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Eucalyptus oil decreases stereotypic behaviours induced by NMDA receptor antagonist ketamine

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Abstract
Natural compounds are able to protect the central nervous system neuropsychiatric disorders including psychosis. Psychosis is a complex and chronic disorder, characterised by group of symptoms such as stereotypic behaviours, hyperlocomotor activity etc. Typical and atypical antipsychotic drugs are available to treat these behavioural changes. However, these synthetic agents exert some serious side effect. Therefore, we have chosen eucalyptus oil and studied its protective effect in Ketamine induced stereotypic behaviours. Ketamine; 50mg/kg, i.p. was used to produce stereotypic behaviours such as turning, falling, weaving and head bobbing in mice. Eucalyptus oil (EO) at the dose of 500, 1000 and 2000 mg/kg, p.o, were administered for 10 consecutive days. Olanzapine; 5mg/kg, i.p. and haloperidol; 1mg/kg, i.p. were used as reference drugs in this study. Eucalyptus oil (EO) was significant to decrease the Ketamine produced stereotypic behaviours dose dependently. These results revealed that Eucalyptus oil (EO) possesses beneficial effective in Ketamine induced stereotypic behaviours.

Keywords: Eucalyptus oil, ketamine, psychosis, stereotypic behaviours

1. Introduction
Neuropsychiatric diseases are predicted as most complicated disorders; psychosis is one of them [1, 2]. Neurotransmitters imbalance, oxidative stress, brain injury, virus, neuroinflammation and drug abuse can induce psychosis like symptoms [3]. Clinical used antipsychotic agents are only on the bases of neuroreceptors [4, 5]. Although the available pharmacotherapy for neuropsychiatric disorders exert inconsistent effects with unwanted side effects [5, 6]. Thus, development of powerful and safe drugs for the management of mental disorders from traditional plants is necessary. Many medicinal plants and essential oils isolated from the various parts of the plants have been studied preclinially for various disorders [7, 8]. Even in "Bible" essential oils are revealed for spiritual, physical and mental health [9]. They are considered as folk medicine, alternative medicine, Chinese medicine and aromatherapy. They are also in used cosmetics industries as well as in food flavourings agents. A number of reports suggest that essential oils have protective effective against in central nervous system disorders [10, 11]. Essential oils are rich in various protective phytoconstituents, which have multiple effects on central nervous system [12-15]. Similarly, many studies have been reported on essential oils from various species of eucalyptus [16]. Thus, it will be valuable to investigate the effect of eucalyptus oil neuropsychiatric disorders. Therefore, we have designed to study protective effect of eucalyptus oil against Ketamine induced stereotypic behaviours.

2. Experimental protocol
2.1 Animal protocol
For this study, young swiss albino mice (either six) were obtained from Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, (Haryana-India). These animals were acclimatized for 7 days before start the study. The protocol was approved by Institutional Animals Ethics Committee. The animal care was taken as mentioned in the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, India.

2.2 Drugs
Ketamine (Neon Pharmaceutical Pvt. Ltd) was diluted in normal saline and used to induce behavioural changes in mice. Haloperidol (RPG Science Pharmaceutical Pvt. Ltd) and olanzapine (Intas Pharmaceuticals Ltd) were individually diluted in normal saline and used as standard drugs. While, eucalyptus oil (CDH Laboratory Chemicals, India) were diluted in 10% of tween-80 and used as test drug.

2.3 Doses of the drugs
Ketamine (Keta); 50mg/kg, i.p., olanzapine (Olz); 5mg/kg, i.p., haloperidol (Halo); 1mg/kg, i.p. and eucalyptus oil (EO); 500, 1000 and 2000 mg/kg, p.o. were used for the present investigation.

2.4 Experimental design
Each group consisted of 6 animals. Control group was treated with vehicle (normal saline) only, Inducer group was treated with Ketamine only, Standard groups were treated with haloperidol and olanzapine and Ketamine was administered after 30 minute of standard drug treatment, Test groups were treated with eucalyptus oil at different concentration and Ketamine was administered after 30 minute of test drug treatment.

2.5 Ketamine induced behaviour changes in mice
A plastic cage of 37 × 24 × 30 cm was used to place animal and observe Ketamine induced stereotypic behaviours in mice. On the 10th day of protocol, Ketamine induced falling, turning, weaving and head bobbing were assessed in each 10 minute after 10 minute for 60 minute [17].

3. Results
3.1 Effect of Eucalyptus oil (EO) against Ketamine induced stereotypic behaviours in mice
Ketamine (50 mg/kg, i.p.) were effect induce stereotypic behaviours such as turning, falling, weaving and head bobbing in mice. EO (500, 1000 and 2000mg/kg, p.o.) significantly to reduce these stereotypic behaviours dose dependently as compared to Ketamine group. Standard drugs haloperidol and olanzapine effectively decreased these stereotypic behaviours as expected (Figure 1, 2, 3, and 4).

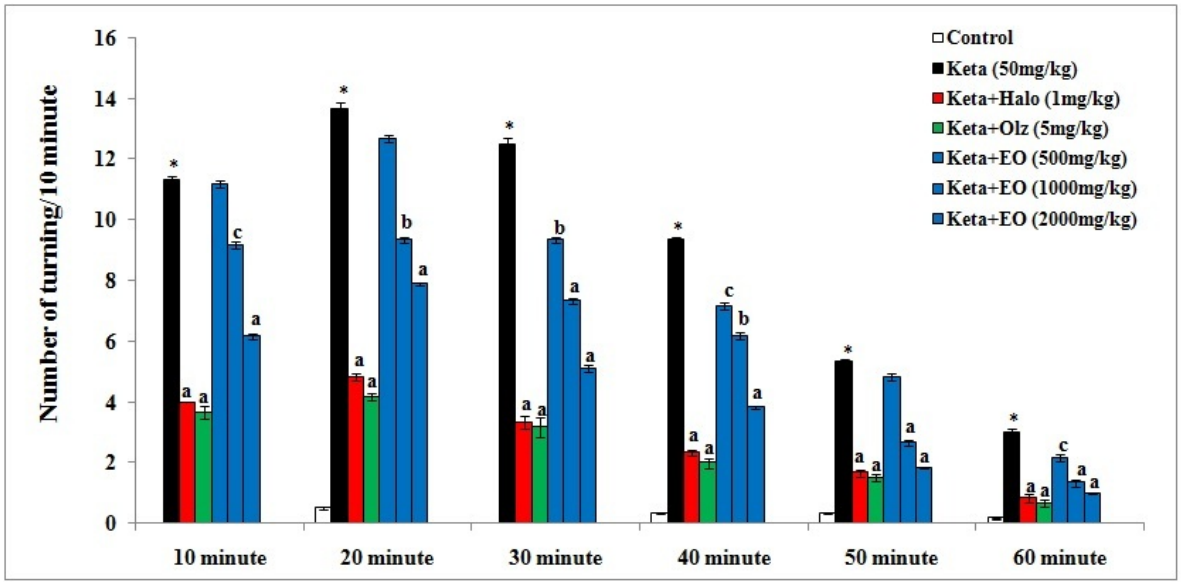

Fig 1: Effect of Eucalyptus oil (EO) on Ketamine induced turning behaviour
* = $p<0.001$ as compared to control animals. a = $p<0.001$, b = $p<0.01$ and c = $p<0.05$ as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test.

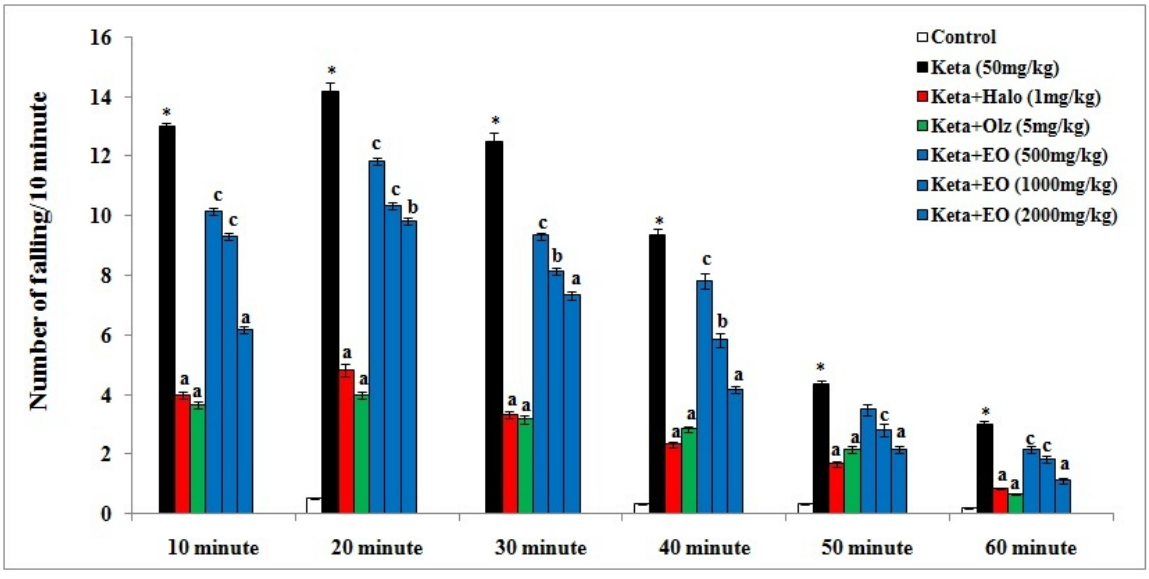

Fig 2: Effect of Eucalyptus oil (EO) on Ketamine induced falling behaviour
* = $p<0.001$ as compared to control animals. a = $p<0.001$, b = $p<0.01$ and c = $p<0.05$ as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test.

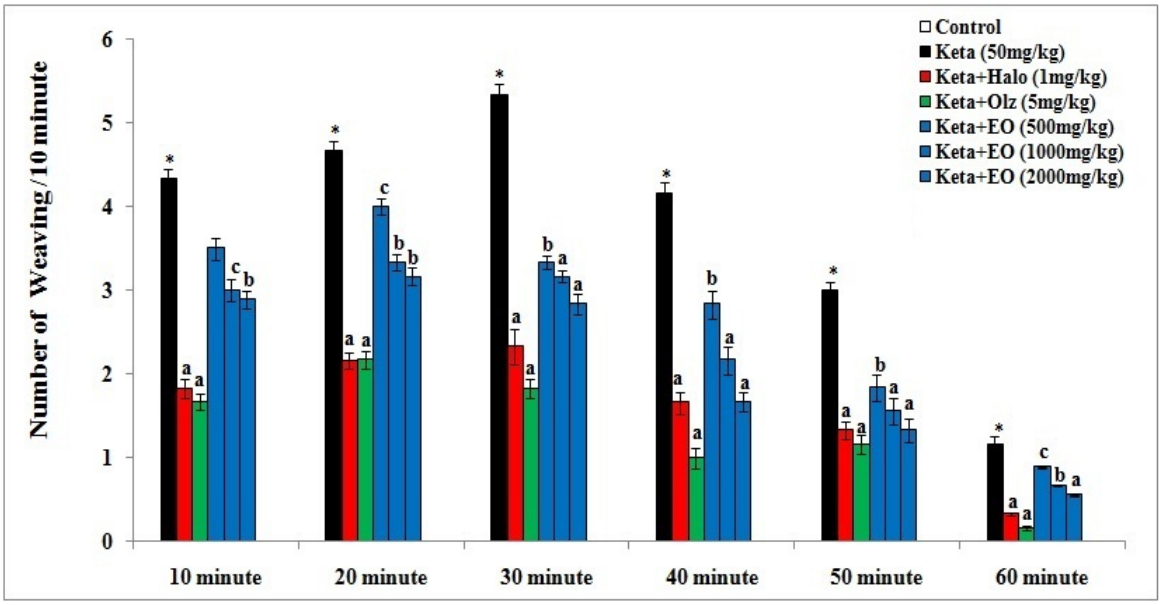

Fig 3: Effect of Eucalyptus oil (EO) on Ketamine induced weaving behaviour

* = $p<0.001$ as compared to control animals. a = $p<0.001$, b = $p<0.01$ and c = $p<0.05$ as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test.

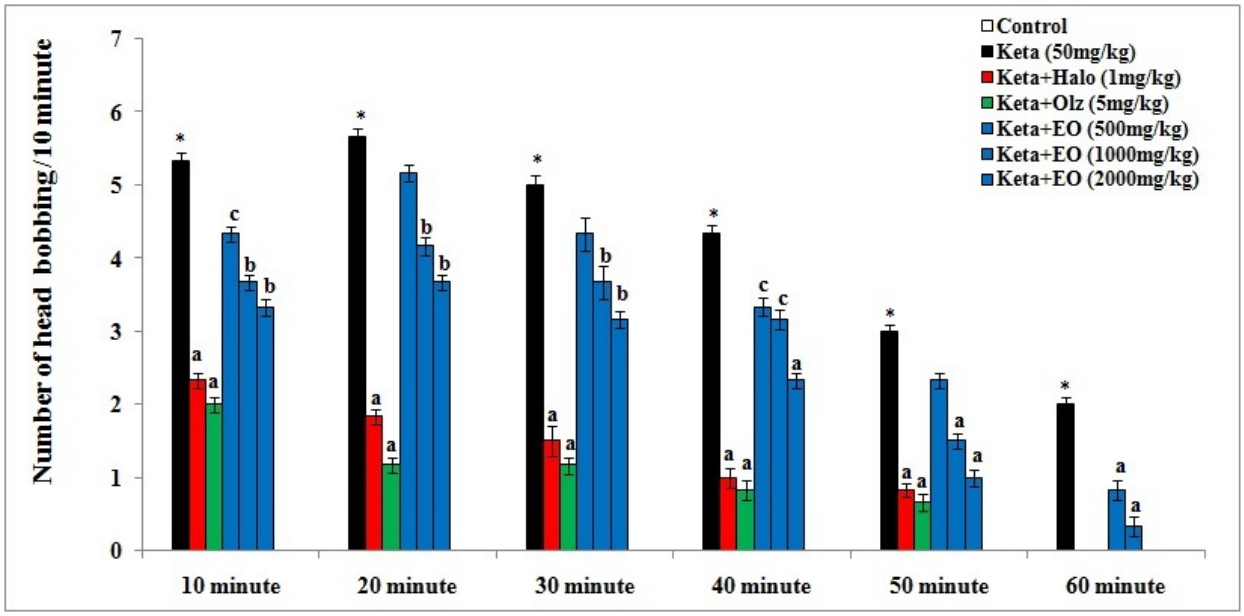

Fig 4: Effect of Eucalyptus oil (EO) on Ketamine induced head bobbing behaviour

* = $p<0.001$ as compared to control animals. a = $p<0.001$, b = $p<0.01$ and c = $p<0.05$ as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test.

4. Discussion

Psychosis is a polygenic mental disorder and affects 1% of world population [3, 5]. Typical and atypical drugs are used treat psychosis like symptoms and these drugs also associated with some adverse effects with partial responses [5, 17]. Therefore, it is necessary to understand the pathophysiology of this complicated disorder and develop new safe as well as effective drugs. Various animal models are used to understand the pathophysiological mechanism of action of this disorder [18, 19]. Ketamine is one of them used to induce stereotypic like behaviors in small animals. Ketamine is a NMDA receptor antagonist act by increasing dopaminergic neurotransmission via decreasing GABAergic control on it [20, 21]. Moreover, it also induces neuroinflammation and oxidative stress. Dopaminergic hyperactivation produce stereotypic behaviours similar to human psychosis. Essential oils are one of the beneficial therapeutic agents used in the treatment of various disorders via various mechanical of action [9, 11, 22]. Hence, we have selected eucalyptus oil (EO) to investigate its effect against Ketamine induced behavioural changes in mice. In our present study, we observed that Ketamine (50mg/kg, i.p.) induced stereotypic behaviours such as turning, falling, weaving and head bobbing in mice. EO, when administered for 10 days were significant to decrease these Ketamine induced behavioural changes. EO is excellent source of various phytconstituents, which are reported to have protective effect. Furthermore, anti-inflammatory and antioxidant effects of essential oils could also responsible for

their beneficial effective neuropsychiatric disorders. These effects might be present in EO and with the virtue of protective effect as well as phytoconstituents EO was effect against Ketamine induced behavioural changes such as stereotypic behaviours in mice.

5. Conclusion

The present study revealed that eucalyptus oil (EO) have significant effects in Ketamine induced stereotypic behaviours. This study indicates that EO might have potential clinically effect against psychosis. But, it is necessary to study the effect of EO on various biochemical parameters and other psychotic symptoms.

6. Acknowledgement

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