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Antihyperglycemic Activity of *Murraya koenigii* Leaves Extract on Blood Sugar Level in Streptozotocin-Nicotinamide Induced Diabetes in Rats

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The effects of *Murraya koenigii* leaves are very less studied in streptozotocin-nicotinamide (STZ-NA) induced diabetes rat model, in spite of several studies reported its antidiabetic effects in alloxan and STZ induced diabetes. The present study was undertaken to assess the effects of *Murraya koenigii* leaves extract on the blood sugar level (BSL) of STZ-NA diabetic rats. Experimental diabetes was induced by STZ injection intraperitoneally (i. p) after 30 min of NA injection i. p in all groups apart from normal control group. Group I (normal control) and Group II (diabetic control) rats received distilled water. Group III rats treated Metformin, Group IV and Group V rats treated *Murraya koenigii* leaves aqueous extract and *Murraya koenigii* leaves methanolic extract respectively. BSL and body weights of rats were measured at each week of the period of 28 days. Our results indicate that oral administration of *Murraya koenigii* leaves reduces BSL significantly compared with the diabetic group. No weight loss was observed in all groups. The findings of the present study suggest that *Murraya koenigii* is proven as anti-diabetic agent in diabetic rats.

Keywords: Streptozotocin-Nicotinamide, *Murraya koenigii*, Diabetes, Blood Sugar Level.

Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycemia and abnormalities in carbohydrate, lipid and protein metabolism, associated with absolute or relative deficiencies in insulin secretion and/or insulin action[1]. WHO Global Report 2016 on diabetes has demonstrated that the number of adults living with diabetes has almost increased to 422 million adults[2]. India faces recently an uncertainty in future about the potential health burden of diabetes. DM is fast growing as a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease[3]. Untreated diabetes leads to many acute and chronic complications in diabetic population. Acute complications involve diabetic ketoacidosis, nonketotic hyperosmolar coma whereas chronic complications consist of cardiovascular disease, stroke, nephropathy, foot ulcers and retinopathy. The prevalence of type 2 diabetes mellitus along with hypertension was found about 20.2 %, 22.2 % in the obese population and were 15.5 % and 8.2 %, in the overweight population respectively[4]. Among the major types of diabetes, viz; type I and type II, type II DM becomes the commonest having 90-95 % of population[5]. China tops the list with 90.0 million followed by India which has 61.3 million persons affected by diabetes. The numbers are estimated to

rise to 129.7 million and 101.2 million, respectively by 2030[6].

Conventional oral hypoglycemic drugs used for treating DM have been proven for their characteristic adverse effects. Therefore, the research has still attention on the existing traditional medicinal plants having well-known scientific evidences for hypoglycemic activity; recurrent attempts to isolate newer orally therapeutic hypoglycemic phytoconstituents and to develop a novel molecular drug with maximum effective and minimum or negligible side effects[5].

Streptozotocin (STZ) is an extensively used as diabetogenic agent for the induction of diabetes in animals. In rodents, type I diabetes can be induced by a single STZ injection while type II diabetes can be induced by at least three approaches, which include STZ injection after a) administration of Nicotinamide (STZ-NA) or b) High Fat Diet (HFD) feeding followed by a low-dose STZ injection, and c) STZ injection during the neonatal period[7]. So this STZ-NA model was chosen as one of these three above mentioned approaches to evaluate the antidiabetic effect of *Murraya koenigii* leaves.

Murraya koenigii is an aromatic pubescent shrub or small tree generally known as "*Kadhipatta*" in India and as common synonym as Curry leaves. It contains several bioactive compounds like euchrestine B, bismurrayafoline E, mahanine, mahanimbicine, mahanimbine[8] and essential oil[9] which contribute to antioxidative, hypoglycaemic, anti-trichomonal, blood protective and hepatoprotective effects[10-13]. Till date reviewing several literature, the antidiabetic activity of *Murraya koenigii* leaves on STZ induced type I diabetes in rats has reported[14]. However, the effect of this plant in STZ-NA induced diabetes in rats has been reported in a very few studies so this research work has proposed. The study was aimed to assess the antihyperglycemic effect of aqueous and methanolic extracts of *Murraya koenigii* leaves on blood sugar levels (BSL) of STZ-NA injected rats.

MATERIAL AND METHODS

Drug and chemicals

Streptozotocin (Sisco Research Laboratories Pvt. Ltd, India), Nicotinamide (Sisco Research Laboratories Pvt. Ltd, India), Metformin pure form powder (Sigma-Aldrich Ltd, India), Methanol (Loba-chemie Pvt. Ltd, India) were purchased. Accu-chek Active blood glucose meter and strips (Roche, India) were procured. All reagents and chemicals used were of analytical grade and stored in a refrigerator at -4°C. The reagents were equilibrated at room temperature for 30 minutes before the start of analysis.

Collection and authentication of plant material

Leaves of *Murraya koenigii* were collected from the local area of Karad in Maharashtra, India (17.2760° N, 74.2003° E), certified and authenticated by Department of Botany, M. S. Shinde Mahavidyalaya, Tisangi, Kolhapur, India. The plant specimen voucher no: V03 (Ref: MHST/2016-17/28) of the plant was deposited in the herbarium. Fresh leaves were purchased from the local market of Karad, washed under tap water thoroughly; dried under shade and powdered by using a mechanical grinder.

Preparation of Metformin solution

Metformin solution was prepared by dissolving 80 mg of Metformin pure powder in 4 milliliter (ml) of distilled water (DW) to attain a concentration of 20 miligmam/mililiter (mg/ml), labeled as MET and its dose was selected as 50 mg/kg body weight per oral (b w, p. o).

Preparation of *Murraya koenigii* leaves extracts

Methanolic and aqueous extracts of *Murraya koenigii* leaves were prepared by soxhletation method. About 50 g of shade dried leaves powder of *Murraya koenigii* was packed in a cloth bag and placed in the thistle of Soxhlet apparatus. In Soxhlet apparatus, hot continuous extraction process was continued for 4 days till the dark brown colour of aqueous extract turned to pale yellow while in case of methanolic extract, the appearance of dark green to colourless. Collected extracts were concentrated in a vacuum rotary evaporator at Govt. College of Pharmacy, Karad, Maharashtra, India and dried by evaporating in hot air oven at 45°C. Percentage yield of methanolic extract of *Murraya koenigii* (MEMK) leaves and aqueous extract of *Murraya koenigii* (AEMK) leaves were calculated with respect to the total quantity of powder used for the extraction.

Preparation of extract solutions

Each extract solution was prepared by dissolving 400 mg of extract in 4 ml of DW to

attain a concentration of 100 mg/ml and its dose was selected as 200 mg/kg b w, p. o.

Acute toxicity study of extracts

Determination of lethal dose 50% LD_{50}: AEMK and MEMK were subjected in the acute toxicity test as per organization for environmental control development (OECD)-423 guidelines[15] for fixing the therapeutic dose. The dose of 2000 mg/kg b w of AEMK and MEMK taken as a starting dose and were orally administrated to healthy Wistar rats. Lethal dose 50% (LD_{50}) was determined and $1/10^{th}$ of LD_{50} was taken as therapeutic dose for antidiabetic activity.

Experimental animals

Healthy albino Wistar rats of either sex were obtained from the Animal House, Krishna Institute of Medical Sciences (KIMS), Karad, India. Animals were maintained under standard husbandry conditions at room temperature, light: dark cycle for an acclimatization period of 7 days. Experiment study was compiled with the guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA) for animal experimentation of laboratory and Institutional Animal Ethics Committee (Reg. No. 255/PO/2000/bc/CPCSEA) KIMS, Karad had approved the study.

Inclusion criteria

Albino Wistar rats of either sex weighing 120-250 gm.

Albino Wistar rats with normal behaviour and activity

Exclusion criteria

Pregnant rats and those that have delivered once

Albino Wistar rats that were previously used for any other experimental purpose

STZ-NA induced diabetes in rats

It was carried out for STZ-NA induced diabetes in rats[16, 5, 17]. The study was performed for 28 days by repeated oral administration. Diabetes was induced in overnight fasted rats of Group II to V was injected intraperitoneally with a single dose of NA (110 mg/kg b w) [5] first followed by a single dose of STZ (55 mg/kg b w) once. After 6 hours, STZ-NA injected rats were fed orally 5% glucose solution for the next 24 h to prevent fatal hypoglycemia. After 72 h of STZ-NA injection, the rats were examined for diabetes by measuring BSL of rats with help of glucometer for confirmation. After development of diabetes, it was stabilized over a period of 7 days. Diabetic rats were labeled as STZ-NA diabetic (STZNAD) rats while normal untreated as non-diabetic (ND) rats.

Experimental design

STZNAD rats of either sex were randomly divided into four groups (six animals per group) and one group consisting 6 ND rats. They had free access to water and animal diet throughout the study period. Oral administration of MET, AEMK and MEMK were given at once daily for 28 days.

Group I-NC: ND rats received DW and served as normal control

Group II-DC: STZNAD rats received DW and served as diabetic control

Group III-MET: STZNAD rats received MET-100 mg/kg/day, p. o

Group IV-AEMK: STZNAD rats received AEMK-200 mg/kg/day, p. o

Group V-MEMK: STZNAD rats received MEMK-200 mg/kg/day, p. o

Monitoring of body weight and blood sugar level during treatment

Body weights of rats were measured on digital weighing machine on (0, 14^{th} and 28^{th} days). Blood samples of rats were collected by cutting tip of tails and BSL checked by using blood glucose test strips with Accu-check glucometer. BSL readings were taken at every week interval of the study period (0, 7^{th}, 14^{th}, 21^{st} and 28^{th} days). All animals were sacrificed by cervical decapitation at the end of study.

Statistical analysis

Data were expressed as mean ± standard error means (SEM). Data analysis was performed by using Graph Pad Prism 5.0 software (Graph Pad, San Diego, CA). All data were analyzed by using two-way repeated Analysis of Variance (ANOVA) and Tukey's test was applied for *Post Hoc* analysis. The value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Percentage yield

Percentage yield was found to be AEMK (14.35%) and MEMK (13.75%) with respect to the total quantity of powder used for the extraction.

Acute toxicity study of *Murraya koenigii* leaves extracts

The acute toxicity study observed no mortality or any toxic reactions within 4 h and after 14 days by oral administration of AEMK and MEMK even at the highest dose (2000 mg/kg). The dose of 200 mg/kg was considered safe at 1/10th dose of LD_{50} which was in agreement with report by Lanjhiyana *et al*., 2011[18].

Effect of *Murraya koenigii* leaves extracts on body weight

No significant changes in body weight (g) of rats were observed during the study period in all groups (Table 1).

Effect of *Murraya koenigii* leaves extracts on blood sugar level

Oral administration of AEMK (200 mg/kg b w) and MEMK (200 mg/kg b w) caused the significant reduction in BSL (mg/dL) as compared to the diabetic group (Table 2).

DISCUSSION

STZ is an antibiotic produced by the soil bacterium *Streptomyces achromogenes* that exhibits broad spectrum of antibacterial properties[19]. STZ leads to pancreatic β-cells damage therefore intraperitoneal injection of NA is administrated prior to STZ administration in this animal model as it partially protects insulin-secreting cells against STZ[5, 17]. Alloxan and STZ are generally used chemicals as they are cytotoxic to pancreatic β-cells which induce hyperglycemia[20] and initiate type I diabetes or insulin dependent diabetes mellitus (IDDM) model. If STZ is injected alone, degenerates pancreatic β-cells totally and makes insulin-deficient; but prior injection of NA leads to the partial protection to insulin-secreting pancreatic β-cells against destructive effects of STZ[21]. The combined STZ-NA model prevents pancreatic β-cells to become completely insulin-deficient so it is suitable for non-insulin dependent diabetes mellitus (NIDDM) model. This study model provides the characteristics of insulin resistance, dyslipidemia and inadequate secretion of insulin by pancreatic β-cells or combined of all[22].

Several alkaloids present in the plant are reported as oral potential hypoglycemic agents

Table 1. Effect of *Murraya koenigii* leaves extracts on body weight in STZ-NA induced diabetic rats

Group	Day 0(g)	Day 14(g)	Day 28(g)
I- NC	201.50 ± 20.43	207.16 ± 20.34	213.16 ± 19.16
II- DC	156.83 ± 08.27	171.83 ± 09.78	166.16 ± 11.64
III- MET	138.83 ± 04.29	149.33 ± 03.85	146.83 ± 05.23
IV- AEMK	187.00 ± 17.70	207.5 ± 21.73	172.6 ± 12.46
V- MEMK	157.16 ± 12.03	174.33 ± 12.81	169.83 ± 12.54

Values are expressed in Mean ± SEM, Number of animals = 6, MET- Metformin (50 mg/kg) AEMK- Aqueous extract of *Murraya koenigii* leaves (200 mg/kg), MEMK -Methanolic extract of *Murraya koenigii* leaves (200 mg/kg)

Table 2. Effect of *Murraya koenigii* leaves on blood sugar level in STZ-NA induced diabetic rats

Group		Day 0(mg/dL)	Day 7(mg/dL)	Day 14(mg/dL)	Day 21(mg/dL)	Day 28(mg/dL)
I-NC		065.00 ± 00.80	066.10 ± 01.20	064.6 ± 02.30	064.3 ± 02.04	066.5 ± 01.90
II-DC		483.83 ± 50.57	450.00 ± 51.37	406.60 ± 22.46	393.50 ± 39.12	396.60 ± 36.22
III-MET		323.30 ± 24.66*	168.50 ± 08.04***	133.60 ± 10.41***	153.50 ± 20.87***	140.00 ± 19.65***
IV-AEMK		336.00 ± 37.21	195.00 ± 12.95***	161.10 ± 09.41***	173.30 ± 24.59***	154.10 ± 17.73***
V-MEMK		380.16 ± 51.55	201.60 ± 04.99***	172.60 ± 33.06***	261.10 ± 41.26*	231.60 ± 39.66**
ANOVA	F	16.215	30.507	46.816	17.685	21.999
	P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Values are expressed in Mean ± SEM, Number of animals = 6, MET- Metformin (50 mg/kg) NS- Not significant, *** - p<0.001, ** - p <0.01, * - p <0.05 (Comparison with II), AEMK- Aqueous extract of *Murraya koenigii* leaves (200 mg/kg), MEMK -Methanolic extract of *Murraya koenigii* leaves (200 mg/kg)

in-vivo and their effects on glucose uptake and GLUT4 translocation in L6-GLUT4myc myotubes in STZ-induced diabetic rats stated in the study by Patel *et al*; 2016[23]. In the reported study by Kumar *et al*. 2013, mahanimbine (1 mM) showed equivalent effect with insulin (1 µM) in the glucose utilization test with 3T3-L1 cells[24]. Hence our current study supports the presence of alkaloid as major chemical constituents of the plant which leads to the glucose utilization in *in-vitro*[25] as well as *in-vivo*[26] models.

In the present study, the antidiabetic study of AEMK and MEMK was evaluated in STZ-NA induced diabetes in rats. Continuous treatment of AEMK and MEMK with same dose at 200 mg/kg/day for a period of 28 days exhibited a significant decline of BSL ($p < 0.05$) in diabetic rats. Our results of the study hypothesized that the late onset and prolonged duration of action may result from the improved pancreatic cyto-architecture[27,28]. *Murraya koenigii* leaves at dose of 200 mg/kg/day could lower glucose in STZ induced type I diabetes in rats in the documented study by Arulselvan *et al*., 2006[14]. Our findings have shown antihyperglycemic effect at dose of 200 mg/kg/day in the present study is in the line with the studies of Arulselvan *et al*., 2006[14]; Paul *et al*., 2011[29]. Based on the report by Adebajo *et al*., 2006[11], the dose of plant extract (200 mg/kg/day) could reduce BSL in both normal and diabetic rats.

Liver is enriched with a variety of antioxidant enzymes which acts as natural free radical scavengers. Contradictory to this, the islets of Langerhans are susceptible to the cytotoxic effects of the free radicals due to lower concentration of such antioxidant enzymes[28] as pancreatic cytotoxicity is achieved through the generating free radicals. Being cytoprotective agent, pancreatic cells of Langerhans islets are partially protected by NA itself against oxidative stress by STZ[21]. *Murraya koenigii* defends pancreatic cells of Langerhans islets on the account of flavonoids and phenolics as well as synergizes hypoglycemic activity due to the major portion of naturally occurring carbazole alkaloids like koenidine and mahanimbine [30, 24, 23].

CONCLUSION

Murraya koenigii could lower BSL in diabetic rats so it is proven as an effective, safe anti-diabetic agent. It is recommended to elaborate different activities of isolated bioactives in the plant and further to be investigated the effect on the lipid profile and antioxidant levels in diabetic rats.

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REFERENCES

1. Valiathan MS. Healing plants. *Curr Sci*. **75**: 122-27. (1998).
2. WHO Global report on diabetes. Accessed on 7th May 2016. Available from: http://www.who.int/diabetes/global-report/en/
3. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. *Australas Med J*. **7**(1):45-8. (2014).
4. Mandal A. Study of prevalence of type 2 diabetes mellitus and hypertension in overweight and obese people. *J Family Med Prim Care*. **3**(1):25-8. (2014).
5. Kumar R, Pate DK, Prasad SK, Sairam K, Hemalatha S. Antidiabetic activity of alcoholic leaves extract of *Alangium lamarckii* Thwaites on streptozotocin-nicotinamide induced type 2 diabetic rats. *Asian Pac J Trop Med*. **4**(11):904-9. (2011).
6. Ramachandran A, Shetty AS, Nanditha A, Snehalatha C. In Chapter 40: Type 2 Diabetes in India: Challenges and Possible Solutions. 186-190. Accessed on 9th September 2017. Available from: http://www.apiindia.org/medicine_update_2013/chap40.pdf
7. Wu J, Yan LJ. Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic â cell glucotoxicity. *Diabetes Metab Syndr Obes*. **8**:181-8. (2015).
8. Tachibana Y, Kikuzaki H, Lajis NH, Nakatani N. Antioxidative activity of carbazoles from *Murraya koenigii* leaves. *J Agric Food Chem*. **49**(11): 5589-94. (2001).
9. Rajendran MP, Pallaiyan BB, Selvaraj N. Chemical composition, antibacterial and antioxidant profile of essential oil from *Murraya koenigii* (L.) leaves. *Avicenna J Phytomed*. **4**(3):200-14. (2014).

10. Phatak RS, Matule SM. Beneficial effects of *Murraya koenigii* leaves chloroform extract (MKCE) on erythrocyte, thrombocyte and leukocyte indices in lead-intoxicated mice. *Biomed Pharmacol J*. **9**(3): 1035-40. (2016).
11. Adebajo AC, Ayoola OF, Iwalewa EO, Akindahunsi AA, Omisore NO, Adewunmi CO, Adenowo TK. Anti-trichomonal, biochemical and toxicological activities of methanolic extract and some carbazole alkaloids isolated from the leaves of *Murraya koenigii* growing in Nigeria. *Phytomedicine*. **13**(4):246-54. (2006).
12. Ghosh D, Firdaus SB, Mitra E, Dey M, *et al*. Protective effect of aqueous leaf extract of *Murraya koenigii* against lead induced oxidative stress in rat liver, heart and kidney: a dose response study. *Asian J Pharm Clin Res*. **5**(Suppl 4):54-58. (2012).
13. Ghosh D, Firdaus SB, Mitra E, Dey M, *et al*. Hepatoprotective activity of aqueous leaf extract of *Murraya koenigii* against lead-induced hepatotoxicity in male Wistar rat. *Int J Pharm Pharm Sci*. **5**(1):285-295. (2013).
14. Arulselvan P, Senthilkumar GP, Sathish Kumar D, Subramanian S. Anti-diabetic effect of *Murraya koenigii* leaves on streptozotocin induced diabetic rats. *Pharmazie*. **61**(10):874-7. (2006).
15. OECD/OCDE. Acute Oral Toxicity–Acute Toxic Class Method. *OECD Guidel Test Chem*. **423**:1-14. (2001).
16. Sze Han Ng, Mohd Shazwan Mohd Zain, Fatariah Zakaria, Wan Rosli Wan Ishak, and Wan Amir Nizam Wan Ahmad. Hypoglycemic and antidiabetic effect of Pleurotus sajor-caju aqueous extract in normal and streptozotocin-induced diabetic rats. *Biomed Res Int.* **2015**: 214918. (2015).
17. Szkudelski T. Streptozotocin-nicotinamide-induced diabetes in the rat. Characteristics of the experimental model. *Exp Biol Med (Maywood).* **237**(5):481-90. (2012).
18. Lanjhiyana S, Garabadu D, Ahirwar D, Bigoniya P, Rana AC, KC Patra, *et al*. Hypoglycemic activity studies on root extracts of *Murraya koenigii* root in Alloxan-induced diabetic rats. *J Nat Prod Plant Resour*. **1**(2): 91-104. (2011).
19. Eleazu CO, Eleazu KC, Chukwuma S, Essien UN. Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *J Diabetes Metab Disord*. **12**(1):60. (2013).
20. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia*. **51**:216-226. (2008).
21. Kuchmerovs'ka TM, Donchenko HV, Tykhonenko TM, Huzyk MM, Stavni-chuk RV, Ianits'ka LV, Stepanenko SP, Klymenko AP. [Nicotinamide influence on pancreatic cells viability]. *Ukr Biokhim Zh (1999).* **84**(2):81-8. (2012).
22. Okonkwo PO, Okoye ZSC. Comparative effects of antidiabetic drug, metformin and deferoxamine, on serum lipids, serum ferritin and endocrine indicators of diabetes mellitus complications in streptozotocin diabetic rats. *Int J Biochem Res Rev*. **4**(6): 536-549. (2014).
23. Patel OP, Mishra A, Maurya R, Saini D, Pandey J, Taneja I, *et al*. Naturally occurring carbazole alkaloids from *Murraya koenigii* as potential antidiabetic agents. *J Nat Prod*. **79**(5):1276-84. (2016).
24. Kumar BD, Krishnakumar K, Jaganathan SK, Mandal M. Effect of mangiferin and mahanimbine on glucose utilization in 3T3-L1 cells. *Pharmacogn Mag*. **9**(33):72-5. (2013).
25. Phatak RS, Khanwelkar CC, Datkhile KD, Hendre AS. Investigation of antioxidant and anti-diabetic activities of *Murraya koenigii* leaves methanolic and aqueous extract by *in-vitro* methods. *Int J Res Pharm Sci*. **9**(4): 1460-64. (2018).
26. Hendre AS, Sontakke AV, Phatak RS. Evaluation of *in-vitro* antidiabetic and antioxidant activity of selected Indian spices. *Int J Res Pharm Sci*. **9**(3): 678-685. (2018).
27. Shah SN, Bodhankar SL, Badole SL, Kamble HV, Mohan V. Effect of Trigonelline: An active compound from *Trigonella foenum graecum* Linn. in alloxan induced diabetes in mice. *J Cell Tissue Res*. **6** (1): 585-90. (2006).
28. Burade KB and Kuchekar BS. Antidiabetic activity of madhunashini (MD-19) in alloxan induced diabetes mellitus. *J Cell Tissue Res.*; **11**(1): 2515-20. (2011).
29. Paul S, Bandyopadhyay TK, Bhattacharyya A. Immunomodulatory effect of leaf extract of *Murraya koenigii* in diabetic mice. *Immunopharmacol Immunotoxicol* **33**(4):691-9. (2011).
30. Dineshkumar B, Mitra A, Mahadevappa M. Antidiabetic and hypolipidemic effects of mahanimbine (carbazole alkaloid) from *Murraya koenigii* (rutaceae) leaves. *Int J Phytomed.* **2**: 22-30.(2012).