IJPSR (2025), Volume 16, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 June 2025; received in revised form, 23 June 2025; accepted, 26 June 2025; published 01 December 2025

POTENTIATION OF PENTOBARBITAL INDUCED HYPNOSIS BY MYRISTICIN IN RATS

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Keywords:

Myristicin, *Myristica fragrans*, Hypnosis, Pentobarbital

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ABSTRACT: Background: Myristicin is a naturally occurring allyl benzene primarily obtained from various plants and spices like nutmeg, fennel, parsley and carrot. Herbs and spices abundant in Myristicin are utilized in traditional medicine to manage conditions like abdominal cramps, diarrhea, rheumatism, anxiety, fever, and halitosis. Nutmeg has been utilized as a mild sedative. Myristicin produces dose-dependent neurological effects. **Methods:** This experimental study was carried out in the Department of Pharmacology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. This study examined the hypnotic effects of Myristicin in rats. The method utilized to evaluate the hypnotic effect of Myristicin was pentobarbital-induced sleep potentiation. Two oral dosages of Myristicin, 10 mg/kg as well as 20 mg/kg, were administered, with propylene glycol serving as normal control. Following 60 minutes of oral dosing, pentobarbitone (30 mg/kg) was given intraperitoneally to produce sleep. Sleep latency and duration of sleep were recorded for each rat. **Results:** The results showed that Myristicin at 10 mg/kg dose can significantly reduce the latency of sleep in comparison to control, while no such difference was noted in the duration of sleep. However, Myristicin at 20 mg/kg dose reduced the latency and increased the duration of sleep significantly in comparison to control. **Conclusion:** The present study reveals that Myristicin can significantly alter the latency and duration of sleep in pentobarbital induced sleep potentiation test and exhibits significant hypnotic effect.

INTRODUCTION: Myristicin (1-allyl-5-methoxy - 3, 4-methylenedioxybenzene) is a naturally occurring phenylpropene and allylbenzene chemical compound. It is present in several plant species, including *Myristica fragrans* Houtt. (nutmeg), *Anethum graveolens* L. (dill weed), *Foeniculum vulgare* Mill. (fennel) and *Petroselinum crispum* (parsley), among others [1]. It is primarily derived from the essential oils of nutmeg, parsley, dill and carrot [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(12).3388-92

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(12).3388-92

The seeds of nutmeg contain nearly 4-8% essential oil, of which Myristicin constitutes up to 4-8.5%. Aril of the *Myristica fragrans* called mace also contains Myristicin, however in lower concentrations as compared to nutmeg. Both the leaves and seed of parsley contain Myristicin although in smaller amounts. Dill and carrot are minor sources of Myristicin and it is also found in black pepper and star anise in trace amounts. It imparts fragrans and flavor to them. It is used as a spice in food and fragrans in cosmetic industry [1-2].

Myristicin [$C_{11}H_{12}O_3$] is a methoxy substituted allyl-benzene with a structure consisting of a benzene ring and attached methylene-dioxy group at positions [3] and [4], an allyl at position 1 and a methoxy group at site [5]. Myristicin has structural similarity to other psychoactive phenylpropenes

like safrole and MMDA (3-methoxy-4,5-methylenedioxyamphetamine). Myristicin is volatile and highly lipophilic in nature and hence crosses blood-brain barrier readily. This explains the neurological effects of Myristicin as excessive consumption of Myristicin containing plants causes hallucinations and toxicity [2]. or equivalent 200 mg of Myristicin), it can induce hallucinations, euphoria, delirium and anxiety. The onset of these effects takes 3-6 hours' post-ingestion and may persist for up to 24 hours. Myristicin's structural resemblance to derivatives of mescaline and amphetamine is thought to be the cause of its psychedelic effects [2].

It is metabolized in liver by enzyme CYP1A1 to form amphetamine like metabolite MMDA (3-methoxy-4,5-methylenedioxyamphetamine), a serotonin receptor agonist with hallucinogenic activity. MMDA also modulates serotonin (5-HT 2a) pathways leading to altered perception and mood [2-4]. Monoamine Oxidase (MAO) enzyme is responsible for metabolism of monoamines like serotonin and dopamine. Myristicin and its metabolites weakly inhibit MAO enzyme thereby increasing the synaptic concentration of monoamines exerting pro-serotonergic effects and cardiovascular symptoms [2]. Myristicin has also been shown to have anti-cholinergic property [2].

It antagonizes the muscarinic acetylcholine receptors and the blockade of the central muscarinic receptors causes delirium and cognitive impairment. The symptoms of Myristicin toxicity resemble to that of anticholinergics with the exception miosis in contrast to mydriasis of anticholinergics [2].

Apart from neurological effects, Myristicin also produces a plethora of other effects like anti-inflammatory, antioxidant, anti-cancer, antimicrobial and anti-obesity effects. Studies regarding anti-inflammatory activity of Myristicin suggest that it is a potent anti-inflammatory agent. It is able to inhibit COX-2 enzyme and decrease the production of prostaglandins and cytokines [5]. Research on the antioxidant activity showed that Myristicin can raise the levels of antioxidant enzymes such as glutathione reductase, catalase, superoxide dismutase, and glutathione peroxidase; as well as decrease the extent of lipid peroxidation. [6] Myristicin exerts antimicrobial effects against various bacteria (*Staph. aureus*, *E. coli*) and fungi (*Candida albicans*) [6]. Even with its risks, Myristicin has a promising therapeutic potential as it has been explored for anti-cancer, anti-obesity and neuroprotection (anti-Alzheimer activity) and other effects [7-8].

The purpose of this study was to assess hypnotic effectof Myristicin on rats.

MATERIALS AND METHODS: This experimental study was carried out in the Department of Pharmacology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. Myristicin was acquired from Sigma-Aldrich. Propylene glycol was used to dissolve it, creating a 2 mg/ml oral solution. Using the potentiation of pentobarbital-induced sleep method, the hypnotic impact of Myristicin was investigated.

Myristicin was administered to the animals orally in a single dosage. One hour later, an injection of pentobarbitone (30 mg/kg, IP) was administered to induce sleep. If the animals remained still and lost their impulse to right themselves when placed on their backs, they were deemed to be asleep. Total sleeping length (the period between the loss and recovery for the righting reflex) was calculated for each animal, and sleep latency was defined as the time gap between the Pentobarbitone injection and the commencement of sleep. If, after being laid down for one minute, the animal was able to right itself (the return to an upright position), it was deemed awake [9].

Charles Foster rats weighing between 150–250 g were collected from Central Animal House facility of Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India. The rats were fed a regular pellet diet and had access to water without any restriction. The rats were housed in a well-ventilated room with temperature regulated between 19-25 °C and a 12-hour light and dark cycle.

Rats were split into three groups of six animals each. The three groups received pentobarbitone, Myristicin, and propylene glycol as per methodology listed below:

1. Oral Propylene glycol 3mL/kg, one hour prior to intraperitoneal Pentobarbitone 30 mg/kg.
2. Oral Myristicin 10 mg/kg, one hour prior to intraperitoneal Pentobarbitone 30 mg/kg.
3. Oral Myristicin 20 mg/kg, one hour prior to intraperitoneal Pentobarbitone 30 mg/kg.

Sleep latency and total sleep duration were measured for each rat and recorded. Mean ± SEM is used to express the gathered data. Tukey's Post Hoc multiple tests of comparison were used after one-way ANOVA to determine statistical significance. A value of $P < 0.05$ was deemed statistically significant. All statistical analysis was done using SPSS software.

RESULTS: This study was conducted to demonstrate the hypnotic response to oral dosages of 10 mg/kg as well as 20 mg/kg of Myristicin. The hypnotic effect of both doses was compared to control group (propylene glycol). The control group received propylene glycol orally followed by intraperitoneal administration of pentobarbitone producing hypnosis elicited by loss of righting reflex.

The average latency time in the group serving as the control was discovered to be 4.25 ± 0.68 minutes and duration of sleep was 152.67 ± 5.34 minutes. In the test group with pretreatment of Myristicin at the 10 mg/kg dosage, the mean duration of latency was found to be 2.98 ± 0.21 minutes and duration of sleep was 148.67 ± 5.8 minutes. Myristicin at the dose 10 mg/kg was able to significantly ($p<0.001$) decrease the latency to sleep, however there was no discernible change in the amount of time spent in sleep.

In the test group with pretreatment of Myristicin with a 20 mg/kg dosage, the mean latency time was found to be 2.23 ± 0.16 minutes and duration of sleep was 201.5 ± 7.34 minutes. Myristicin at 20 mg/kg dosage decreased the sleep latency and lengthened the sleep duration. The reduction in latency and increase in duration of sleep was found to be highly significant ($p<0.001$).

DISCUSSION: Myristicin is a derivative of safrole that has a methoxy group attached to its carbon-4. This methoxy group provides strong sedative action to Myristicin similar to the methoxy group of phenylpropanolamine [10]. Myristicin is metabolized to 3-methoxy-4,5-methylenedioxyamphetamine (MMDA)- an amphetamine congener similar in structure and action to methylenedioxy-methylamphetamine (MDMA). This metabolite also confers sedative property to the Myristicin [10].

Muchtaridi *et al.* demonstrated that Myristicin inhibits locomotor activity in mice [10]. Sonavane *et al.,* demonstrated that oral ingestion of nutmeg seeds increases pentobarbital-induced sleep, which may be attributed to Myristicin [11]. Sedative and hypnotic effects of Myristicin are also possibly due to modulation of GABA activity and serotonergic pathways [12].

Mishra *et al.* demonstrated the hypnotic effect of ethanolic extract of *Myristica fragrans* seeds in rats. The ethanolic extract of *Myristica fragrans* was able to significantly increase the duration of sleep and decrease the latency of sleep which is most likely due to Myristicin [13]. These studies provide strength to the observations of current experimental work exhibiting hypnotic effect of Myristicin.

CONCLUSION: In summary, the findings of current study demonstratethe hypnotic effects of Myristicin. At low dosages of 10 mg/kg, Myristicin can only decrease the latency of sleep; at high doses of 20 mg/kg, the reduction in latency and increase in sleep duration were highly significant. The main factors behind this hypnotic effect seems to be the formation of metabolite MMDA and the presence of methoxy group in the structure of Myristicin.

TABLE 1: EFFECT OF MYRISTICIN ON LATENCY AND DURATION OF SLEEP

Groups	Latency (minutes)	Duration (minutes)
Propylene glycol	4.25 ± 0.68	152.67 ± 5.34
Myristicin 10 mg/kg	2.98 ± 0.21 ***	148.67 ± 5.8
Myristicin 20 mg/kg	2.23 ± 0.16***	201.5 ± 7.34***

Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001 as compared to control.

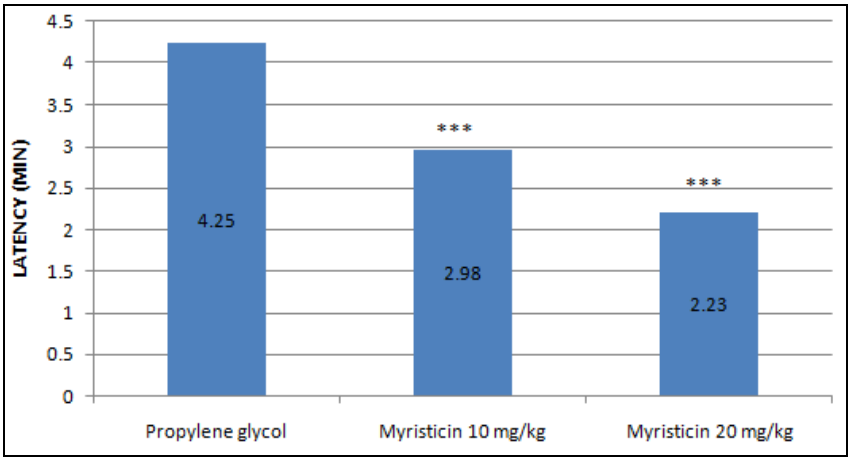

FIG. 1: EFFECT OF MYRISTICIN ON LATENCY OF SLEEP. Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001 as compared to control.

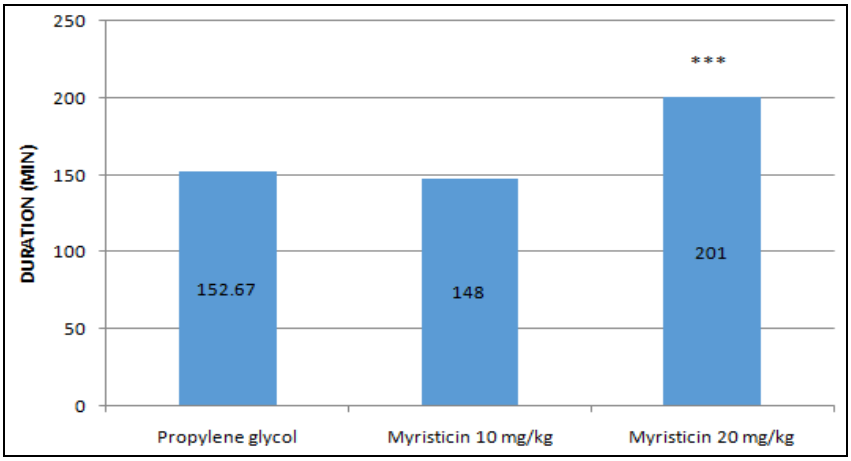

FIG. 2: EFFECT OF MYRISTICIN ON DURATION OF SLEEP. Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001 as compared to control.

ACKNOWLEDGEMENT: Nil

Funding: This research received no specific grant from any funding agency.

Animal Ethics Approval: This work was permitted by Institutional Animal Ethics Committee, Jawaharlal Nehru Medical College, AMU, Aligarh, Uttar Pradesh. Registration number -401/GO/Re/S/2001/CPCSEA. Resolution Number – 1496

CONFLICT OF INTEREST: None declared.

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How to cite this article:
Zeefahem A and Rahman SZ: Potentiation of pentobarbital induced hypnosis by Myristicin in rats. Int J Pharm Sci & Res 2025; 16(12): 3388-92. doi: 10.13040/IJPSR.0975-8232.16(12).3388-92.