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Protective effect of *Brassica oleracea* juice against Ketamine-induced stereotypic behaviours in mice

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Abstract
Now-a-days, stressful life style and unhealthy food habits may produce various neuropsychiatric disorders. WHO has promoted the investigation of therapeutic effects of dietary supplements and medicinal plants for psychotic disorders due to lack of safety with allopathic drugs. *Brassica oleracea* (Brassicaceae) commonly known as cabbage, is widely used in our daily diet and well known for tremendous source of nutrients all over the world. In spite of this there is no CNS report on cabbage. Therefore, we have selected this plant and studied against Ketamine-induced stereotypic behaviours in mice. Haloperidol and Olanzapine were used as standard drugs as standard drugs in the present study. *Brassica oleracea* juice (4% v/v, 8% v/v and 16 v/v, p.o.) for significantly diminished the Ketamine induced falling, turning head bobbing and weaving behaviors in mice. These findings indicate that *Brassica oleracea* juice possesses protective effective in Ketamine induced stereotypic behaviours. Thus consumption of cabbage on regular basis through daily diets would help in protecting us from developing mental problems.

Keywords: *Brassica oleracea,* cabbage, Ketamine, stereotypic behaviours

1. Introduction
In recent years, it has been investigated that functional foods possessing bioactive phytoconstituents can influence physiological as well as cellular activities in human & animals and provides beneficial impacts on health [1, 2]. Therefore, with the virtue of their positive effect on health the research on natural compounds has been increased [3]. *Brassica oleracea var. capitata* (Brassicaceae) is commonly known as cabbage, one of the prominent leafy vegetable used as traditional medicine in the management of various diseases [4]. Previous studies have revealed that *Brassica oleracea* possesses antioxidant [5], antiulcer [6], hepatoprotective [7], anticancer [8], antibacterial [9], antidiabetic [10], antidiuretic [11], anti-inflammatory [5] properties. Further, literature review showed no reports that support its effect against mental disorder. However, this plant possesses various neuroprotective phytoconstituents such as coumarins glucobrassicin, flavonoids, polyphenols, saponins, sinigrin, sulforaphane, thiocyanates and terpenoids [12, 13, 14]. Consumption of these functional food and nutrients enriched diet may protect us from neuropsychiatric problems because phytoconstituents found in this type of functional food have broad spectrum chemical diversity and structurally specificity [15, 16, 17]. The protective mechanism of action behind these phtyoconstituents are modulates neurotransmitter systems, free radical scavenging effects, suppress the levels of inflammatory mediators, decreases excitotoxicity, reverse mitochondrial dysfunction, increase in ATP levels and diminishes apoptosis [18, 19, 20, 21]. Therefore, we have selected this functional food to investigate the effect of *Brassica oleracea* juice against Ketamine induced stereotypic behaviours in mice.

2. Experimental protocol
2.1. Animal protocol
In the present study, swiss albino mice of either six (20-25g) were used and purchased from Disease Free Small Animal House, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (India). The animals were housed in the group of six in a cage under suitable laboratory conditions and acclimatized for seven days before start the protocol. The experimental protocol was approved by Institutional Animals Ethics Committee and care of animals was taken according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India.

2.2. Plant material
Fresh leaves of the *Brassica oleracea* were procured from horticulture garden of CCS Haryana Agricultural University, Hisar, Haryana (INDIA) and authenticated from National Institute of Science Communication and Information Resources (NISCAIR), New Delhi (vide No. 2015/2836/29).

2.3. Preparation of *Brassica oleracea* Juice
Cabbage (*Brassica oleracea*) leaves was washed and homogenized with a juicer filtered through muslin cloth. The obtained filtrate was considered to be 100% purified *Brassica oleracea* juice further diluted with distilled water as required.

2.4. Drugs
Ketamine, haloperidol and olanzapine were obtained from Neon Pharmaceutical Pvt. Ltd, RPG Science Pharmaceutical Pvt. Ltd & Intas Pharmaceuticals Ltd, India respectively and diluted into normal saline. While, cabbage leaves juice were diluted into distilled water.

2.5. Experimental design
Following groups were used in the present study and each group comprised of 6 mice

Group 1 (Control): Normal saline was administered for 10 successive days. On 10th day, number of stereotypic behaviors was recorded after saline administration.

Group 2 (Negative control): Ketamine (50mg/kg, i.p.) was injected for 10 successive days. On 10th number of stereotypic behaviors was recorded after Ketamine administration.

Group 3 and 4 (Positive control): Haloperidol (1mg/kg, i.p) + Ketamine (50mg/kg, i.p.) and Olanzapine (5mg/kg, i.p) + Ketamine (50mg/kg, i.p.) were administered in separate groups of animals for 10 successive days. On 10th number of stereotypic behaviors was recorded after Ketamine administration.

Group 5, 6 and 7 (Test groups): BOJ (4%) + Ketamine (50mg/kg, i.p.), BOJ (8%) + Ketamine (50mg/kg, i.p.) and BOJ (16%) + Ketamine (50mg/kg, i.p) were administered for 10 successive days. On 10th number of stereotypic behaviors was recorded after Ketamine administration.

2.6. Ketamine- induced stereotypic behaviour in mice
The mouse was placed into a plastic cage (37 × 24 × 30 cm) which was divided into quadrants by lines on the floor. Before start the experiment mouse allowed to explore the plastic cage for 30 minute. After the last dose of Ketamine (50 mg/kg, i.p.) stereotypic behaviours (falling; number of falls on the floor), (turning; number of turns around), (head bobbing; number of neck turn up-down and left-right), (weaving; number of grooming, rearing) was produced by mice. These stereotypic behaviours were measured by counting the total number of falling, turning, head bobbing and weaving each 10 minute at an interval of 10 minute over 60 minute [22].

3. Results
3.1. Effect of BOJ, haloperidol and olanzapine against Ketamine-induced stereotypic behaviours
In the present study, Ketamine (50 mg/kg, i.p.) were significantly produced stereotypic (falling, turning, head-bobbing and weaving) behaviours in mice. BOJ (4% v/v, 8% v/v and 16% v/v, p.o.), was effective to reduce stereotypic behaviours dose dependently as compared to Ketamine treated animals. Established antipsychotic drugs viz. haloperidol (1mg/kg, i.p.) and olanzapine (5mg/kg, i.p.) remarkably reversed the stereotypic behaviors behavior as expected (figure 1, 2, 3, and 4).

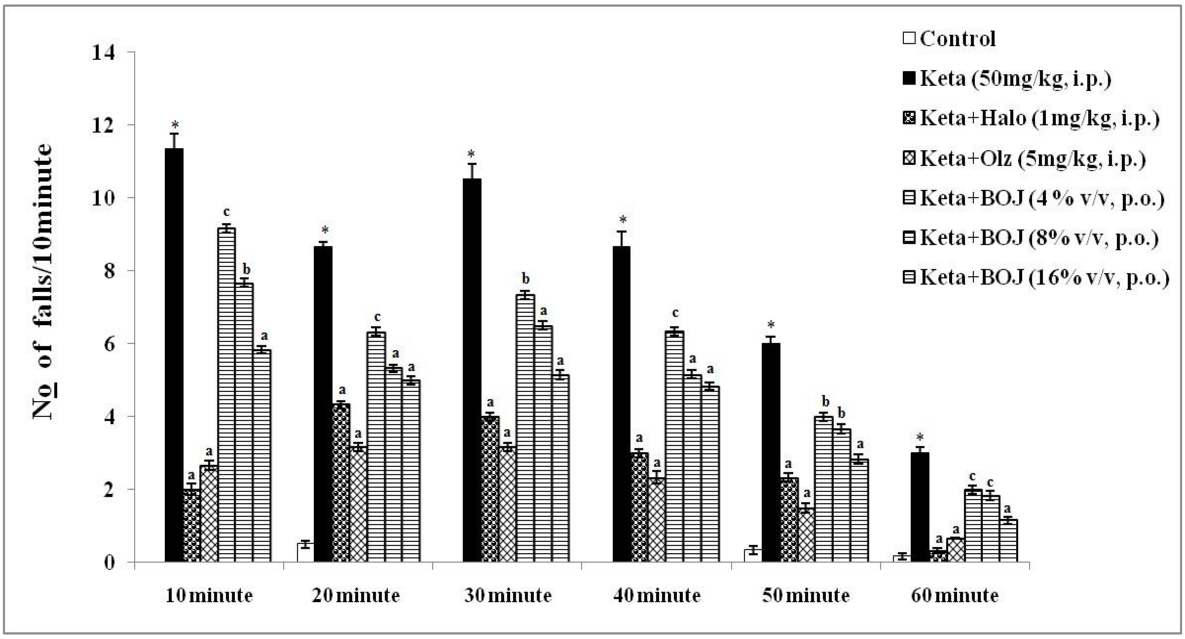

Fig 1: Effect of BOJ on Ketamine induced falling behaviour

* = $p<0.001$ 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. Halo=Haloperidol, Olz= Olanzapine and Keta=Ketamine.

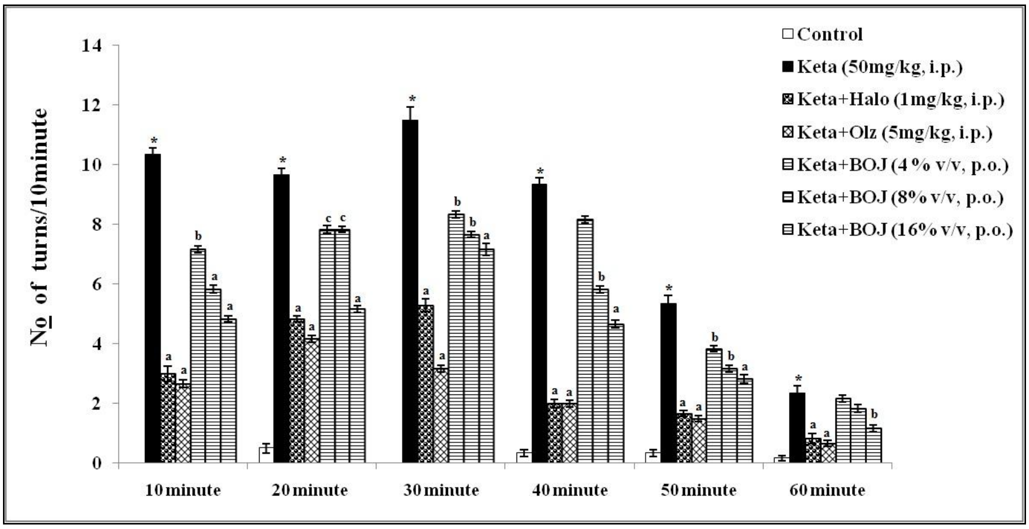

Fig 2: Effect of BOJ on Ketamine induced turning behaviour
* = p<0.001 as compared to control animals. a = p<0.001, b = p<0.01 and c = p<0.05 as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test. Halo=Haloperidol,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

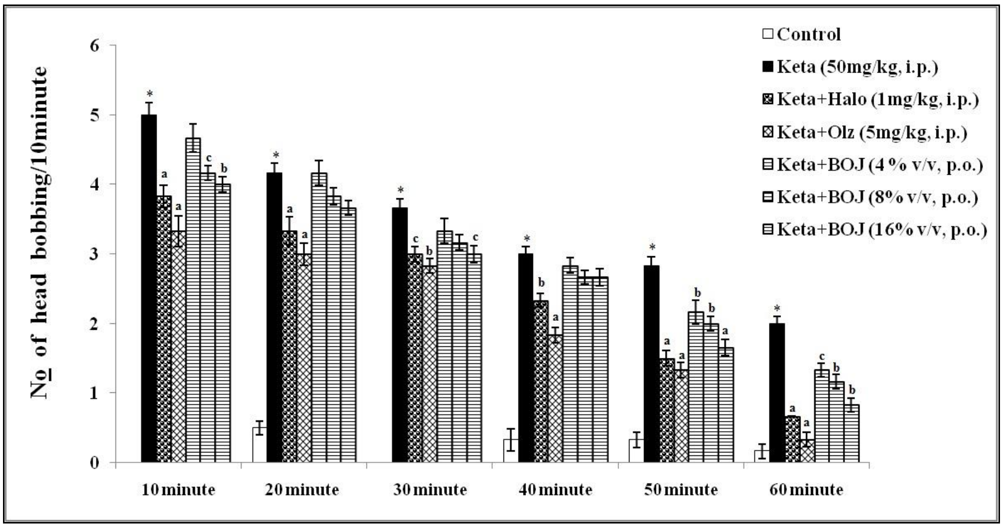

Fig 3: Effect of BOJ on Ketamine induced head bobbing behaviour
* = p<0.001 as compared to control animals. a = p<0.001, b = p<0.01 and c = p<0.05 as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test. Halo=Haloperidol, Olz= Olanzapine and Keta=Ketamine.

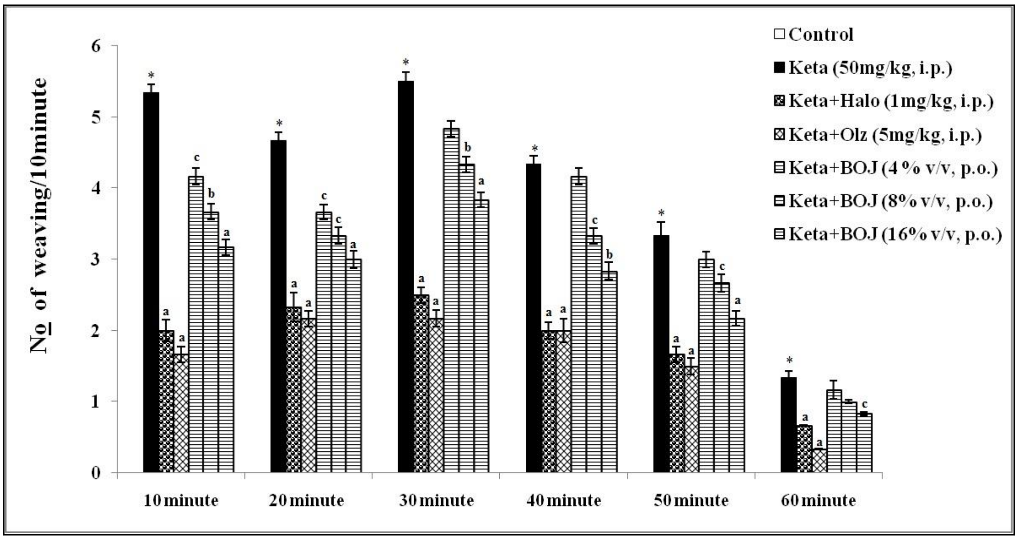

Fig 4: Effect of BOJ on Ketamine induced weaving behaviour
* = p<0.001 as compared to control animals. a = p<0.001, b = p<0.01 and c = p<0.05 as compared to Ketamine treated animals. Results are expressed as mean ± SEM (n = 6). Data were analyzed using one way ANOVA by Tukey's test. Halo=Haloperidol, Olz= Olanzapine and Keta=Ketamine.

4. Discussion
Haloperidol and olanzapine clinically used to treat stereotypic behaviours and psychosis however these drugs have some serious side effects. It has been reported that synthetic drugs possess some limitations such as psychological as well as physiological dependence and also produce some adverse effects [3]. Natural compounds may prove to be favourable to develop new drugs in the management of psychiatric disorder due to its antioxidant and anti-inflammatory property with no side effects [22, 23]. *Brassica oleracea* belongs to Brassicaceae possess excellent phytoconstituents is widely used as dietary supplements. It has antioxidant and anti-inflammatory [5]. Despite of wide uses and excellent phytoconstituents, there is no scientific report of *Brassica oleracea* on CNS. Therefore, we have taken this project to evaluate the protective effect of *Brassica oleracea* juice (4% v/v, 8% v/v and 16 v/v, p.o.) in Ketamine induced stereotypic behaviours in mice.
Stereotype behaviours are regarded as abnormal behaviours have been observed in psychiatric patients [24]. Ketamine, NMDA receptor antagonist, produced characteristic stereotypic behaviours mediated by dopaminergic hyperactivity due to loss of GABAergic inhibitory control [25, 26]. Further, Ketamine produces oxidative stress, which further can produce other psychiatric problems [27]. In the present findings, Ketamine (50mg/kg, i.p.) was used to induce stereotypic behaviours viz. falling, turning, head bobbing and weaving in mice. These stereotypic behaviours were significantly reduced with the administration of *Brassica oleracea* juice at the doses of 4% v/v, 8% v/v and 16 v/v, p.o., for 10 consecutive days. Haloperidol (1mg/kg, i.p.) and olanzapine (5mg/kg, i.p.) were effective to diminish the Ketamine induced stereotypic behaviors. These results may be attributed due to presence of flavonoids and polyphenols in *Brassica oleracea.* In previous reports, it has been reported that flavonoids and polyphenols have GABAergic property and increases the GABA release [28, 29]. It has been seen that increased GABA levels control dopaminergic neurotransmission and reduces Ketamine induced hyperactivity including stereotypic behaviours; these reports support our study [30, 31]. *Brassica oleracea* has other constituents that are reported for their protective effect on brain therefore it might act synergistically. Moreover, antioxidant and anti-inflammatory properties of *Brassica oleracea* may also responsible for their protective effective against Ketamine induced stereotypic behaviours.

5. Conclusion
The finding of present study exhibited that *Brassica oleracea* juice possess protective effects against Ketamine induced stereotypic behaviours. The study suggests that the *Brassica oleracea* might have promising clinical application against other psychiatric disorders. Therefore, it is valuable to investigate the effective of *Brassica oleracea* preclinically and clinically in the treatment of various mental diseases.

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