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Protective Effect of *Murraya koenigii* Leaves Extract in Glucose Dysregulation and Its Progression of Depression in Streptozotocin Induced Diabetic Rat

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Abstract

Depression in diabetes contributes to poor metabolic control, decreased quality of life, and increased medical morbidity and mortality. Depression is believed to contribute to the development or progression of diabetic complications through its behavioral and metabolic effects. The main approach of the present study was the treatment of diabetes as well as management in the progression of depression using ethanolic extract of *Murraya koenigii* leaves (MKL). In the present study diabetes was induced by the intravenous administration of streptozotocin (55 mg/kg i.v.) in male Wister rat and the MKL (300 mg/kg and 500 mg/kg p.o.), standard glibenclamide (10 mg/kg p.o.) were started after 13 days of streptozotocin. While in the second study the effect of chronic treatment of MKL on progression of depression was evaluated after 9 week in streptozotocin (70 mg/kg i.v.) induced diabetic rats.

The results of the first study showed that administration MKL (300 mg/kg and 500 mg/kg) for 15 days significantly ($P< 0.05$) decreases blood glucose level dose dependently which was comparable to standard glibenclamide. While the results of the second study showed to increased in the immobility period ($P<0.05$) in diabetic rat (70 mg/kg i.v.) after 9 week in streptozotocin induced diabetic animals indicates in progression of depression. While chronic treatment with MKL (500 mg/kg) up to 9 week decreases the immobility period ($P<0.05$) which was comparable to standard antidepressant fluoxetine (20 mg/kg p.o.). Thus the study concludes that *Murraya koenigii* has potent antidiabetic activity at both doses (300 mg/kg and 500 mg/kg) it decreases blood glucose level dose dependently and also has potential to decrease the progression of depression in diabetes so it could be helpful in diabetic patient for prevention of depression.

Keywords: MKL; Diabetes; Muscle strength; Depression; Force swimming

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Introduction

Depression is significantly more prevalent in diabetes, affecting 15% to 20% of patients with either the insulin-dependent or non–insulin-dependent. Several reports reveal that the presence of diabetes doubles the odds of comorbid depression [1]. Evidence from prospective and cross-sectional studies has indicated that depression is associated with factors related to glucose dysregulation, including obesity and no adherence to treatment, which increase the risk of diabetic complications [2]. Depression is known to have a profound adverse influence on patients' quality of life and overall functioning. It has additional relevance in diabetes because of its association with poor glucose control [3,4]. The symptoms of depression most commonly related to diabetes are weight loss, psychomotor retardation, muscle weakness, tiredness, hypersomnia, feelings of worthlessness, and diminished sexual drive [4].

The diabetes, depression is complex and associated with many neurochemical and neurovascular factors. Reduced brain tryptophan levels and reduced brain turnover of catecholamines and serotonin in diabetic rats suggest involvement of reduced monoamine activity in diabetic depression [5]. All of these lines of evidence indicate that depression may be related to diabetes.

The treatment of depression is necessary to improve the quality of life of diabetic patients, to increase treatment compliance, and to decrease the risk of diabetic complications e.g. micro vascular

and macro vascular complications [6-8].

Novel approaches in antidiabetic therapy are aimed not only to decrease high blood glucose levels, but also to eradicate long-term diabetic depression which may cause a diminished life expectancy and/or a poor quality of life. Treatment with antidepressants can directly interfere with blood glucose levels or may interact with hypoglycemic agents. In a recent preclinical study it was demonstrated that prolonged treatment with nortriptyline increases blood glucose in diabetic and nondiabetic mice, while fluoxetine and sertraline decrease it [9]. Diabetes is associated with high medical costs. The economic burden of diabetes approached $132 billion in 2002 [10]. Concurrent depression in patients with diabetes further increases health care use and expenditures, even after adjustments for differences in age, gender, race/ethnicity, health insurance coverage, and comorbidity [11,12]. Thus to decrease the high medical cost and expenditure the renewed interest has been focus on herbs and are increasingly gaining acceptance among various country [13-15] because of its safety profile.

Thus the main approach of the present study was the prevention in progression and management of depression in diabeties including glycemic control by using chronic treatment with herb *Murraya koenigii* leaves which is commonly known as Karry tree or Meethi neem in India. Our previous finding on fruit juice of *Murraya koenigii* indicates to have antidiabetic activity [16]. The leaves are used extensively as a flavoring agent in curries and chutneys. Almost every part of this plant has a strong characteristic odour and is used traditionally as antiemetic, antidiarrhoeal, febrifuge and blood purifier. The people of the plains, particularly of southern India, use the leaves of this plant as a spice in different curry preparations [17,18].

Materials and Methodology

Plant

The fresh leaves of *Murraya koenigii* were collected from its natural habitat was authenticated by Dr. N. M. Dongarwar of Botany Department; RTM Nagpur University, Nagpur India. A voucher specimen (No: 9439) was deposited at Herbarium, Department of Botany, RTM Nagpur University Nagpur.

Preparation of extracts of *Murraya koenigii* leaves

The collected leaves of *Murraya koenigii* were dried under shade and undergone crushing in electric blender to form powdered and subjected to extraction by using soxhlet's extractor. The extract was concentrated by evaporation at room temperature and was used in present study.

Administration of extract

Suspension of ethanolic extract was prepared in 0.5% carboxymethyl cellulose using tween 20 (0.2% v/v) as a suspending agent. The extract was administered in a dose of 300 mg/kg and 500mg/kg respectively. Control groups were given only 0.5% carboxymethyl cellulose with tween 20 (0.2% v/v).

Experimental animals

All the experiments were carried out in male Wister rat (180gm to 220gm). The animals had free access to food and water, and they were housed in a natural light-dark cycle. The animals were acclimatized to the laboratory conditions for at least one week before experiments. Experiments were carried out between 0900 h and 1800 h. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and the care of laboratory animals was taken according to the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (registration number 729/02/a/CPCSEA).

Drugs

Streptozotocin {Gift sample from Nicholas Piramal, Mumbai (Sigma Aldrich, USA)} prepared in cold citrate buffer (pH 4.5, 0.1 M) and injected intravenously in a single dose, Fluoxetine (Davis Pharma, Hyderabad, India), Glibenclamide (Gift sample from Glenmark Laboratory Mumbai) were prepared similarly as plant extract and given orally. All the drugs were injected in a constant volume of 1 mL/kg of body weight after stabilization of blood glucose level on 13th day of streptozotocin injection. Glucose, Glycogen, Triglyceride, and Total cholesterol estimation kits were used for biochemical estimation which was obtained from Bio-Lab Mumbai.

Induction and Assessment for Antidiabetic Activity

The antidiabetic activity was evaluated in STZ (55mg/kg) induced diabetic rats. At 13th day, blood samples were collected, and plasma glucose levels were estimated with the GOD-POD diagnostic kit. The survival animals with fasted serum glucose levels of more than 250 mg/dl were considered as diabetic and used for the antidiabetic evaluation in the present study.

Induction and Assessment of Depression in Chronic Diabetic

STZ was injected intravenously in a single dose of 70 mg/kg to Wister rat. The age-matched control rats received an equivalent volume of citrate buffer and were used along with diabetic animals. After 9 week of streptozotocin immobility was measured in forced swimming test for evaluation of progression of depression in diabetic animals [19].

Statistical Analysis

Blood glucose level and immobility time (in sec) were analyzed by ANOVA followed by Dunnet test. The significant difference was compared at P<0 .05 and P<0 .001. Data of grip strength, glycogen content, cholesterol, and triglyceride were analyzed by student unpaired t test at P<0 .05.

Experimental Design

Preliminary hypoglycemic study of MKL

The hypoglycemic activity was performed in normal glycemic and glucose (3.0 gm/kg p.o) loaded rat (oral glucose tolerance test (OGTT) model). Wister rats (180gm to 220 gm) were assigning to each contain 6 animals. Four groups of animals were used for normal glycemic model and OGTT models respectively [20].

In normoglycemic group 1 was normal control (without any treatment), group 2 was vehicle control while group 3 and 4 orally received 300 mg/kg and 500mg/kg of MKL respectively. While in OGTT model group 1 was vehicle control, group 2 was standard Glibenclamide (10 mg/kg p.o.) and group 3 and 4 orally received 300 mg/kg and 500 mg/kg of MKL.

In normoglycemic and OGTT model initial blood was taken by retro-orbital after 30 min of administration while in OGTT model immediately glucose (3.0 gm/kg p.o) was given to all groups of animals and subsequent blood samples were taken at time interval of

Table 1: Hypoglycemic effect of MKL in Normoglycemic and in oral glucose tolerance test Data expressed as means ± s.d of absorbance (n=5). The values in parenthesis are in percentage '+' indicate percent rise and '–'indicate decline in blood glucose compare to 0 min. reading; In OGTT model 3 gm/kg glucose was given after 0 min reading.

Treatments	0.0 min.	30 min	60 min	120 min
	Effect in Normoglycemic			
Normal	78.7 ± 3.14	77.79 ± 3.96 (-1.17)	78.34 ± 4.69 (+0.46)	77.96 ± 3.47 (-0.94)
Vehicle control	77.73 ± 3.77	76.13 ± 5.80 (-2.10)	76.75 ± 4.68 (-1.27)	76.54 ± 2.53 (-1.55)
MKL-300	75.58 ± 3.74	72.06 ± 3.20 (-4.88)	71.45 ± 2.68 (-5.78)	67.36 ± 2.95 (-12.20)
MKL-500	77.24 ± 4.42	72.3 ± 3.1 (-6.83)	68.19 ± 2.82 (-13.27)	62.9 ± 2.07 (-22.79)
	Effect in OGTT			
Vehicle control	76.31 ± 4.15	137.36 ± 5.14 (+80.0)	130.14 ± 4.65 (+70.54)	116.36 ± 6.77(+52.48)
Glibenclamide	75.23 ± 3.28	110.87 ± 4.97(+47.37)	94.35 ± 4.95 (+25.41)	85.86 ± 5.36(+14.13)
MKL-300	74.09 ± 5.02	124.69 ± 4.94(+68.29)	114.54 ± 5.13 (+54.59)	104.5 ± 4.75(+41.04)
MKL-500	74.75 ± 6.48	115.36 ± 5.56(+54.32)	105.36±5.53 (+40.94)	91.37±5.58(+22.23)

Table 2: Antidiabetic activity of Murraya koenigii in streptozotocin induced Diabetic rat Data expressed as means ± s.d; n = 5. The data are statistically ($p<0.05$) significant (ANOVA followed by Dunnet test). *indicates significant ($p<0.05$) induction of diabeties compare to vehicle control at 0 hr. [a]indicates significant ($p<0.05$) hypoglycemic effect of drugs in diabetic animals compared to 0 hrs reading of respecting group. [ab]indicates significant ($p<0.05$) decline in blood glucose level compared to day 5 reading in respective group.

Time Interval	Vehicle control	Diabetic	Glibenclamide	MKL-300	MKL-500
0 hrs	80.93 ± 3.84	308.56 ± 18.83*	302.60 ± 14.21*	304.66 ± 14.56*	307.98±10.22*
1hrs.	80.61 ± 6.20	309.62 ± 19.08	291.038 ± 15.48	294.87 ± 16.63	294.45±11.52
3hrs.	79.48 ± 4.35	309.99 ± 19.11	276.58 ± 17.10[a]	283.51 ± 15.43	280.73±12.29[a]
5 hrs.	80.89 ± 5.51	309.06 ± 20.20	260.42 ± 16.21[a]	273.72 ± 14.82[a]	267.65±10.92[a]
5th Day	79.84 ± 4.55	310.55 ± 21.4	223.15 ± 15.43	239.65 ± 16.00	236.95±9.36
10th Day	78.56 ± 4.41	312.85 ± 21.67	194.49 ± 16.08	215.77 ± 16.65	204.92±9.80
15th Day	79.54 ± 3.84	316.12 ± 18.52	169.57 ± 11.98[ab]	195.94 ± 14.93[ab]	174.39 ± 12.56[ab]

30 min, 60min and 120 min intervals respectively.

Antidiabetic activity in Streptozotocin induced Diabetic rats

13 days after streptozotocin, control and survival diabetic rats were randomly divided in five groups, each consisting of six animals: Group one as a normal vehicle control received 0.5% sodium CMC with twin 20 (0.2%v/v). Group 2 as a diabetic control and received vehicle. Group 3 diabetic animals received glibenclamide (10 mg/kg, p.o.) Group 4 and 5 diabetic animals received 300 mg/kg and 500 mg/kg MKL extract respectively. After 15 days of above treatments schedule animal's blood was withdrawal by retroorbital plexus (fasted animals) for determination of glucose level, triglyceride, and cholesterol [21-23]. Liver was isolated from respective group of animals for determination of glycogen content.

Assessment for Antidepressant Activity

Evaluation of Grip/Muscle strength

The grip strength of 9 week diabetic animals was measured by simply hanging of animals with their fore limb on fine rope which was hold at two end of pole. The time taken from holding of rope to fall on the surface was considered for the muscle strength determination [16,24]. The animals whose muscle or nerves get damage or weak it get fall soon on the floor.

Antidepressant screening by forced swimming test (FST)

13 days after streptozotocin, control and survival diabetic rats were randomly divided in four groups, each consisting of five or six animals: Group one as a normal vehicle control received 0.5% sodium CMC with twin 20 (0.2%v/v). Group 2 as a diabetic control and received vehicle. Group 3 diabetic animals received standard fluoxetine (20 mg/kg, p.o.) Group 4 and 5 diabetic animals received 300 mg/kg and 500 mg/kg MKL extract. All the groups of animals given chronic treatments with above treatments schedule up to 9 week and thereafter the immobility period was measured using the forced swimming test for evaluation of antidepressant activity [19].

Briefly, rats were placed individually in tank/cylinder (60 cm height, 30 cm diameter) filled with water (28°C–30°C) to a depth of 30 cm; at this depth the rat cannot stand on the cylinder bottom. The frequency and total duration were calculated for each of the following categories by two expert observers. Behavior was scored by two trained observers and the scores were averaged. Behaviors scored were: 1) passive/immobile behavior (floating on the surface of water without any movement of body) 2) Active/mobile behaviors (swimming with slow movements of legs), 3) Floating (with rhythmical simultaneous kicks and occasional pushes off the wall to give speed and direction to the drift) [19, 25]. Experiments were conducted during the period of 9 a.m. to 5 p.m.

Results and Discussion

Diabeties mellitus is a chronic disease characterized by high blood glucose level due to absolute or relative deficiency of circulating insulin level or insulin resistance [26]. Through different types of oral hypoglycemic agents are available along insulin for the treatment of diabeties, there is an increasing demand by patient to use the

Table 3: Effect of Murraya koenigii on biochemical parameters in Diabetic rat Data expressed as mean ± s.d., n = 5. Values were statistically significant at P<0.05: *normal control vs. diabetic control, **significant compared to diabetic control. (Students unpaired t test at level of (p<0.05).

Treatments	Glycogen content Liver	Heart	Total cholesterol	Triglycerides
Vehicle control	1.85 ± 0.06	0.66 ± 0.08	116.37 ± 18.71	58.6 ± 3.3
Diabetic	1.02 ± 0.08*	0.30 ± 0.06*	252.29 ± 24.77*	85.6 ± 4.8*
MKL-300	1.64 ± 0.05**	0.55 ± 0.07**	181.03 ± 16.53**	71.6 ± 4.6**
MKL-500	1.32 ± 0.83**	0.43 ± 0.06**	172.12 ± 15.62**	68.3 ± 2.5**
Glibenclamide	1.41 ± 0.09**	0.51 ± 0.07**	153.87 ± 16.31**	64.6 ± 3.4**

Table 4: Effect of MKL on body weight after 9 week in diabetic rats Data expressed as mean ± s.d., n = 5. *Values were statistically significant ($P < 0.01$) compared to 0 day of respective group. (ANOVA followed by Dunnet test).

Days after STZ Treatment	Vehicle control	Diabetic Control	MKL-300	MKL-500	Fluoxetine
0 Day	209.6 ± 9.38	204.71 ± 9.33	207.43 ± 8.51	210.85 ± 10.78	206.42 ± 11.6
9th week	289.3 ± 9.09*	122.45 ± 8.98*	142.98 ± 12.16*	149.55 ± 9.78*	155.3 2± 13.21*

Table 5: Effect of MKL on mobility behavior after 9 week in diabetic rats All the values are represent in sec. Data expressed as mean ± s.d., n = 5. Values were statistically significant at $P < 0.05$ (student unpaired t test): [a]vehicle control vs. diabetic control, [b]significant compared to diabetic control.

Treatments	Struggling	slow movement	Floating
Control	38.33±6.05	98.66±11.59	16.33±1.52
Diabetic	35.5±6.24	153.4±26.60[a]	58.25±19.77[a]
MKL-300	33.05±5.89	112.3±17.46[b]	28.73±9.76[b]
MKL-500	32.25±6.39	100.75±16.70[b]	32.75±7.63[b]
Fluoxetine	34.33±6.50	115.66±18.22[b]	22.66±5.033[b]

natural products with antidiabetic activity to overcome the side effects and toxicity of synthetic drugs [27]. Herbal antidiabetic drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost [27]. Thus the aim of the present work was to evaluate the antidiabetic activity of ethanolic extract of *Murraya koenigii* leaves.

Diabetic complications chiefly seen in the long term are persistently deleterious to a large extent. Major complications include nephropathy, neuropathy, retinopathy and heart disease, which affect thousands of diabetics every year [4,28]. While some of these complications are closely related to a lack of compliance during antidiabetic therapy, are apparent even with an optimal therapeutic regimen. Thus novel approaches in antidiabetic therapy are aimed not only to decrease high blood glucose levels, but also to eradicate long-term diabetic complications which may cause a diminished life expectancy and/or a poor quality of life. Thus in the present study the emphasis was also given on prevention and management of depression in diabeties which is necessary to improve the quality of life of diabetic patients, to increase treatment compliance, and to decrease the risk of diabetic complications e.g. micro vascular and macro vascular complications [28].

The results of our first study demonstrate to showed antidiabetic activity of *Murraya koenigii*. The effect of extract on normoglycemia was more potent at a dose of 500 mg/kg by the maximum percentage (22.79%) reduction in serum glucose level after 2 hours. Whereas at 300mg/kg reduction in serum glucose level was found to 12.20%. The results of OGTT revealed that the percentage increase in serum glucose level was lowest at the dose of 500 mg/kg (54.32%), at 30 min which was comparable to standard glibenclamide (47.37%) while at 300 mg/kg the serum glucose level was found to 68.29% compared to their 0.0.min reading. The reduction in the blood glucose level results could be either due to delaying absorption of the glucose from the gastro intestinal tract by the extract. The MKL at both doses found to decrease maximum blood glucose level after 120 min. Moreover, percentage reduction in serum glucose level was highest at the dose of 500 mg/kg (26.25%) which was comparable to standard glibenclamide (29.12%) at 120 minute than 300 mg/kg (19.31%). This could be due to increase in the disappearance of glucose from circulation soon it is absorbed in the circulation, by the extract. The result of both normoglycemic and OGTT concludes that at both doses (300 mg and 500 mg) of MKL possess possible hypoglycemic activity (Table 1).

Rats treated with STZ develop almost identical diabetic states and exhibit diabetes symptoms as hyperglycemia, glucosuria, polyuria, polyphagia, polydipsia and weight loss. The ability of STZ to produce such diabetes has previously been reported in numerous studies [21]. Throughout this study untreated diabetic rats exhibited lower body weight compare to normal control. Loss of body weight in diabetic rats could be result from derangements in protein metabolism such as decreased protein synthesis and increased breakdown [29]. However, the loss of the body weight in the diabetic animals was less after the treatment with extract and glibenclamide compared to diabetic control. After single oral doses of the extract (300 mg/kg and 500 mg/kg) produced significant (p<0.05) decrease serum glucose levels at 5h compared to 0 hrs on day 1 which was comparable to standard glibenclamide (Table 2). While there was no significant (p<0.05) difference in the serum glucose level at 5h compared to 3h, indicates the decline in further reduction of serum glucose levels in extract and glibenclamide treated diabetic animals. Once daily repeated oral administration of extract (300 mg/kg and 500 mg/kg p.o) and glibenclamide (10 mg/kg p.o.) for 15 days produced significant (p<0.05) decrease in serum glucose levels on day 5, 10 and 15 which demonstrate antidiabetic activity in the extract (Table 2). The results of the present study was similar our previous finding on the fruit juice of *Murraya koenigii* [16]. The results also supported with recent finding on the leaves powder in diet [30].

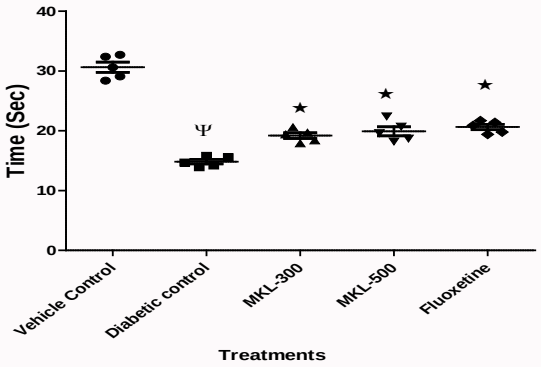

Figure 1: Effect of MKL on grip strength after 9 week in Diabetic rats readings (in seconds) were taken in a mean of three for each animal. Data expressed as mean ± s.d., n = 5. Values are statistically significant at P<0.0001 (ANOVA followed by Dunnet test) ᴪvehicle control vs. diabetic control, *significant compared to diabetic control.

The serum cholesterol and triglycerides level gets altered in diabetes because of the metabolic disturbances. Lipid abnormalities in diabeties mellitus are twice as common as in nondiabetic condition. The most common lipid abnormalities associated with type 2diabetes are hypertriglyceridemia, hypercholestremia and reduced HDL level [31,32]. In type 2 diabeties mellitus lipid profile improve with better glycemic control [33]. Similar results were found in extract and glibencalmide treated groups (Table 3). In which the levels of triglycerides and cholesterol in serum were significantly ($p<0.05$) low compared to diabetic control. Though the levels of triglyceride and cholesterol was not completely normalized but low levels indicate gradual normalization of metabolic disturbance as diabetes get controlled in extract and glibenclamide treated diabetic animals.

Depression is known to have a profound adverse influence on patients' quality of life and overall functioning. It has additional relevance in diabetes because of its association with poor glucose control [3,4]. The symptoms of depression most commonly related to diabetes are weight loss, psychomotor retardation, muscle weakness and fatigue, tiredness, hypersomnia, feelings of worthlessness, and diminished sexual drive [4]. In the present study the psychomotor retardation which was observed after 9 week in diabetic animals indicated by significant decreased in body weight and muscle strength of diabetic animals ($p<0.001$) after 9 week in Streptozotocin compared to vehicle control. All these results indicate the progression of depression after 9 week in diabetic animals (Table 4, Figure 1).

The classical selective serotonin reuptake inhibitor (SSRIs) fluoxetine has extensively used for treatment of depression in diabetic patient because in contrast to the MAOIs and TCAs, the SSRIs are not associated with hyperglycemia and improve metabolic control through their positive effect on weight loss [34,35]. Thus in the present study fluoxetine was used as a standard to compare the protective effect of MKL in progression of depression in diabeties.

The forced swimming test (FST) was first described and has been extensively validated for studying the antidepressant profile of new drugs [19,25]. Animal when exposed to an aversive situation from which there is no possibility of escaping eventually stop struggling and assume a typical immobile posture indicative of behavioral depression [25].

After evaluating the depressive symptoms in diabetic animals [Table 4, Figure 1), the protective effect of chronic treatment up to 9 week with MKL on the progression of depression in diabetic animals was evaluated by measuring the immobility period in FST model. The results of the study indicates to significant ($p<0.05$) increase in the slow movement and floating time after 9 week in streptozotocin treated diabetic rat compared to vehicle control rat indicates decreases in active mobility in diabetic rat (Table 5). While prior treatment with MKL decreases the immobility behavior which is comparable to standard antidepressant Fluoxetine (Table 5). Previously, it was reported that antidepressants prevent or inhibit the development of depression in diabetes. Similarly, we have observed in our present study that MKL protect from progression of depression in diabetes.

Phytochemically there was found to show presence of carbohydrates, gums, mucilage, proteins, Triterpenoids, cardiac glycosides, alkaloids, flavonoids and phenolic compounds. Previously antioxidant carbazoles have been reported to be present in MKL [36,37]. Oxidative stress plays a role in depression, and diabetes presents a situation of increased oxidative stress in the brain. There is a positive correlation with decreased glutathione and catecholamines in the brain with depression, and there is a significant increase in their levels with antidepressants [38,39]. Few studies have demonstrated the antidiabetic potential of *Murraya koenigii* and its effective role in decreasing the oxidative stress produced due to diabetes [30-40]. Thus based on our finding as well as reported literature demonstrate that the presence of antioxidant carbazole alkaloids of *Murraya koenigii* might be involved in stabilization both glycemic level as well as the prevent the progression of depression in streptozotocin induced diabetic rats in present study. While further studies are required to elucidate the exact protective mechanism of *Murraya koenigii* in progression of depression in diabeties. In conclusion our study demonstrated beneficial effect in diabeties. It decreases blood glucose level dose dependently and also has potential to decrease the progression of depression in diabeties so it would be helpful in diabetic patient for prevention of diabetic complication like depression.

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