International Journal of Basic & Clinical Pharmacology
Pooja SG et al. Int J Basic Clin Pharmacol. 2023 Mar;12(2):178-185
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20230383

Original Research Article

Celastrus paniculatus and memantine prevent alcohol dependence and improve decision making in alcohol dependent C57BL6 mice

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Received: 24 November 2022
Revised: 27 December 2022
Accepted: 28 December 2022

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ABSTRACT

Background: Alcohol use disorder poses a huge burden with only a handful of approved drugs. AUD is associated with impaired decision-making that leads to compulsive drinking despite negative consequences. A drug that decreases alcohol consumption as well as improves decision-making may thus prove more useful. This study was planned to evaluate the effect of two drugs, Celastrus paniculatus and memantine on alcohol preference and decision impairment in alcohol-dependent mice.
Methods: In part 1, the effect of both the study drugs on alcohol consumption was studied using intermittent access model in 70 male C57BL6 mice. In part 2, effect of drugs on decision making was studied using the rodent version of Iowa gambling task. Mice were divided in seven study groups: Group 1-3: Celastrus paniculatus (140, 280, and 560 mg/kg), Group 4: memantine (25 mg/kg), Group 5: vehicle control 1 (Milk), Group 6: vehicle control 2 (normal saline) and Group 7: naltrexone(1mg/kg).
Results: Percentage alcohol preference was lower in test groups i.e., Celastrus paniculatus at medium (40.90±15.18%) and high doses (31.79±7.46%) vs. milk (82.74±8.53%; $p<0.05$); and in memantine group (36.28±10.99%) vs. normal saline (83.27±5.51%; $p<0.05$). The results were not significantly different to Naltrexone (19.70±6.90%). Percentage preference to disadvantageous arms was also lower in Celastrus paniculatus, at medium (50.52±1.92%) and high doses (48.11±2.43%) compared to milk (54.47±2.73%; $p<0.05$) and memantine (47.45±1.67%) compared to normal saline (54.00±2.73%; $p<0.05$), indicating better decision-making ability in the test groups. The findings were comparable to Naltrexone group (45.43±2.52%).
Conclusions: These results indicate that Celastrus paniculatus and memantine reduce alcohol consumption and improve decision making in alcohol-dependent mice.

Keywords: Alcoholism, Naltrexone, NMDA, Celastrus oil, Iowa gambling task, Intermittent access model

INTRODUCTION

Alcohol use disorder (AUD) is a chronic relapsing disease of the central nervous system characterized by compulsive use of alcohol, loss of control over intake and a negative emotional state when alcohol access is prohibited.[1] Alcohol use is associated with at least 60 acute and chronic diseases like acute pancreatitis, ischemic heart disease, Alzheimer's and other dementias, and various malignancies. The risk of all-cause mortality and cancer-specific mortality increases with the levels of consumption.[2,3] In the WHO Global status report on

alcohol and health 2018, 2.3 million deaths among men and 0.7 million deaths among women in 2016 have been attributed to alcohol use. Approximately 13.5% of the total deaths in the age group of 20-39 years are attributable to AUD reflecting its burden on early life.[4] The prevalence of AUD in India is 4.6-4.9%.[5,6] There is clear evidence that AUD is associated with impairment in cognition, attention, memory, and decision making.[7]Around 50-80% of patients show significant cognitive impairment in comparison with the closely matched non-alcoholic subjects.[8] The main abnormality, especially with repeated cycles of abstinence and relapse, is the inability to suppress a behaviour leading to impulsivity. As a consequence, there occurs impaired decision making leading to compulsive drinking despite the negative consequences.[9] From brain imaging studies like PET and fMRI, the neuropathological basis for cognitive impairment has been found to be the neuronal loss in the areas involved in the high order functions, namely, superior frontal association cortex, amygdala, and hippocampus.[10] There is evidence suggesting that the neuronal loss is due to the excitotoxicity caused by the super sensitivity of NMDA receptors.[11] Therefore, it is postulated that suppression of NMDA receptors would improve cognition and ameliorate the impairment in the decision-making ability of the patients. This may promote abstinence and prevent relapse. To date, only three drugs have been approved by the US FDA for the treatment AUD, namely, disulfiram, naltrexone, and acamprosate. Due to poor compliance and side effects, Disulfiram is no longer a first-line therapy.[12] Naltrexone requires regular monitoring of liver function tests and is contraindicated in patients with hepatic failure. Moreover, body of evidence is less for use of oral naltrexone and it can cause high incidence of adverse events due to fluctuations in plasma levels.[13] It is less effective for complete abstinence[14] and is associated with a 40% relapse rate at 24 months.[15] In a large RCT, the US COMBINE study, acamprosate failed to show a significant effect on drinking either alone or in combination with naltrexone.[16] Thus, there is a need for new safe and efficacious therapeutic option for treatment of AUD. Our aim in the present study was to test the efficacy of two different NMDA antagonists in animal model of AUD and test whether they improve impaired decision-making ability in alcohol-dependent animals. The first study drug Celastrus paniculatus oil is derived from Ayurveda, the traditional Indian medicinal system and second drug memantine is a modern drug approved for the treatment of Alzheimer's disease.

Ayurveda mentions the use of medicinal plants in the treatment of cognitive dysfunction, epilepsy, and insomnia. One such plant is Celastrus paniculatus which has been used for many years to improve learning and memory.[17] It is known as the 'elixir of life' and is similar to the most medhya rasayana, the cognitive restorative agents from the Ayurveda.[18] The seeds of this plant yield an oil called Celastrus oil referred to as Jyothishmati Thalia in the Ayurveda.[19] It is used in the treatment of epilepsy, insomnia, rheumatism, gout, and dyspepsia. Current research has also shown its therapeutic effects in stress, chronic pain, and inflammation.[20] A study conducted by Godkar et al showed that Celastrus paniculatus oil exerts neuroprotection against glutamate toxicity by NMDA antagonism.[18] A study conducted by Nalini et al has shown that it decreases the concentration of dopamine (a principal neurotransmitter in the reward pathway) in the rat brain. This study has also proved that the oil does not have any lethal or neurotoxic effects.[21] However, there is no literature regarding the effect of this plant in alcohol use disorder. Memantine, a non-competitive NMDA receptor antagonist selectively blocks extra synaptic glutamate activity that prevents the excitotoxicity caused by the glutamate without disturbing the normal synaptic function. Memantine was previously shown to reduce alcohol intake and prevent alcohol induced neurotoxicity.[22] Memantine has been shown to reduce NMDA receptor-mediated neuronal toxicity which can improve cognitive decline. An in-vitro study by Wang has shown that memantine reduces alcohol-induced caspase-3 activity and apoptosis in neuronal cells by decreasing intracellular calcium.[23] However, effect of memantine on impaired decision making in alcohol dependence has not been explored. Therefore, we planned the present study, to evaluate the effect of Celastrus paniculatus and memantine on alcohol preference and decision impairment in alcohol-dependent mice.

METHODS

Animals and housing

The study was conducted from June 2018-April 2019 at the central animal house, Seth GS medical college and KEM hospital, Parel, Mumbai.The study was conducted using 70 male C57BL/6 mice. The sample size was calculated using the Power & Sample size calculator software. Considering the effect size of 2.34 and standard deviation of 1.6 from the previous study, the sample size came to be 9 animals per group keeping power of 85% and confidence interval as 95.[22] To account for the loss of animals due to morbid conditions/deaths, 10 animals per group were taken. The study animals were housed in air-conditioned rooms with 12-15 filtered fresh air changes, temperature 22±3°C, and relative humidity of 30-70%. One animal per cage was housed in plastic cages with stainless steel top grills having facilities for the provision of food pellets. Alcohol and drinking water were provided in polypropylene bottles with stainless steel sipper tubes with ball bearing to avoid leakage. Standard rodent feed was provided. Aqua guard drinking water was provided ad libitum.

Study drugs

Authenticated standardized pure oil was procured from M/s. Pharmanza Herbals, Dharmaj, Gujarat (Batch No: CCOE/RAD/001). The raw material in form of seeds was purchased from Paras Herbals, Vadodara, Gujarat. Celastrus paniculatus seeds (1.5 kg) were grinded and added to 2 litre hexane in a glass vessel. This mixture was mixed well and extracted on heating mantle for 2 hours at

65°C. The procedure was repeated for total 2 cycles and filtrate from 2 cycles were mixed and distilled to recover hexane and obtain pure oil of Celastrus paniculatus. The total yield of oil was 500 ml. The extractive value was 0.25%. The doses were selected from an animal study which used rats.[24] Three doses of Celastrus paniculatus (140, 280, and 560 mg/kg) were selected based on a previous study in rats and were converted to mice using Pagets and Barnes conversion table. The Celastrus paniculatus seed oil was administered orally, by diluting in freshly boiled and cooled milk. Memantine (obtained from Sun Pharmaceuticals Ltd.) 25 mg/kg intraperitoneal dose was selected from the previous study by Escher et al Naltrexone 1 mg/kg intraperitoneally was used as the positive control (obtained from Sigma Aldrich). Two vehicle groups were included: milk and normal saline for Celastrus paniculatus and memantine respectively.[22,25]

Study procedure

The study was conducted in 2 parts as follows. In Part 1, we evaluated the effect of Celastrus paniculatus and memantine on alcohol preference using the Intermittent access model of alcohol.[26]

Intermittent access model

Mice (n=70) were subjected to a 12-hour reversed light/dark cycle (lights off at 7 am) and were habituated to this scenario for an initial period of 7 days. Two bottles were secured to the wire mesh cage lid and presented to mice 3 hours into the dark cycle i.e., at 10:00 am. The bottles were kept in place for 24 hours and were weighed at 10:00 am the next day. Water was provided throughout this period ad libitum. Mice were weighed before every alcohol drinking session. The model required intermittent access to alcohol to be provided for over 3 weeks. Therefore, in the first week, mice were given increasing concentrations of 3, 6, and 10% (w⁄v) alcohol solutions on Monday, Wednesday, and Friday in one bottle and water in a second bottle. In the following 2 weeks of the experiment, mice received 1 bottle of 20% alcohol and 1 bottle of water provided every Monday, Wednesday, and Friday for 24 hours. Bottles were removed and weighed exactly 24 hours later and the alcohol solution in the first bottle was substituted by water which remained in place until the next alcohol drinking session. To prevent the development of side preferences, the position of the bottles was alternated. After the development of alcohol dependence, on day 22, the mice were randomly divided into 7 groups consisting of 10 animals each and were provided with continuous access to 20 % w/v alcohol and water for 15 days. During this period, the study drugs were administered once daily, every morning, to the respective groups. Daily intake of alcohol and water was measured for each animal over 15 days. The intake of water and alcohol on the last day (Day 36) was compared among the groups. Percentage alcohol preference was calculated. The study variables were absolute alcohol intake in g/kg/day, water intake measured as g/kg/day, percentage alcohol preference. Alcohol intake was measured in ml/kg/day and converted to g/kg/day using the following formula: alcohol intake (ml/kg/day) X 0.2 X 0.79; where, 0.2 is the concentration of alcohol, 0.79 is the specific gravity of alcohol. This was followed by evaluation of study drugs on decision making in alcohol-dependent mice using rodent version of Iowa gambling task over 9 days.[27] Alcohol administration was stopped and study drug administration continued during this period.

Rodent version of Iowa gambling task

The model developed by Van den bos et al was used.[27] The apparatus (Figure 3) consisted of an eight-arm radial maze with dimensions as follows: diameter of the octagonal maze center, 22 cm; wall height, 23.5 cm; arm length, 22 cm; arm width, 9.0 cm; arm height, 5.0 cm. The cylindrical wall of the central maze area was made opaque so that the mice were not distracted and could not directly see the researcher while he/she rebated the arms. Internal cues above the entrance of the arms were attached, which helped the mice to differentiate the goal arms. These cues consisted of a cross or a circle (5x5 cm), either black or white. Mouse food pellets sweetened with sugar were used for reward and quinine coated bitter food pellets were used for punishment. Two arms were used as the start arms, and four as the goal arms and the other two arms were kept empty to rule out the non-specific arm entries. Out of the four goal arms, two arms were advantageous where a small reward (a single pellet) and less frequent punishments (2-3 out of 15 trials) were given. Two arms were disadvantageous in which there were bigger rewards (three pellets) but frequent punishments (8-9 times among the 15 trials) making them disadvantageous in the long run. This is in accordance with the advantageous and disadvantageous decks in the human Iowa Gambling Task. Mice were given 15 trials a day over 9 days. During this period, food regimen was such that the mice received a specified amount of food between 16:00 and 07:00 h. During the weekend, they were allowed access to food ad libitum. Water was freely available throughout. Each mouse was given one habituation session of 5 minutes before the first experimental day. Before the start of the first trial on each daily session, the mice were confined for 30 secs in one of the start arms. A trial was started by lifting the octagonal slide door of the center of the maze. Once the mice had hopped into one of the goal arms, the octagonal slide door was lowered and the animal was allowed to sample the arm's contents. To avoid the development of habituation in mice, the order of start arms during sessions was randomized across trials. The animals were allowed to explore the arms and eat the pellets for 2 minutes at maximum. Whenever the mice did not leave the start arm or did not make a choice within 2 min, the same trial was given again. Occasionally, the animals were gently pushed out of the start arm. After each mouse, the floor of the maze was cleaned with 70% alcohol. The study drugs were administered every morning in the dark cycle of the animals and the trials were given after half an hour of drug administration. The number of entries to the goal arms were noted for each mouse and the percentage preference

for disadvantageous arms over the 9 days (135 trials) was calculated and compared across the groups.

Statistical analysis

Results are expressed as mean±SD. The level of significance was set at p<0.05. GraphPad In Stat software version 3.06 was used for statistical analysis. The baseline data regarding alcohol intake and water intake before and after the development of alcohol dependence was analysed using Wilcoxon Signed Rank test as the data was non parametric. For Part 1 and 2, analysis of variance (ANOVA) test with post-hoc Tukey's test was applied for parametric data and Kruskal Wallis with post hoc Dunn test was applied for non-parametric data.

RESULTS

Seventy C57BL6 mice were used in the study (10 per group). One mouse in the normal saline group died on the first day of drug administration period (Day 22).

Table 1: Mean intake of alcohol and water in alcohol dependent mice (n=69).

Variable	Day 1	Day 21
Alcohol intake in g/kg/day	1.83±1.67	22.44±2.76 #
Water intake in g/kg/day	140.41±21.32	28.49±14.83 *

Values expressed as Mean±SD, *p<0.001, compared to water intake of Day 1, using Wilcoxon signed-rank test, #p<0.001, compared to alcohol intake of Day 1, using Wilcoxon signed-rank test.

Table 2: Mean intake of absolute alcohol and water in g/kg/day.

Groups	Absolute alcohol Intake in g/kg/day (mean±SD)	Water intake (g/kg/day) (mean±SD)
Normal Saline (N=9)	23.4±2.43	29.48±10.53
Milk (N=10)	21.33±2.91	29.29±14.84
Naltrexone (N=10)	4.69±1.83 *#	120.40±20.80*#
Memantine (N=10)	9.25±4.38 *	102.63±25.01*#
CP Low (N=10)	17.27±4.29	42.09±18.07
CP med (N=10)	10.68±5.56#	88.63±18.15#
CP high (N=10)	8.98±3.20#	107.49±17.25#

The values are expressed in mean±SD, CP-Celastrus paniculatus, *p<0.001 compared to Normal saline group according to ANOVA and post hoc Tukey's test, #p<0.001 compared to Milk according to ANOVA and post hoc Tukey's test.

In intermittent access model, alcohol intake increased significantly on day 21 compared to day 1 whereas the intake of water reduced significantly on day 21 compared to day 1 indicating the development of dependence (Table 1).

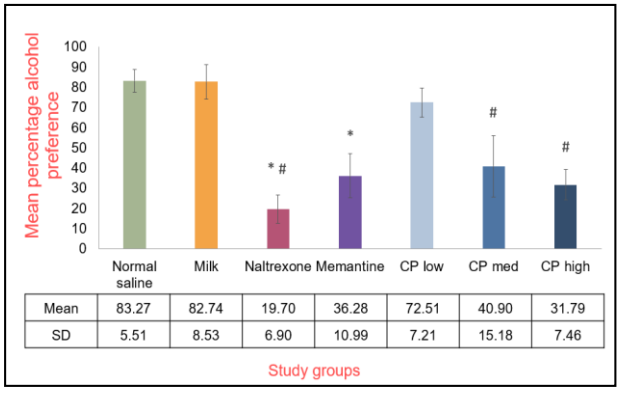

Figure 1: Effect of Celastrus paniculatus and memantine on percentage alcohol preference (*p<0.01 compared to Normal saline group, # p<0.01 compared to Milk, ANOVA with post hoc Tukey's test, CP-Celastrus paniculatus, CP low-140 mg/kg, CP med-280 mg/kg, CP high-560).

In part 1 (Table 2), the intake of alcohol was significantly low in mice treated with Celastrus paniculatus at doses 280 mg/kg and 560 mg/kg compared to the milk group. This was accompanied by an increase in the intake of water in these mice. Memantine at 25 mg/kg also significantly reduced alcohol consumption and increased water intake when compared to the normal saline. The effect of both the test drugs was statistically comparable to that of Naltrexone. The percentage alcohol preference was significantly lower in medium and high doses of Celastrus paniculatus compared to the milk group (Figure 1). The preference in the low dose group (72.51±7.21%) was lower than the milk group but was not statistically significant. Mice in the memantine group showed significantly lower preference to alcohol compared to the normal saline group (p<0.01). The findings suggest a dose-dependent increase in the effect of Celastrus paniculatus. Further, the effect produced by both test drugs was statistically comparable to naltrexone. Between the two test drugs, the percentage alcohol preference of memantine was comparable to the high dose of Celastrus paniculatus. In Part 2 (Iowa gambling task), as shown in the (Figure 2), mice treated with Celastrus paniculatus and memantine showed less preference to dis-advantageous arms compared to the vehicle control groups indicating better decision-making ability in the test groups. There was statistically significant

difference between the two doses of Celastrus paniculatus (medium and high dose) and memantine compared to the vehicle control group in terms of percentage preference for the disadvantageous arms. The two study drug groups showed comparable results with naltrexone group.

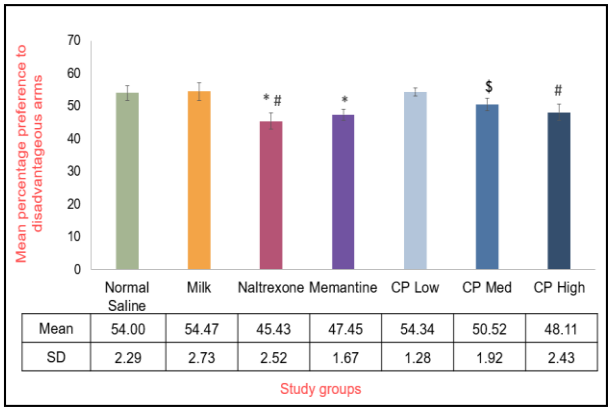

Figure 2: Effect of Celastrus paniculatus and memantine on percentage preference for disadvantageous arms (*p<0.01 compared to Normal saline group, #p<0.01 compared to Milk, ANOVA and post hoc Tukey's test, CP-Celastrus paniculatus, CP low 140 mg/kg, CP med-280 mg/kg, CP high-560 mg/kg).

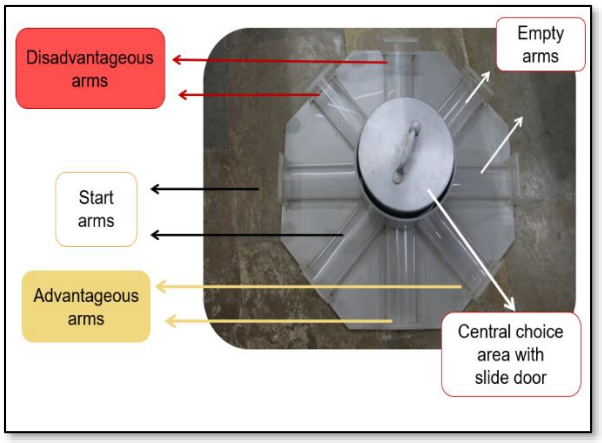

Figure 3: Apparatus of rodent version of Iowa gambling task.

DISCUSSION

Alcohol-induced cognitive impairment in the form of impaired decision-making leads to decreased chances of abstinence. The present study has shown that Celastrus paniculatus and memantine decreased alcohol preference and improved decision making in the alcohol-dependent C57BL6 mice. As CP and memantine are known to block NMDA receptors, these effects could be attributed to prevention of NMDA receptor-mediated excitotoxicity by these drugs. Intermittent access of alcohol model in mice was chosen because of its high construct and face validity.[26,28] In this model, a kindling-type of shift is seen which is thought to bring about escalating alcohol intake leading to dependence. Also, this model induces neurotoxic effects of alcohol leading to higher brain NMDA activity which is important in this study as the possible mechanism of the effect of study drugs is 'NMDA antagonism'.[29] C57BL6 mouse strain was chosen since it has been found to consume the highest amount of alcohol per unit body in comparison to other strains.[26] The findings of Part 1 show that naltrexone decreased alcohol intake and increased water intake. Thus, the effect was not an overall suppression of fluid intake but alcohol alone. Similarly, Celastrus paniculatus at doses 280 mg/kg and 560 mg/kg also reduced alcohol consumption and increased water intake ($p<0.01$) in dose dependent manner. To our knowledge, there is no published literature regarding the effect of Celastrus paniculatus in AUD model. Another study recently conducted by Satam et al-also showed that Celastrus paniculatus reduced relapse and prevented alcohol withdrawal-induced anxiety in AUD models.[30] Memantine also showed decreased alcohol consumption comparable to naltrexone. In a previous study by Malpass et al, memantine decreased alcohol consumption at a dose of 10 mg/kg in rats. A dose-dependent increase in the effect was observed in this study.[31] Similar effect was also observed by Escher et al, who reported reduced self-administration of alcohol by memantine in schedule induced polydipsia model in C57BL6 mice at a dose of 10 and 25 mg/kg.[22] However, both these studies have not reported significant alteration in the water intake as was observed in our study. Despite the positive results shown by experimental studies, in a study on human participants, Sarin et al has shown that memantine at the dose of 20 mg in adults reduced craving but not alcohol consumption.[32] Reduction of craving was also noted in another double-blind placebo controlled clinical study, albeit in small number of patients.[34] The present study has further generated evidence for efficacy of–memantine in AUD. Iowa Gambling Task (IGT) has been widely used to assess decision-making both in research and in clinical practice.[32] The rodent version of IGT developed by Bechara et al, is known to have both predictive and construct validity.[33,34]

The findings of part 2 of the study indicate that mice treated with Celastrus paniculatus and memantine showed lower preference to disadvantageous arms compared to the vehicle. This is, suggestive of a better decision-making ability in these animals. This is the first study to evaluate the effect of Celastrus paniculatus and memantine on alcohol induced decision impairment. The effect of memantine on alcohol induced cognitive impairment in terms of spatial memory was reported by Wang et al. using Morris water maze and radial arm maze.[34] Prior evidence suggests that NMDA receptor antagonism affects multiple alcohol related behaviours, like cue-induced alcohol seeking, alcohol self-administration, memory reconsolidation, behavioural and neurotoxic effects of alcohol. Therefore, addressing this pathway provides a multi-pronged approach for pharmacotherapy which is lacking in the current therapeutic options. Inhibitory effect of Celastrus paniculatus against NMDA receptor mediated

glutamate toxicity shown by earlier authors may be responsible for its effects in the present study. It has been shown in experimental studies that alcohol induced impairment in memory leads to impulsivity and impaired decision making resulting in relapse.[7] Celastrus paniculatus is known to improve memory and cognition. We hypothesize that the same mechanism might underly its effect on impaired decision-making. NMDA antagonists have been shown to affect dopaminergic transmission in the reward pathway. LY-274614, a competitive NMDA antagonist and MK-801, a non-competitive antagonist have demonstrated reduced volitional consumption of alcohol in Myer's high preferring rats.[35] Ketamine is another NMDA antagonist that has been shown to reduce harmful drinking[36] Moreover, the study by Satam et al has demonstrated that Celastrus paniculatus decreases dopamine levels in the striatum of alcoholic rats.[30] Similarly, Nalini et al have shown that Celastrus paniculatus reduced brain dopamine levels in addition to other biogenic amines[21] Therefore, it can be hypothesised that beneficial effect of Celastrus paniculatus on alcohol consumption could also be mediated by decreasing the release of dopamine, which is the principal neurotransmitter of the brain reward pathway.

Our study is similar in design to a study reported by Jadhav and Marathe wherein potassium clavulanate was shown to improve decision making in the alcohol addicted C57BL6 mice.[37] The role of oxidative stress, neuroinflammation and apoptosis in alcohol related neuronal damage are reported by many researchers.[38–40] Celastrus paniculatus has a documented anti-oxidant effect. In a study by Godkar et al there was a dose dependent attenuation of hydrogen peroxide induced toxicity by Celastrus paniculatus seed oil in embryonic forebrain neuronal cells.

The effect of memantine on oxidative stress has also been reported in a study by Wang et al in which memantine reduced ethanol-Induced Caspase-3 Activity and apoptosis in H4 Cells by decreasing intracellular calcium.[23] Thus, it is possible that antioxidant potential of Celastrus paniculatus and memantine may also have contributed to their beneficial effects observed in our study. One of the limitations of present study is that, we did not study the central mechanism of action of the study drugs. Future studies should explore the effect of Celastrus paniculatus and memantine on neuroplasticity in prefrontal cortex, ventral tegmental area and amygdala to explore their mechanisms underlying improved decision-making capacity.

CONCLUSION

Administration of Celastrus paniculatus and memantine at the doses tested in the present study reduced alcohol consumption and improved decision making in alcohol dependent mice. The present study significantly adds two new compounds to the repertoire of drugs that could be tested clinically for the management of AUD.

ACKNOWLEDGEMENTS

Authors would like to thank Diamond Jubilee Society Trust of Seth GSMC and KEM Hospital for providing generous financial assistance. Authors would also like to thank Sun Pharmaceutical Industries, Ltd. for providing gift sample of memantine and M/s. Pharmanza Herbals, Gujarat for providing Celastrus paniculatus seed oil. Authors are grateful to laboratory staff, Mr. Sanjay and Mr. Sandeep for their co-operation for conducting the study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Pooja SG, Raut SB, Kamat SK, Sa SD, Marathe PA, Rege NN. Celastrus paniculatus and memantine prevent alcohol dependence and improve decision making in alcohol dependent C57BL6 mice. Int J Basic Clin Pharmacol 2023;12:178-85.