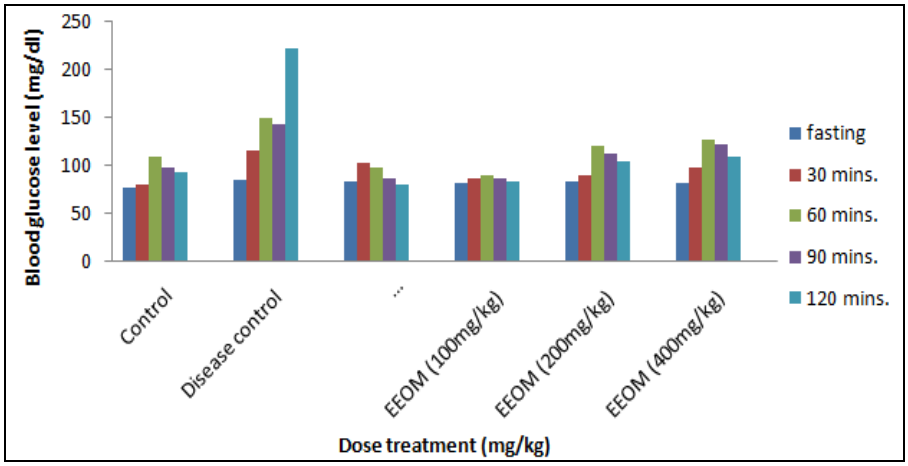

FIG. 2: EFFECT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA (EEOM)* ON ORAL GLUCOSE TOLERANCE TEST (OGTT) IN NORMAL AND STREPTOZOTOCIN INDUCED DIABETIC RATS

Effect of Ethanolic Extract on Streptozotocin - induced Diabetic Rats: The diabetes rats were confirmed with increasing level of fasting plasma glucose level. The effect of ethanol extract at different doses of *Origanum majorana*, on fasting plasma glucose level of normal and streptozotocin induced are given in **Table 3**. The difference between the experimental and control rats is lowering the fasting plasma glucose levels were statistically significant by compare with diabetic rats.

TABLE 3: EFFECT OF SINGLE DOSE TREATMENT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA (EEOM)* (100, 200, 400 mg/kg) ON BLOOD GLUCOSE LEVEL IN NORMAL AND STREPTOZOTOCIN INDUCED DIABETIC RATS

Groups	Treatment of Dose (mg/kg)	Blood Glucose Levels (mg/dl)			
		Basal value	1 hour	2 hours	4 hours
I	Normal control	81.05 ± 0.62	79.35 ± 0.49	76.08 ± 0.72	77.05 ± 0.83
II	Disease control (STZ induced)	249.41 ± 1.53	255.26 ± 1.89	251.05 ± 1.61	253.18 ± 1.79
III	Diabetic + EEOM (100mg/kg)	238.36 ± 2.28	224.62 ± 1.52	212.72 ± 3.15	198.32 ± 2.65
IV	Diabetic + EEOM (200 mg/kg)	234.23 ± 1.54	218.21 ± 1.42	209.25 ± 2.31	191.05 ± 2.33
V	Diabetic + EEOM (400mg/kg)	231.18 ± 2.79	219.05 ± 2.96	189.22 ± 2.43	174.27 ± 1.95
VI	Diabetic + Glibenclamide (4mg/kg)	248.35 ± 3.21	216.28 ± 4.09	181.09 ± 2.76	169.45 ± 3.56

Values are expressed as mean ± SEM (Number of animals, n=6); significantly different at *P<0.05, when compared with diabetic control group

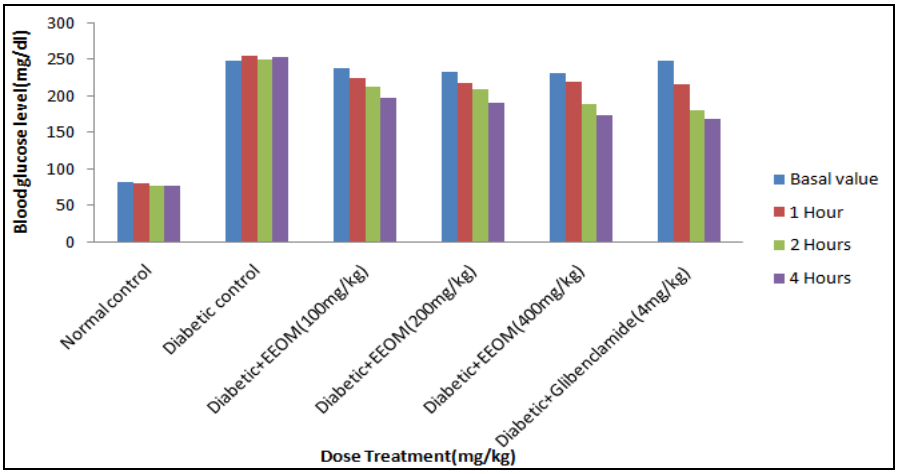

FIG. 3: EFFECT OF SINGLE DOSE TREATMENT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA (EEOM)* ON BLOOD GLUCOSE LEVEL

TABLE 4: EFFECT OF MULTIPLE DOSE TREATMENT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA* LEAF (ONCE DAILY), ON BLOOD GLUCOSE LEVEL AFTER 21 DAYS IN NORMAL AND STREPTOZOTOCIN INDUCED DIABETIC RATS

Groups	Treatment of Dose (mg/kg)	Blood Glucose Levels (mg/dl)				
		Basal value	Day 1	Day 7	Day 14	Day 21
I	Normal control	78.23 ± 0.73	87 ± 0.52	98 ± 0.28	91 ± 0.54	85 ± 0.69
II	Disease control (STZ induced)	248.57 ± 1.85	252.5 ± 2.15	259.8 ± 1.89	263.5 ± 2.24	266.25 ± 2.71
III	Diabetic+ EEOM (100mg/kg)	244.37 ± 2.98	235.15 ± 2.85*	162.8 ± 2.45 **	140.25 ± 1.24**	125.5 ± 0.54
IV	Diabetic+ EEOM (200 mg/kg)	242.67 ± 3.05	231.05 ± 3.81 *	188.5 ± 1.63**	142.35 ± 1.53 **	110.05 ± 0.67 **
V	Diabetic+ EEOM (400mg/kg)	239.48 ± 3.26	225.5 ± 2.04 *	170.23 ± 0.59 **	137.32 ± 0.83**	112.38 ± 1.55 **
VI	Diabetic+ Glibenclamide (4mg/kg)	240.36 ± 2.29	228.52 ± 2.14*	154.2 ± 0.16 **	130.05 ± 1.29 **	101 ± 1.412 **

Values are expressed as mean ± SEM (Number of animals, n=6); significantly different at *p<0.05, **p<0.01and ***p<0.001 was considered significant comparing to Diabetic control group.

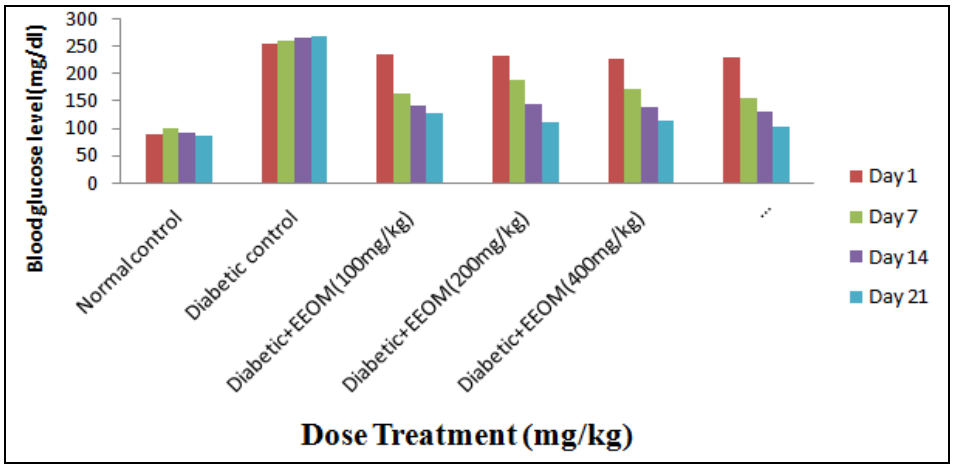

FIG. 4: EFFECT OF MULTIPLE DOSE TREATMENT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA* LEAF (ONCE DAILY), ON BLOOD GLUCOSE LEVEL AFTER 21 DAYS IN NORMAL AND STREPTOZOTOCIN INDUCED DIABETIC RATS

Effect of Ethanolic Extract on Biochemical Parameters in Streptozotocin-induced Diabetic Rats: The effect of different doses of the ethanolic extract on diabetes induced hyperlipidemia was also evaluated. It was observed that due to diabetes there was an increase in the total cholesterol levels

as well as triglyceride levels. The HDL levels were reduced in the diabetic animals and the LDL levels were increased significantly (**Table 5**). The ethanol extract showed a significant decrease in the total cholesterol levels and triglyceride levels. It also increased the HDL level and was successfully it suppressing the LDL and VLDL levels as compared to the standard drug (**Table 5**).

TABLE 5: EFFECT OF ETHANOLIC LEAF EXTRACT OF *ORIGANUM MAJORANA* ON SERUM BIOCHEMICAL PARAMETERS AFTER 21 DAYS TREATMENT

Group	Treatments	Lipid Profiles (Mg/Dl)				
		TC	HDL	LDL	VLDL	TG
I	Normal control	136 ± 1.89	43.25 ± 0.75	92 ± 0.81	16.23 ± 0.62	72.84 ± 0.96
II	Disease control	184.6 ± 0.91	20.17 ± 0.39	109.7 ± 1.62	18.89 ± 0.56	98 ± 2.86
III	Diabetic+ glibenclamide (4mg/kg)	151.05 ± 1.49 ***	44 ± 1.25 ***	82.55 ± 2.92 ***	17.65 ± 0.37 ***	84.2 ± 1.55 ***
IV	Diabetic + Extract (100mg/kg)	169.23 ± 1.24	37.18 ± 1.39**	96.40 ± 1.65*	22.25 ± 0.35**	95.2 ± 2.36*
V	Diabetic +Extract (200mg/kg)	154.25 ± 2.15	42.16 ± 1.17**	93.05 ± 1.85**	23.21± 0.72*	91.80 ± 2.23**
VI	Diabetic +Extract (400mg/kg)	156.5 ± 2.05	43.5 ± 0.11*	90.05 ± 1.25*	21.51 ± 0.62**	88.15 ± 1.93**

Values are expressed as mean ±SEM, n=6. Statistical significance test for comparison was done by ANOVA, followed by Dunnett's *t*-test.***p<0.001, **p<0.01, *p<0.05.

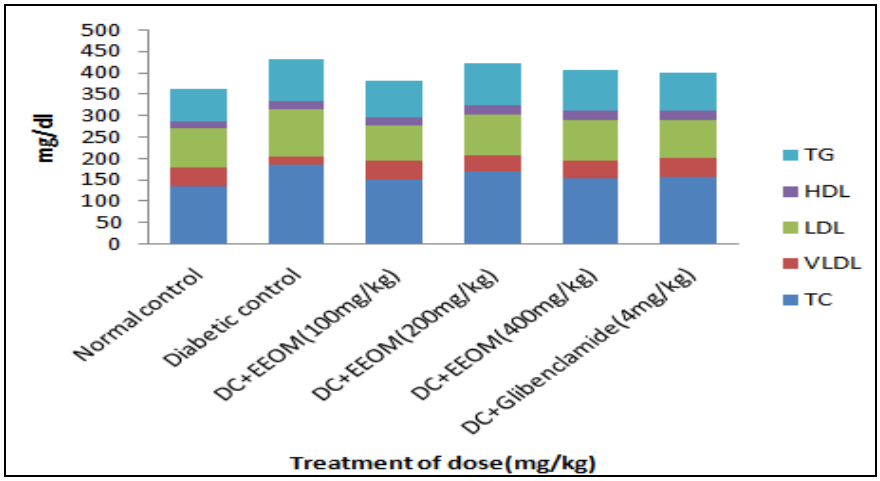

FIG. 5: LIPID PROFILE (mg/dl)

DISCUSSION: In these above study animals were observed for any sign of mortality till 7 days. The acute toxicity study of ethanol extract of *Origanum majorana* on laboratory animals showed that no lethality up to the dose of 2000 mg/kg body weight. As a result, three doses of 100 mg/kg, 200 mg/kg and 400 mg/kg b.w were taken as effective dose for the study. After 21days treatment, blood from all the groups was collected from tail vein puncture for estimating blood glucose levels. In Glucose tolerance test, the glucose levels were estimated before drug treatment and at different intervals thereafter. In the normal control group the blood glucose was found to increase linearly from fasting blood glucose value of 77.5 ± 0.63 mg/dl to 80.5 ± 0.59 mg/dl in the first 30 minutes. After 60 minutes of glucose loading, the blood glucose was increased. The maximum value of 110.39 ± 0.66 mg/dl was seen at the 60th minute. Whereas in the extract treated animals, only a little elevation in the blood glucose were seen and maximum glucose tolerance was observed at 60th minute.

The extract was evaluated for *in-vivo* hypoglycemic activity using streptozotocin at a dose of 50mg/kg. it was observed that there was a short phase of hypoglycemia followed by marked elevation in the blood glucose level, the diabetic rats with fasting blood glucose levels > 200 mg/dl, were selected for further studies.

In addition, after 21 days of treatment, the serum insulin levels of the treated diabetic rats were significantly enhanced compared to the untreated diabetic rats. It was observed that there was an increase in Serum Total Cholesterol (TC), Serum Total Triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels and decrease in hogh density lipoprotein (HDL) levels in diabetic rats. After continuous administration of ethanolic leaf extract of *Origanum majorana* for 21 days has led to significant decrease in serum total cholesterol, triglycerides, LDL and VLDL levels, while it increased HDL levels in diabetic rats [30, 31].

The beneficial effect of *Origanum majorana* and glibenclamide given immediately after diagnosis of diabetes which decreases serum total cholesterol, serum total triglycerides, LDL and VLDL levels and increases serum insulin and HDL levels was observed after 21 days treatment. Hence, the results indicate that treatment of diabetic rats with *Origanum majorana* may prevented the complications arises by diabetes.

CONCLUSION: The ethanolic leaf extract of *Origanum majorana* possesses significant antidiabetic and antihyperlipedimic activities in Streptozotocin induced diabetic rat. But further study is required to evaluate the antidiabetic activity from the plant extract by particular isolated chemical constituents.

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CONFLICT OF INTERSET: Nil

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