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Investigation of Nootropic and Neuroprotective Activity of *Myristica malabarica* Bark Extracts on STZ induced Cognitive Impairment in Experimental Animals

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ABSTRACT

The present study aims to assess the *Myristica malabarica* Bark (MM) extracts in the diabetes-induced cognitive impaired rat model for its nootropic and neuroprotective activity. Memory enhancing activity was evaluated by Y maze and Morris water maze test, respectively. Neuroprotective effects of MM bark extracts were assessed by measuring the acetylcholinesterase, lipid peroxide, superoxide dismutase (SOD), total nitric oxide (NO), catalase (CAT) and glutathione (GSH) levels in the brain of diabetic rats. The *Myristica malabarica* bark methyl alcohol extract (MMMA) (100 and 200 mg/kg) was observed to affect a significant improvement in spontaneous alteration ($P<0.01$, $P<0.001$) and transfer latency ($P< 0.01$ $P<0.001$) in retention trials on Y maze and Morris water maze test respectively. However, a significant reduction in acetylcholinesterase activity ($P<0.001$), lipid peroxide ($P<0.001$), total NO ($P< 0.001$) and a substantial increase in SOD, CAT and GSH ($P<0.001$) levels was observed in animals treated with MMMA (200 mg/kg) related to the diabetic control group. The current results indicate that *Myristica malabarica* extracts were defending the cognitive decline in diabetes condition and which requires some additional studies to clarify its mode of action.

Keywords: *Myristica malabarica*; Nootropic; Neuroprotective; Cognitive decline.

INTRODUCTION:

Diabetes mellitus (DM) is a clinical condition with a set of symptoms, considered by hyperglycemia owing to a complete or comparative lack of insulin or non-responsiveness of tissues to insulin which affects at least 382 million people worldwide [1]. DM is regarded as a cause of high mortality and morbidity rate due to many physiological complications. Cognitive dysfunction has been considered the greatest prevalent and significant one, especially in older people with type 2 diabetes mellitus (T2DM) [2].

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Alzheimer's disease (AD), a chronic neurodegenerative disease, is the utmost common form of dementia regarded as a warning sign of temporary memory loss i.e., difficulty in remembering recent events, this happens to owe to the loss of intelligence cells [3]. Correlation between Alzheimer's disease and diabetes have been well established. Many clinical and epidemiological studies revealed that the pathophysiological features of diabetes and neuropathic disease are comparable to both, which share complex and connected mechanisms, including insulin resistance, inflammation, and oxidative stress [4].

Besides, the impairment of insulin signaling in the brain may injure the capability of neurons to self-repair and could enhance the development of neurodegenerative disorders [5]. Many preclinical studies, both type-1 and type-2 diabetic models, used to cause severe memory

deficits [6]. The augmented oxidative stress in diabetes produces oxidative damage in many regions of the rat brain including hippocampus.

Plants show a principal role in discovering new therapeutic agents [7] and have been considered as sources of biologically active substances including antioxidants and hypoglycemic and neuroprotective agents [8, 9]. *Myristica malabarica* Lam (*Myristicaceae*) is widely distributed in the Western Ghats Forest region and is commonly called Malabar nutmeg or Kaatuhjathi. The plant was known to be used for antioxidant, antidiabetic, anti-ulcer, anti-inflammatory, analgesic, sedative, hypnotic, and antimicrobial actions [10]. The current study intended to assess the effectiveness in animals with *Myristica malabarica* (**MM**) on various cognitive and oxidative changes in STZ induced young diabetic rats having severe hyperglycemia (FBS ≥ 250 mg/dl).

MATERIAL AND METHODS:

Collection of Plant Materials

Myristica malabarica (**MM**) bark was collected from the tree in December 2018 from the Thiruvananthapuram, Kerala, India.

Chemicals

Piracetam (Alkem Laboratories Ltd), Metformin (Cipla Pharmaceuticals), Diagnostic Kits (Bio Lab, India), and Streptozotocin were bought from Sigma Aldrich, USA. Other chemicals used in the study were of analytical grade.

Experimental Animals

For this study the strains of wistar rats (150±50 gm) of both gender were selected and procured from Mahaveer enterprises, Hyderabad and acclimated to the fixed research laboratory temperature, needed humidity and with 12 h light/dark conditions set for one week. The animals remained fed through a consistent pellet diet and water *ad libitum*.

Preparation of MM Bark extracts

Soxhlet extractor was used for the extraction of **MM** bark for 72 hrs at the temperature below the boiling point of the solvent *via* increasing polarity order petroleum ether (**PE**), ethyl acetate (**EA**) and methanol (**MA**). Whatman filter paper (No.1) was used to filter the extract and later concentrated under vacuum. Finally, dried at 45°C and the dried extracts were remained preserved in a disinfected container and frozen till usage.

Phytochemical Investigation

Every plant extract remained vaporized to the residue and dilute hydrochloric acid was added to it. Subsequently mixed, dissolved and then filtered. The filtrate used for performing the identification tests for various phytochemical constituents [11].

Acute toxicity study

The acute toxicity test was performed as per the OECD guidelines No. 423. In each step, three animals were employed. The dosage range was chosen consisting of the four fixed-dose levels, *i.e*., 5, 50, 300, and 2000 mg/kg body weight *p.o* [12].

Diabetes Induction

After acclimatization all rats were kept in overnight fasting condition and randomly divided in to ten groups, each group contain six rats. For induction of diabetes in the experimental animals, 55 mg/kg of streptozotocin (STZ) was given *i.p* to the animals. For confirmation of diabetes, estimated the glucose level in the next 48 hours of STZ injection under light anesthesia. The glucose levels was evaluated by the GOD-POD method and the animals were observed to possess more than 250 mg/dl of blood glucose reflected as diabetic and recommended for additional investigation [13, 14].

Y maze Test

The treatment protocol was illustrated in Table 1. The restrained Y maze study was performed for prompt memories, which provides the complete alteration in behaviour. Animals to be situated on the end of any arm and recognized to way easily over the maze. The period limit continued steady to 8 mins so, every period ended 8 mins later. Limb admittance was considered when the back legs of the rat stayed totally inside the arm. Natural

alteration behaviour was perfect as entrance into wholly three arms on consecutive selections. After acclimatization all rats were kept in overnight fasting condition and randomly divided into ten groups, each group contain six rats. After recording initial reaction time, treatment with standard drugs (metformin and piracetam), PEMM (100 and 200 mg/kg), EAMM (100 and 200 mg/kg) and MAMM (100 and 200 mg/kg) was given to each rat. The each rat was kept in Y maze in order to record percentage spontaneous variations on day 71 & 75 [15].

Table 1: Protocol for evaluation of memory enhancing activity by Y maze test of MM extracts using rats.

Group	Status	Treatment
I	Normal Control (NC)	0.1% Sodium CMC
II	Disease Control (DC)	0.1% Sodium CMC+55 mg/kg Streptozotocin
III	Diabetes+Metformin	0.1% Sodium CMC+10 mg/kg Metformin
IV	Diabetes+Piracetam	0.1% Sodium CMC+5 mg/kg Piracetam
V	Diabetes+PEMM	0.1% Sodium CMC+100 mg/kg extract of PEMM
VI	Diabetes+PEMM	0.1% Sodium CMC+200 mg/kg extract of PEMM
VII	Diabetes+EAMM	0.1% Sodium CMC+100 mg/kg extract of EAMM
VIII	Diabetes+EAMM	0.1% Sodium CMC+200 mg/kg extract of EAMM
IX	Diabetes+MAMM	0.1% Sodium CMC+100 mg/kg extract of MAMM
X	Diabetes+MAMM	0.1% Sodium CMC+200 mg/kg extract of MAMM

PEMM=Petroleum Ether extract of Myristica malabarica. EAMM=Ethyl Acetate extract of Myristica malabarica. MAMM=Methyl alcohol extract of Myristica malabarica

Morris Water Maze Test

The treatment protocol was illustrated in Table 2. On day one rats were educated to swim for 60 sec in the non-existence of the stage. Throughout four consecutive days, rats remained assumed the probationary session through the stage. If rat locates the stage, allowed remaining continuously it intended for 10 sec. The rat not finds, placed again for same time and now detached on platform. After acclimatization all rats were kept in overnight fasting condition and randomly divided into ten groups, each group contain six rats. After recording initial reaction time, treatment with standard drugs (metformin and piracetam), PEMM (100 and 200 mg/kg), EAMM (100 and 200 mg/kg) and MAMM (100 and 200 mg/kg) was given to each rat and now rats stayed separately exposed to investigation test session the stage remained detached as of the pool and might swim for 120 sec to examine aimed at it. On day 71, animals were tested for latency time was determined [16].

Table 2: Protocol for evaluation of memory enhancing activity by Morris water maze test of MM extracts using rats.

Group	Status	Treatment
I	Normal Control (NC)	0.1% Sodium CMC
II	Disease Control (DC)	0.1% Sodium CMC+55 mg/kg Streptozotocin
III	Diabetes+Metformin	0.1% Sodium CMC+10mg/kg Metformin
IV	Diabetes+Piracetam	0.1% Sodium CMC+5mg/kg Piracetam
V	Diabetes+PEMM	0.1% Sodium CMC+100mg/kg extract of PEMM

Group	Status	Treatment
VI	Diabetes+PEMM	0.1% Sodium CMC+200mg/ kg extract of PEMM
VII	Diabetes+EAMM	0.1% Sodium CMC+100mg/kg extract of EAMM
VIII	Diabetes+EAMM	0.1% Sodium CMC+200mg/kg extract of EAMM
IX	Diabetes+MAMM	0.1% Sodium CMC+100mg/kg extract of MAMM
X	Diabetes+MAMM	0.1% Sodium CMC+200mg/kg extract of MAMM

Neurotoxicity Studies

After treatment schedule all group animals were forewent by cervical dislocation and brain was removed and weighed. Total brain was washed through ice cold saline and make uniform by take 20 mg of the tissue per ml in chilled phosphate buffer (pH 7.4). The homogenates were centrifuged at 800 rpm for 5 mins at 4°C to distinct the nuclear fragments. The obtained supernatant was centrifuged at 1050 rpm for 20 minutes at 4°C to get the supernatant. Such attained supernatant was then used for neurochemical estimation.

Estimation of Acetylcholinesterase (AChE)

AchE estimated by method of Ellman's named later George Ellman was used [17]. A total of 0.4 ml supernatant was added to 2.6 ml of phosphate buffer (0.1 mol/L, pH 8) and 100 µL of 5, 5′-dithiobis-(2-nitrobenzoic acid), then estimated absorbance by a spectrophotometer at 412 nm. The 20 µL of substrate mixed with acetylthiocholine-iodide and recorded the changes in absorbance for a period of 10 minutes at intervals of 2 minutes. Alteration in the absorbance per minute was measured and acetylcholinesterase activity was expressed as µM/l/min/gm of tissue [17].

TBARS Assay

Lipid peroxidation property of plant extracts evaluated as per the method of Wills et al [18]. Formation of MDA is crucial for thiobarbituric acid reactive substances (TBARS) levels, and it is stated in MDA/mg of protein.

Total nitric oxide levels

The 500 µl of Greiss reagent added to 100 µl of supernatant liquid then absorbance was estimated at 546 nm. The amount of nitrite was measured by using a standard curve for sodium nitrite and it is expressed as ng/mg of protein [19].

Superoxide dismutase (SOD) levels

SOD levels were estimated as per the method of Kono and for this supernatant (100 µl), sodium carbonate (1ml), of nitroblutetrazolin (0.4 ml) and ethylene diamine tetra acetic acid (0.2 ml) was added, later the absorbance was estimated at 560 nm and expressed in µg/mg of protein [20].

Catalase (CAT) levels

CAT amount in entire treatment groups estimated by the method of Claiborne et al [21]. A supernatant of 100 µl added with 1.9 ml of phosphate buffer measure the absorbance at 240 nm and it is specified as µg/mg of protein.

Glutathione (GSH) levels

In total treatment groups as GSH levels were assessed as per the method of Jollow et al [22]. The GSH levels were estimated at 412 nm and stated as ng/mg protein.

Results Analysis

The data were explored through one way ANOVA followed by Dunnett's multiple comparison tests with Graph pad prism 5.0 and p value < 0.05 must be deliberated as significant.

RESULTS

Evaluation of Phytochemicals

The outcomes showed methanolic extract entail of the bioactive composites like glycosides, phenols, alkaloids, flavonoids and tannins.

Toxicity Study

MM bark extract up to 2000 mg/kg ensures no death of

animals due to that 100 and 200 mg/kg body weight were selected for future studies

Nootropic study

Spontaneous alterations (% SA) in Rectangular maze

All the results were compared with disease control [**Figure 1**].The spontaneous alteration existed greatly (P<0.001) diminished in diabetic controls compared with control. The treatment group-X (200 mg/kg), standard drug treatment group IV (5 mg/kg) displays more significant effect on % spontaneous alterations (P<0.001) but group-VI (200 mg/kg) and IX (100 mg/kg) shows less significant effect (P<0.01).

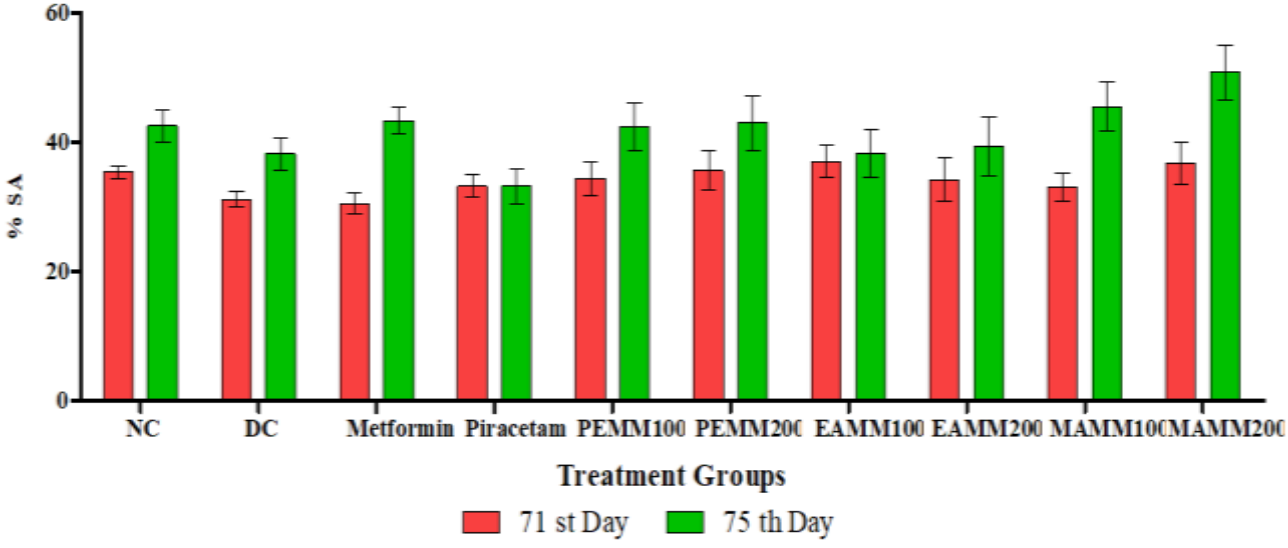

Figure 1: The effect of % SA of MM extracts

Effects of MM extracts on transfer latency (TL) in Morris water maze

The transfer latency were significantly (P<0.001) increased in diseased controls compared with control. The treatment group-X (200 mg/kg), standard drug treatment group IV (5 mg/kg) displays more significant effect in reduced transfer latency (P<0.001) but group-VI (200 mg/kg) and IX (100 mg/kg) shows less significant effect (P<0.01). All the results were compared with disease control [**Figure 2**].

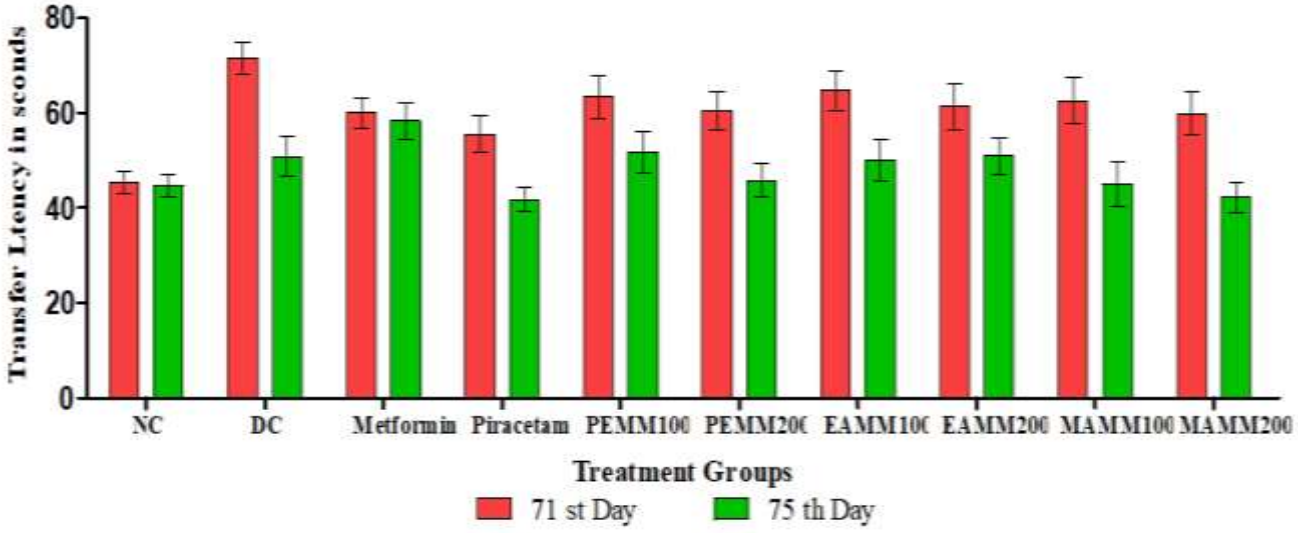

Figure 2: The effect of TL of MM extracts

Acetylcholinesterase (AChE) estimation

The AchE effectiveness were significantly increased (P<0.001) in diseased controls when compared with normal controls it suggesting cholinergic dysfunction. The treatment group-X (200 mg/kg), standard drug treatment group IV (5 mg/kg) exhibit more significantly decrease in activity (P<0.001) but group-VI (200 mg/kg) and IX (100 mg/kg) shows less significantly reduce the enzymatic activity (P<0.01). The outcomes existed were compared with diseased controls [**Figure 3**].

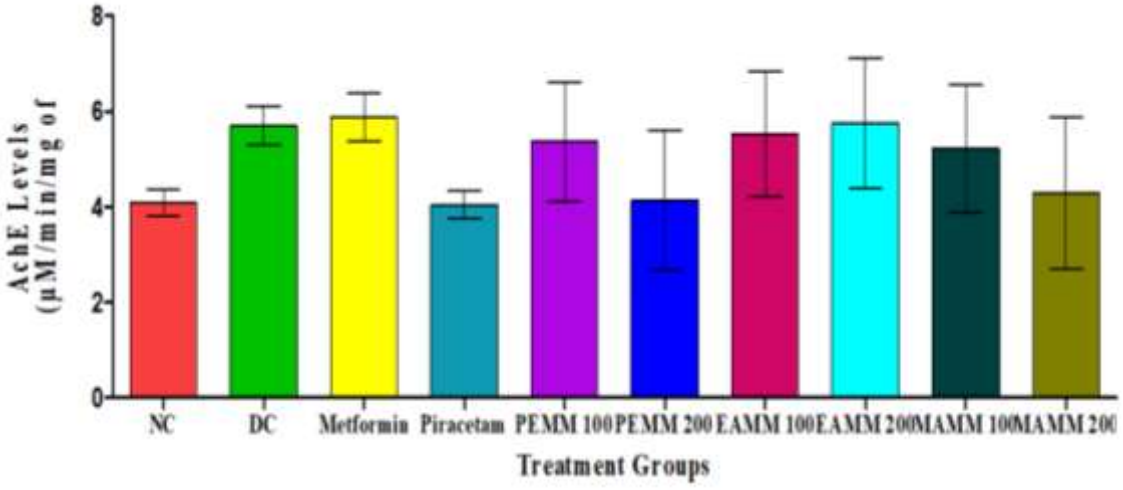

Figure 3: Effects of MM extracts on AchE activity

TBARS Assay

TBARS levels are significantly (P<0.001) augmented in diseased rats while compared to normal controls [Table **4]**. The treatment group-IV **(**5 mg/kg) and X (200 mg/kg), shows significantly (P<0.001) reduce the MDA levels. In group-VI (200 mg/kg) and IX (100 mg/kg) animals shows significantly (P<0.01) decreases MDA levels.

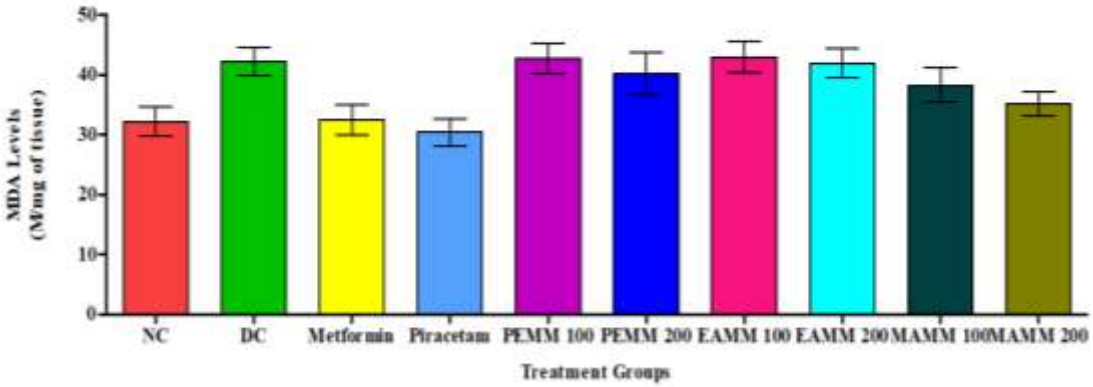

Figure 4: Effect of MM extracts on MDA levels

Nitric oxide levels

Nitric oxide levels are significantly (P<0.001) augmented in diseased rats while compared to normal controls [**Figure 5]**. The treatment group III (10 mg/kg), IV **(**5 mg/kg), and X (200 mg/kg), shows significantly (P<0.001) reduce the nitric oxide levels. In group-VI (200 mg/kg) and IX (100 mg/kg) animals shows significantly (P<0.01) decreases nitric oxide levels.

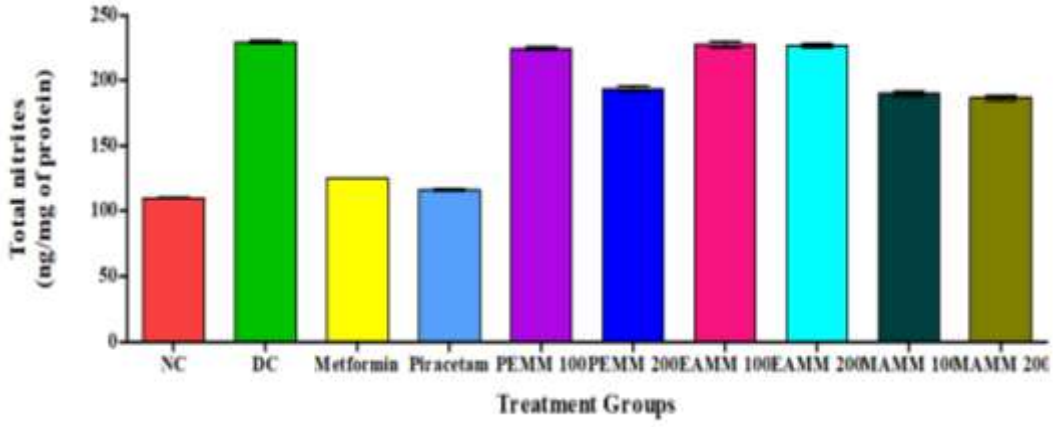

Figure 5: Effect of MM extracts on Total nitrites

CAT, SOD and GSH levels

In group-II the SOD, CAT and GSH levels were showed significantly (P<0.001) deducted when compared to control. The treatment group III (10 mg/kg), IV **(**5 mg/kg), and X (200 mg/kg), shows significantly (P<0.001) increase all antioxidants like SOD, CAT and GSH. In group-VI (200 mg/kg) and IX (100 mg/kg) animals shows significantly (P<0.01) increase [**Figure 6, 7 & 8].**

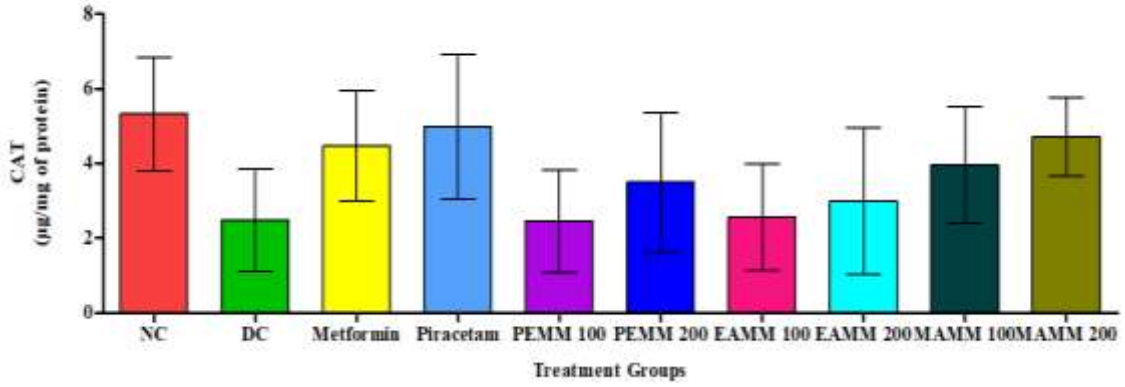

Figure 6: Effect of MM extracts on CAT levels

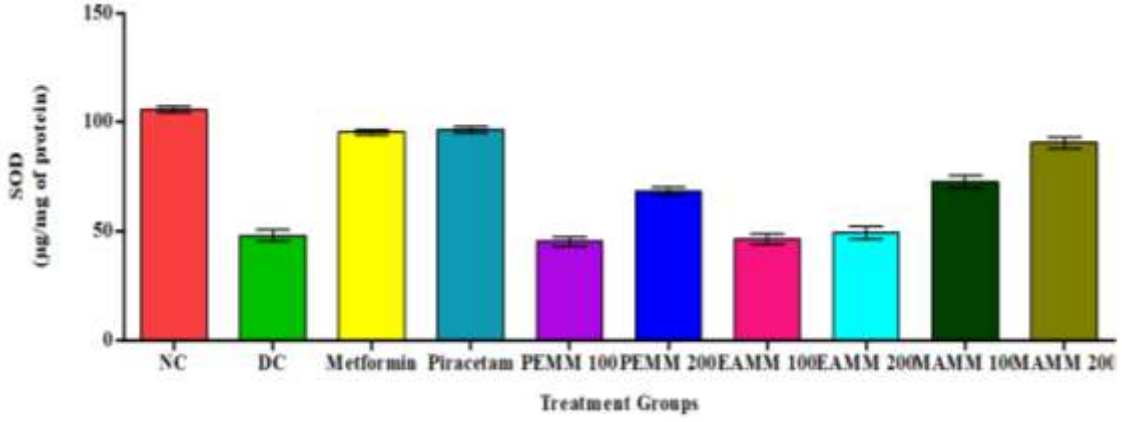

Figure 7: Effect of MM extracts on SOD levels

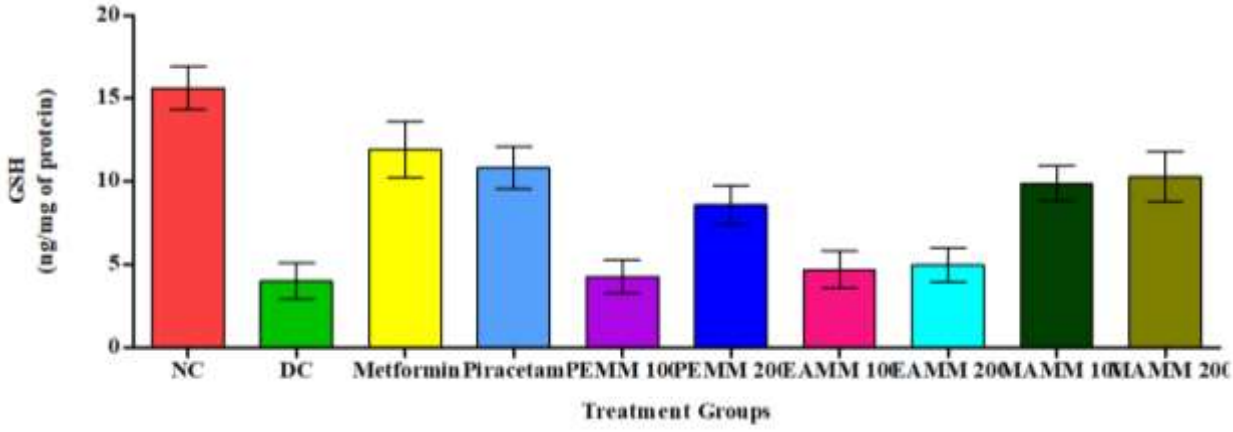

Figure 8: Effect of MM extracts on GSH levels

DISCUSSION:

Enormous quantities of plants are utilized in treatment of memory impairment. From the previous studies methanolic extract of *Myristica malabarica* leaf is evaluated for *in vitro* insulin emission studies on islets of Langerhans at concentration of 1mg/ml through inhibition of intestinal alpha-glucosidase and preserve blood glucose level through insulin secretagogues action [23]. The ethanolic extract of *Myristica malabarica* leaf extract studied anticonvulsant, antidepressant, sedative, and hypnotics [24].

The current investigation analyzed the impacts of S. grandiflora solvent extracts treatment on memory loss, oxidative stress, and cholinergic transmission impairment in chemically induced (i.e., STZ) animal model of diabetes in mice. Previous investigations have proposed that DM is associated with various neurological impairments in the focal sensory network like cognition and learning capabilities. STZ can induce type 1 or type 2 diabetes depending on the concentration used. In this present investigation, the intension is to get not exclusively the diabetes type of model, and to those additional defects in memory was also considered. Chemically STZ is a glucosamine-nitrosourea derivative, have got anti-microbial properties and found to be poisonous to the pancreatic β-cells and is used to produce exploratory diabetic condition in experimental animals. When STZ administered through the intraperitoneal routes, it creates cognition impairment and enhances cerebral masses of Amyloid-β and tau protein. STZ injection can produce the AD like pathophysiological condition in animal brain by causing the neuroinflammation and oxidative stress, which is the suitable experimental model. Moreover, the treatment of STZ causes the brain cells to become insulin-resistant, which produces the normal dementia like condition with loss of memory, progressive cholinergic deficiencies, carbohydrate hypometabolism, stress due to reactive oxygen species (ROS), and finally neurodegeneration. Subsequently, from the previously mentioned studies, it is known that STZ creates most pervasive sort of memory disability. In the current examination, STZ treated mice indicated a continual cognition decline in passive avoidance test; observed substantial reduction in step-down latency time; and in Morris water maze test, it was evidenced in increase of escape latency. The intellectual and memory decrements in DM can be resulted from hyperglycemia. Although these are multifactorial disorders, adequate information is accessible for overproduction of ROS.

Therefore, in the current study we explored the effects

of *Myristica malabarica* on diabetes (STZ) induced cognitive decline in experimental animals along with its role in oxidative stress and acetylcholinesterase activity. The chief phytoconstituents identified from the petroleum ether and ethanolic extract are alkaloids, glycoside, tannin and phenolic compound, flavonoids, protein and amino acid, phytosterols, terpenoids and carbohydrates [25]. Many phytochemicals like glycosides, phenols, alkaloids, flavonoids, and tannins were reported in the present study. The treatment group-X (200 mg/kg) methanolic extract of *Myristica malabarica* shows more significant effect on percentage spontaneous alterations ($P<0.001$) spontaneous alteration in Y maze and also exhibit more significant effect in reduced transfer latency ($P<0.001$) in morris water maze which indicates up gradation of learning and memory in STZ induced cognitive impairments. Similar works carried out in *Carica papaya* seed [26] extracts, **Clitorea ternatea** leaves [27] and *Olea europaea* [28] fruit extracts revealed significant ($P<0.001$) effect in increase in the spontaneous alterations and transfer latency in diabetes induced cognitive impairment.

Influx of acetylcholine in the hippocampus is absolutely for prepare to function memory task [29] and with a great execution on a hippocampus-reliant, unrestrained modification task [30]. In diabetes the acetylcholinesterase levels are viewed as high this catalyst hydrolyses acetylcholine present in the mind and results in intellectual decline [31]. The present study noticed a huge rise in acetylcholinesterase movement in the cerebrum of diabetic rodents. Several studies have established relationship between increase AChE activity in the brain and cognitive impairment and significantly inhibited by cinnamic acid, *Peristrophe bicalyculata*, *Clitorea ternatea* Linn and *Carica papaya* in diabetes animals [31-33].

Treatment with methanolic extract of MM significantly ($P<0.001$) increase in acetylcholinesterase activity in the brain of diabetic animals.

Under physiologic conditions, enzymatic antioxidants such as glutathione peroxide (GPX), superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR) as well as non-enzymatic antioxidants such as reduced glutathione (GSH), prooxidants in the body [34].

These systems are however, overwhelmed during oxidative stress conditions leading to their gradual depletion. Treatment with MM caused substantial increases in catalase and reduced gluthathione levels in treated animals compared to the untreated diabetic group. This reduction in oxidative stress markers particularly in the brain could be a factor responsible for the reversal of the DM-associated cognitive dysfunction in treated rats.

The overproduction of nitric oxide is equally lethal to neurons and nitrite level is measured as its indicator [35].

We assayed brain nitrite level in the experimental animals to establish possibility of nitrative stress as a provider to cognitive impairment in DM. Animals in the diabetic control group shows significant increase in brain nitrite level compared to control implying nitrative stress in this group. This effect was reversed with MM treatment as treated animals showed dose dependent decrease in brain nitrite levels compared to the untreated diabetic groups.

CONCLUSIONS:

Overall, natural components and extracts display antioxidant actions at central level, as well as a applicable capability to lessen vascular injury, causative overall to border neurodegeneration and cognitive resulting modifications. So, although the final fundamental mechanisms keep on mostly unidentified, they might pay to enlarge beneficial choices to treat or diminish central difficulties allied with DM.

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التحقيق في النشاط العدواني والحيوي العصبي لاستخراج لحاء *Myristica malabarica* على ضعف الإدراك الناجم عن STZ في الحيوانات التجريبية

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ملخص

تهدف الدراسة الحالية إلى تقييم مستخلصات (MM) Myristica malabarica Bark في نموذج الفئران المعرفي الناجم عن مرض السكري لنشاطه العدواني والحماية العصبية. تم تقييم نشاط تعزيز الذاكرة بواسطة اختبار المتاهة Y واختبار متاهة الماء موريس، على التوالي. تم تقييم التأثيرات العصبية الواقية لمستخلصات لحاء MM عن طريق قياس أستيل كولين استريز، بيروكسيد الدهون، ديسموتاز سوبروكسيد (SOD)، إجمالي أكسيد النيتريك ,(NO) مستويات الكاتالاز (CAT) والغلوتاثيون (GSH) في دماغ الفئران المصابة بالسكري. لوحظ أن مستخلص كحول الميثيل لحاء Myristica malabarica (MMMA) (100 و 200 مجم / كجم) يؤثر على تحسن كبير في التغيير التلقائي ($P < 0.01, P < 0.001$) ووقت الاستجابة للنقل ($P < 0.001$ $P < 0.01$) في تجارب الاحتفاظ على متاهة Y واختبار متاهة الماء Morris على التوالي. ومع ذلك، انخفاض كبير في نشاط أستيل كولين استريز($P < 0.001$)، بيروكسيد الدهون (($P < 0.001$، إجمالي ($P < 0.001$) NO وزيادة كبيرة في ,SODلوحظت مستويات CAT و ($P < 0.001$) GSH في الحيوانات المعالجة بـ 200) MMMA مجم / كجم) المتعلقة بمجموعة مكافحة مرضى السكري. تشير النتائج الحالية إلى أن مقتطفات Myristica malabarica كانت تدافع عن الانخفاض المعرفي في حالة مرض السكري والذي يتطلب بعض الدراسات الإضافية لتوضيح طريقة عملها.

الكلمات الدالة: *Myristica malabarica*، Nootropic، الحماية العصبية، تراجع الإدراك.

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