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Effect of *Myristica Dactyloides* on Memory Problems in the Rotenone Model of Parkinson's Disease

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Abstract

Dementia, stiffness, bradykinesia, postural instability, and tremor are all symptoms of Parkinson's disease, a complex neurological disease. On a neuropathological level, PD is characterised by the progressive degeneration or death of dopaminergic neurones. Neuroinflammation, mitochondrial dysfunction, and increased oxidative stress were all seen in PD patients. In both animal and cell line models, the isoflavone rotenone, which is derived from plants in the Fabaceae family like the jicama vine, causes mitochondrial malfunction, inflammation, oxidative stress, and cell death. Cell line and animal models of Parkinson's disease found it helpful in evaluating neuroprotective properties. In animal models of Parkinson's disease, medications with antioxidant potential were useful in regulating cellular stress, free radical production, and neurotransmitter levels. The fragrant spice nutmeg has anticonvulsant, memory-enhancing, and antioxidant qualities. The presence of pharmacologically active components make it a good brain stimulant and body detoxifier. These substances include eugenol, isoelemicin, isoeugenol, methoxyeugenol, myristic acid, myristicin, saponins, and lignin. Macelignan, a component of nutmeg, has the potential to cross the blood-brain barrier because to its hydrophobicity and low molecular weight. Using behavioural tests such as the Morris water maze, T-maze, and Elevated plus maze, this research investigated the cognitive profile of rotenone-induced PD models treated with MDSE extract (MDSE). Male Wistar albino rats were intraperitoneally injected with rotenone at a dosage of 2.5 mg/kg everyday for a duration of 30 days. In a rotenone-induced PD paradigm, rats treated with MDSE shown a substantial improvement in cognition. The fact that it has neuroprotective and anti-cholinesterase effects could explain it.

Introduction

The locomotory behaviour of elderly people is mostly impacted by PD, a chronic neurological disease. Dementia, bradykinesia, resting tremor, rigidity, difficulty to start movements, and poor balance are all symptoms of Parkinson's disease. According to Parashar and Udayabanu (2017), Parkinson's disease is characterised by the progressive degeneration of dopaminergic neurones in the nigrostriatal pathway (SN), the buildup of insoluble α-synuclein within neurones, and the subsequent formation of intracellular structures known as Lewy bodies. New evidence reveals a cascade of events culminating in neurodegeneration, including increased oxidative stress, mitochondrial failure, and neuro-inflammation (Schapira and Jenner, 2011). While the exact cause of PD is unknown, it may be passed down via families (~10%) or be caused by random environmental factors (~90%) (Sherer et al., 2003). In experimental models of Parkinson's disease, pesticides that block mitochondrial complex I, such as rotenone, cause the selective destruction of dopaminergic neurones (Cicchetti et al.,

2009; McDow-ell and Chesselet, 2012). The isoflavone rotenone, which is derived from plants in the Fabaceae family like the jicama vine, has been shown to cause oxidative stress, mitochondrial malfunction, inflammation, and cell death in animal models and cell lines (Gobi et al., 2018; Dhanalakshmi et al., 2016). Aromatic spices have been used to enhance the flavour and scent of food since ancient times. Their many pharmacologically active components make them a promising, risk-free, and naturally occurring therapy for a wide range of illnesses. Nutmeg, a spice plant in the Myristicaceae family, is grown for its aromatic and flavorful seeds (Myristica dactyloides) Houtt (Mishra et al., 2018). According to Panayotopoulos and Chisholm (1970), it is used to flavour a wide variety of foods, including baked goods, puddings, candies, sausages, meats, dishes, veggies, and drinks. It was prescribed for gastrointestinal dysfunction, rheumatism, obesity, diarrhoea, and sleep problems in Ayurveda, Unani, Chinese, and folkloric medicine (Neeraja and Margaret, 2016; Vangoori et al., 2018). It showed properties that prevented the growth of fungi, spasms, and cancer as well as protecting the liver from viral infections and oxidative stress. The inclusion of pharmacologically active chemicals, including eugenol, isoelemicin, isoeugenol, methoxyeugenol, myristic acid, myristicin, saponins, and lignin, makes it a great brain stimulant and body detoxifier (Vangoori et al., 2018). Nutmeg, according to research by Jissa et al. (2014), reduced acetylcholinesterase activity and ameliorated memory impairments in rats when administered orally. According to Sonavane et al. (2002), nutmeg showed anticonvulsant effects in rats when exposed to lithium sulfate-pilocarpine nitrate, maximal electroshock, and pentylenetetrazol. A recent study by Veronica et al. (2018) found that a rat puppy's brain mitochondria had a more positive and productive impact after prolonged nutmeg seed consumption, which was associated with an increase in DA receptors. Paracetamol and high-fat diet-induced hepatotoxicity models were studied using extracts from the kernel and seeds of Myristica dactyloides, which showed anti-oxidant, anti-inflammatory, and antiapoptotic effects (Dkhil et al., 2019; Sethi and Dahiya, 2018). So, we looked at how a PD animal that was given rotenone and then given Myristica dactyloides seed extract (MDSE) acted cognitively.

MATERIALS AND METHODS

Chemicals

Rotenone was procured from Sigma Chemical Com- pany, Bangalore, India.

Animals

Male Albino Wistar rats (225–250 g) were obtained from CDRI, Lucknow ,under normal conditions 12 hrs light / dark cycle and 60% humidity, without any restrictions to a standard pellet diet and water ad libitum. Animals were adapted for a week before initiating the experimental protocol. The experimental procedures were permitted by the Animal Ethics Committee of the Institute).

Experimental design

In the study, 36 rats were randomly divided into different groups. The control group received 0.5 ml of sunflower oil injected into the abdominal cavity for 30 days. Another group received only rotenone, which was injected at a dose of 2.5 mg/kg/day in sunflower oil for 30 days. The third group, referred to as group II in the study by Morais et al. (2012), received rotenone and a low dose of MDSE. The MDSE was administered orally at a dose of 5 mg/kg in saline, starting one hour after the rotenone treatment and continuing for 30 days. The fourth group received rotenone and an intermediate dose of MDSE, administered orally at a dose of 10 mg/kg in saline for 30 days. The fifth group received rotenone and a high dose of MDSE, administered orally at a dose of 20 mg/kg in saline for 30 days. The sixth group was treated with MDSE alone, receiving a dose of 20 mg/kg/day orally for 30 days. The T-maze test, Morris water maze test, and Elevated plus Maze Test were conducted.

Group I: Control (0.5 ml of sunflower oil i.p. for 30 days)

Group II: Received Rotenone **(**2.5 mg/kg/day i.p in sunflower oil for 30 days)

Group III: As group II + (After 1-hour ROT) *MDSE* (5mg/kg) p.o. for 30 days

Group IV: Received.as group II + (After 1 hour ROT) *MDSE* (10mg/kg) p.o. for 30 days

Group V: Received as.group II + (After 1 hour ROT) *MDSE* (20mg/kg) p.o. for 30 days

Group VI: *MDSE* (20mg/kg) p.o for 30 days

Preparation of nutmeg extract

MDSE extract was prepared, as mentioned by Ghor- baniana *et al.* (2019).

T-maze test

This test was conducted as stated in the study by Yang et al. in 2017. The animal training sessions were place over two consecutive days, namely on the 23rd and 24th. In the T-maze, incentives in the form of Kellogg's chocolate chips were placed at the end of one arm. Identification of food-related stimuli linked to working memory. Each practice session consisted of 9 rounds, with each round consisting of two parts: a mandatory run and an optional run. During the forced run, one of the arms was closed using a sliding door, while the other arm was kept open by placing food at its end. After a duration of 30 seconds, the option to engage in a running activity was permitted. Both upper limbs were unrestricted, and edible incentives were positioned at the extremities of the two upper limbs. The correct choice was to choose the recently opened arm, which had been closed throughout the forced run. On the 28th day, examinations were conducted and their findings were recorded. The analysis consisted of three consecutive trials. Animals had two voluntary runs after one mandatory run. Following the trial sessions on the 23rd and 24th day, the animals were provided with food for just one hour, which may be described as a partial limitation to their diet. On the 25th day of the experiment, the participants were not allowed to eat before the test. Once the animals finished their behavioural testing, there are no limitations on food consumption, allowing them to eat freely.

Morris water maze test

Evaluations regarding environmental knowledge and memory were the goals of this exam. Within a circular tub of 71 inches in diameter and 24 inches in depth, rats were allowed to swim to a platform in the testing room. The tub was filled to a depth of 16 inches with tap water, which had a temperature of 82±20 ◦F. A 4-inch-diameter circular stage was set below 2 centimetres of water level, and white talcum powder was added to the water to make it opaque. The animals were taught in sessions with four trials on the 27th day. Each of the four trials started from a different place. Up to a maximum of two minutes was the time it took to find the stage recorded. The stage was maintained in its original location throughout the trial. There was meticulous documentation of the time it took to board the stage. After twenty-eight hours, or the 28th day, rats were evaluated after being randomly put over the pool's edge. The retention delay was calculated as the duration it took to enter the concealed stage on the 28th day (Su et al., 2010).

Elevated Plus-Maze (EPM) Test

Through the use of this EPM approach, the animal's cognitive ability was examined. The apparatus was maintained at a height of 50 cm and had two sets of arms, one closed and one open. Its dimensions were 50 x 10 x 40 cm, and it had an open ceiling. Transfer latency (TL) was defined as the time it took for the exposed arm to reach the closed arm. The open arm was used to gently introduce rats at first, with TL considered. We gently coaxed the experimental animal into entering the closed section if it failed to do so within 90 seconds; TL took 1.5 minutes. The rats were given 20 seconds to explore the labyrinth after entering the closed arm, after which they were put back in their cages. According to Itoh et al. (1991), the TL was recorded on days 0 and 30.

RESULTS

There was a remarkable improvement in rotenone-induced cognitive impairment in the T-maze test after administration of MDSE, as shown in Figure 1. Using one-way analysis of variance, the findings are shown as the mean ± standard deviation for each group (n=6). The comparisons with the normal group and the rotenone group are shown by #P<0.001 and *P<0.001, respectively. The rotenone group had severely reduced exact replies indicative of impaired functional memory in our research, in contrast to the MDSE group, which showed an increase in the number of correct answers. The

ability to quickly identify food was one way in which MDSE enhanced working memory.

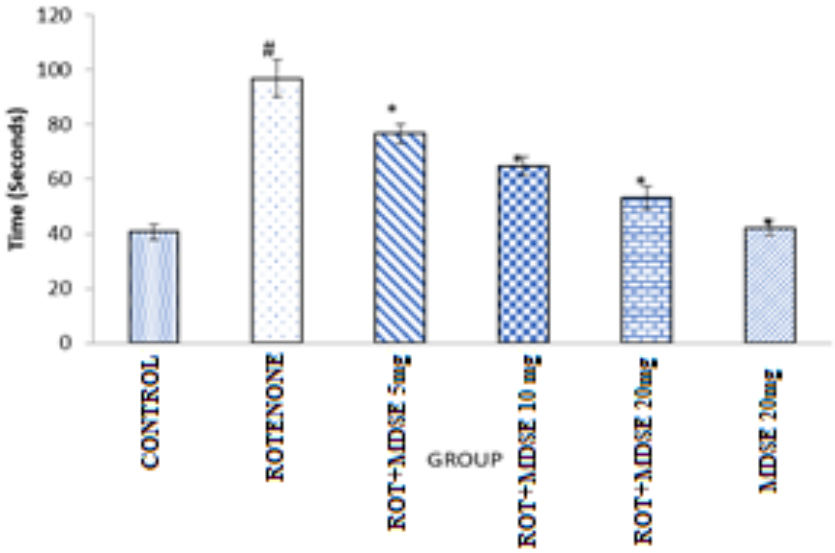

Figure 1: Effect of *MDSE* on T- maze test of experimental animals

Effect of MDSE on memory evaluation in the Mor- ris water maze test

When compared to the control group, the rotenone-only group showed significant spatial memory loss. The MDSE + Rot group of rats showed a progressive improvement in spatial memory from dosages of 5–20 mg (Figure 2). By one-way analysis of variance, each bar represents the mean±standard deviation (n=6) with comparisons to the normal group and the rotenone group marked by #P<0.001 and *P<0.001, respectively. The behavioural profile of the control groups and the MDSE 20 mg group was quite comparable.

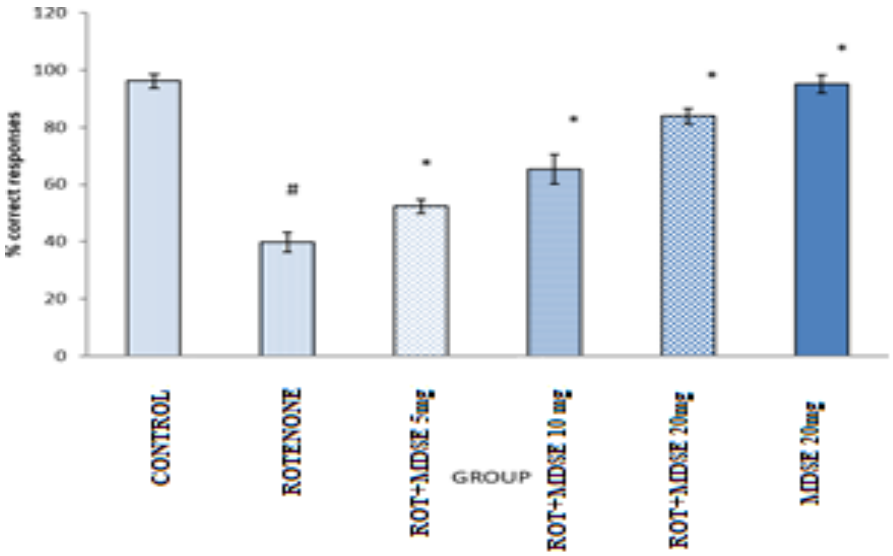

Figure 2: Evaluation of memory by Morris water maze test

MDSE attenuates the cognitive skill in the EPM test

With respect to the control group, TL was remark- ably increased in the rotenone intoxicated group. On relating with rotenone intoxicated group, rot + *MDSE* group exhibited a sharp decline in TL. Each bar shows mean±SD, n=6, #P<0.001 com- pared with normal group and *P<0.001 compared with rotenone group using one-way analysis of vari- ance (Figure 3).

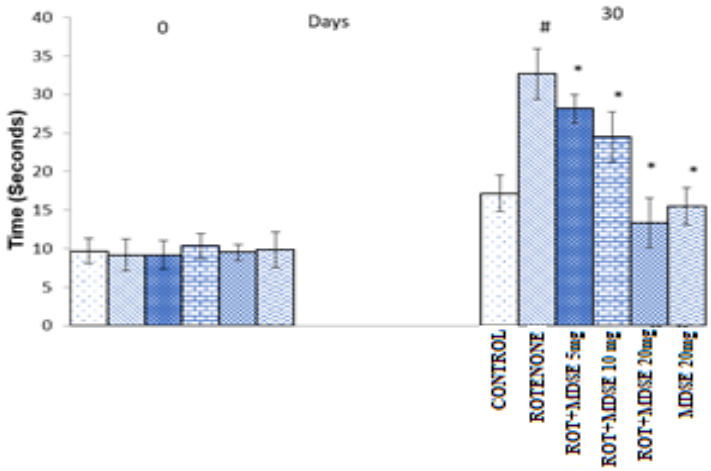

Figure 3: *MDSE* treated groups displayed gradual decline in TL in EPM test

DISCUSSION

Rotenone is a pesticide that, if released into the environment, may cause neurological diseases such as Alzheimer's, Parkinson's, Huntington's, and Leber optic neuropathy. To lessen the danger, one must take the necessary precautions (Zhang et al., 2006). According to research conducted by Kaur et al. (2011), cognitive and learning deficiencies may be caused by chronic administration of rotenone. In PD, cognitive abilities were shown to deteriorate. According to Shinomol and Muralidhara (2011), cholinergic neurones were linked to central nervous system processes including sleep and cognition. Due to their severe cholinergic deficiencies, cholinesterase inhibitors were suggested for PD patients (van Laar et al., 2011). The cognitive impairment and decreased memory index were brought about by the intra-peritoneal injection of rotenone. Cholinergic interneurons make up the striatum, and research suggests that these neurones contribute to striatal function (Müller and Bohnen, 2013). The cognitive deterioration that was seen might have been exacerbated by this. Animal models of Parkinson's disease showed that anti-oxidant drugs were useful in regulating cellular stress, free radical formation, and neurotransmitter levels. Consequently, they are highly sought after for their potential anti-neurodegenerative effects. According to Kamal et al. (2015), cholinesterase inhibitors may help with cognitive disorders. The effectiveness of various plant-based compounds, pepper, and medications like piracetam and Ceftriaxone in treating experimental PD dementia has been demonstrated in previous studies (Chompoopong et al., 2016; Mehraein et al., 2018; Ogunruku et al., 2019). Clinical studies against PD are presently underway for marine-derived natural compounds, such as omega-3 fatty acid, ino-sine, etc. (Huang et al., 2019). Additionally, D-cycloserine was shown to be beneficial in the treatment of biochemical and biological deficits in experimental PD, as reported by Ho et al. (2011). These deficits include cognitive impairments and motor dysfunction. Jissa et al. (2014) demonstrated that rats' cognitive and intellectual capacities were improved by MDSE. The ability of MF extract to decrease acetyl-cholinesterase activity makes it an attractive candidate for use in Alzheimer's disease therapy (Singh et al., 2020). Ayaz et al. (2017) found that nutmeg oil helped with epilepsy control. A nutmeg component called macelignan has the potential to cross the blood-brain barrier due to its low molecular weight and hydrophobic properties (Wu et al., 2016). A neuroprotective impact is provided by the chemical allylguaiacol, which is found in several spices including nutmeg, basil, cinnamon, and cloves. It controls transcription factor p65 and has anti-oxidant and anti-apoptotic properties. The memory problems associated with Alzheimer's disease, Parkinson's disease, and other diseases may be amenable to treatment with allylguaiacol (Lim et al., 2018). According to a recent research (Singh et al., 2020), MDSE effectively controls memory losses in Alzheimer's disease. The results showed that the groups treated with MDSE performed much better on the T-maze test, the MWM test, and the EPM test, with significantly

shorter times to reach the concealed stage and TL, respectively.

CONCLUSION

Memory impairments in a rotenone-induced PD model were successfully countered by MDSE, according to this research. The drug's anti-oxidant, anti-carcinogenic, anti-epileptic, and cholinesterase inhibition claims may be to blame. However, to fully understand the process and compound at work, further in-depth study is required.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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