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Indian classical *Mohana Raga* (instrumental music) overcomes anxiety, depression and memory impairment in chronic unpredictable mild stress rat model – A behavioural study

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Stress is a reaction to possibly threatening stimuli. Chronic stress leads to oxidative stress and damage to the prefrontal cortex and hippocampus, leading to anxiety disorders, depression, changes in synaptic plasticity, decreased neurogenesis, increased neurodegeneration, and impaired learning and memory. Music triggers emotional and cognitive aspects that help improve cognitive functions. Music therapy reduces anxiety, improves mood, and generates calming effects. The effect of *Mohana Raga* on human mental health is an interesting area of study, as Indian classical music, particularly ragas, is believed to have therapeutic potential. While there is limited specific research on *Mohana Raga* alone, there are studies and scholarly works that explore the general effects of Indian ragas, including Mohana, on mental health, emotional well-being, and psychological states. Also, listening to the raga Bhupali (Mohana) improved learning and memory. Animals were exposed to a chronic, unpredictable mild stress protocol for 28 days, followed by exposure to Indian classical music for 1 hour for 21 days, starting from the last week of the stress protocol. Post-treatment, the animals were subjected to an elevated plus maze, sucrose preference test, forced swim test, novel object recognition test, and T-maze alteration task for behavioural analysis. Animals exposed to chronic, unpredictable mild stress showed increased anxiety-like behaviour, anhedonia, behavioural despair, and impaired recognition and working memory. Remarkably, in stressed animals exposed to Indian classical music for one hour per day for 3 weeks, there was a complete recovery in anxiety, depression, and memory. In conclusion, our study posits that a short duration of music exposure is beneficial for chronic stress conditions.

Keywords: Classical music, Chronic stress, Memory, *Mohana Raga*

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Stress is a reaction to possibly threatening stimuli[1]. Stress is caused either by external environmental factors or internal perception of an individual which advances to anxiety, negative emotions, pain perception, tension, sadness, and mood disorders[2]. Chronic stress initiates several processes that initiate a variety of psychiatric disorders[3]. During stressful situations, the hypothalamic-pituitary-adrenal (HPA) axis becomes activated, leading to an increased release of glucocorticoid hormones. Elevated levels of glucocorticoids cause hippocampal atrophy and inhibition of long-term potentiation, which is crucial for memory formation[4]. Damage to the structure of hippocampal neurons impairs their normal inhibitory control over the HPA axis. This disruption causes an excessive release of glucocorticoids, which in turn worsens hippocampal atrophy[5].

Prolonged stress decreases dendritic complexity, promotes cell death, decreases the volume, and changes the synaptic plasticity[6-7]. Also, it causes damage to the hippocampal neurons, and neuronal excitability, and decreases neurogenesis[8,9], reduces cell proliferation[1], neurodegeneration in the hippocampus with cognitive dysfunction, anxiety, and depression-like behaviours[3,10,11]. Chronic stress negatively influences prefrontal cortical mediated cognitive processes by disturbing glutamatergic signalling in rats[12,13].

To reduce the psychological and physiological symptoms of chronic stress yoga, meditation, music therapy, and other mindfulness-based therapeutic approaches have been exclusively used[14-16]. Listening to music positively affects emotional well-being,

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Abbreviations:
CUMS: Chronic unpredictable mild stress, EPM: Elevated plus maze, SPT: Sucrose preference test, FST: Forced swim test, NORT: Novel object recognition test, ANOVA: Analysis of variance

reduces pain responses, and helps manage chronic pain, anxiety, and depression; music therapy reduces anxiety, improves mood, and reduces pain[17]. Indian classical music, which is made up of various ragas and talas, has been shown in a study to produce a calming effect regardless of the tala or rhythm used[18,19]. Hence, this study aimed to investigate the effects of daily exposure to instrumental Indian classical *Mohana Raga* for one hour over three weeks on learning and memory impairments induced by chronic unpredictable mild stress in rats.

Material and Methods

Experimental animals

The protocol was submitted to and approved by the Institutional Animal Ethics Committee at KLE College of Pharmacy, Bengaluru. Adult male Wistar rats (2 months old) were obtained and housed in polypropylene cages. They were maintained on a 12 h light/dark cycle with constant access to nutrient pellets and water, except during experimental procedures that required food and water deprivation.

Animal grouping

The animals were randomly assigned to four groups (Fig. 1a) as follows: Control group, consisting of animals housed under standard laboratory conditions (n=8); Stress group, subjected to a 28-day chronic unpredictable mild stress (CUMS) protocol (n=8); CUMS + Music exposure group, subjected to 28 days of CUMS followed by 21 days of 1 h daily music exposure (n=8); and CUMS + Standard group, subjected to 28 days of CUMS followed by 21 days of standard drug treatment (n=8).

Induction of stress

In this study, stress was induced using the chronic unpredictable mild stress (CUMS) model over 28 days. This model involved exposing the animals to various mild stressors in a random and unpredictable sequence. The stressors included 24 h food deprivation, 12 h overnight illumination, 24 h water deprivation, 2 h restraint stress, 24 h wet bedding, 7 h cage tilting at 45 degrees, and 24 h social or isolation stress[20,21].

CUMS procedure

Stressor	Days of CUMS procedure
Restraint stress	1, 12, 18, 25
Overnight illumination	2, 13, 17, 22
Food deprivation	3, 10, 21, 27
Water deprivation	4, 9, 15, 28
Wet bedding	7, 11, 20, 26
Cage tilting	6, 8, 16, 23
Social or isolation stress	5, 14, 19, 24

Music exposure

Animals were exposed music for CUMS + Music group. The animals were placed 1 meter away from the speaker in a sound attenuated room[22] and taped Indian classical (instrumental) music was played with an average sound level of 65-75 dB (checked with a sound level meter) for 1 h for a period of 21 days[23,24]. The music tape used was played in the *Raga Mohana*[25] on Veena.

Standard drug treatment

Animals were treated with standard drug (Fluoxetine HCl, 10 mg/Kg b.w.), administered by oral route for 21 days for CUMS + Standard group.

Behavioural analysis

Elevated plus maze (*EPM*)

The animals were evaluated for anxiety-like behavior using the elevated plus-maze, a procedure consistent with methods described in previous studies. Each rat was allowed 5 min to explore the maze, during which its activity was recorded using a

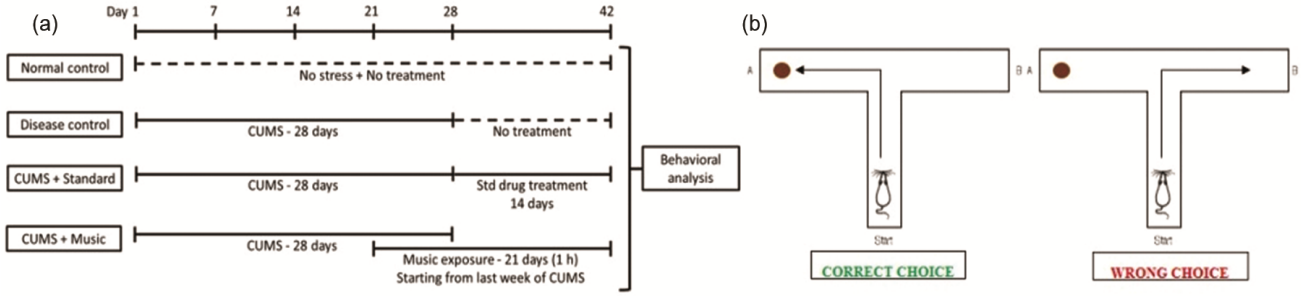

Fig. 1 — (a) Experimental design, CUMS: Chronic unpredictable mild stress, (b) T-maze rewarded alteration task

camera. Multiple parameters were documented and subsequently analyzed[26].

***Sucrose preference test* (*SPT*)**

Anhedonia behaviour in the animals was studied using SPT. This experimental procedure was conducted following methods described in previous studies. The test spanned three days, during which each animal was housed individually in polypropylene cages. The volume of sucrose and water consumed was measured every 24 h, ensuring no place preference was induced. Animals underwent 18 h of food and water deprivation before a 2 h testing session. Sucrose preference was calculated as the percentage of total fluid consumed[8].

***Forced swim test* (*FST*)**

The Forced Swim Test (FST) was conducted over two days to assess behavioral despair in the animals. After the swim sessions, video recordings of the sessions were analyzed to determine immobility, defined as passive floating with minimal movements to keep the head above water. Climbing and active swimming along the bucket walls were not considered immobile. Results were expressed as the percentage of time spent[7].

***Novel object recognition test* (*NORT*)**

The purpose of NORT was to evaluate the natural tendency of exploratory behaviour of rodents in a novel environment and understand the recognition memory. It is a three-step procedure including habituation, training/familiarization and testing sessions. The procedure involved habituation, training/familiarization and testing session. All sessions were video-recorded for later analysis. The parameters assessed included the time spent with familiar objects (Tf, in seconds) and the time spent with novel objects (Tn, in seconds), their recognition and discrimination indices[27,28].

$$\text{Discrimination index} = \frac{T_n - T_f}{\text{Total time spent with both objects}}$$

$$\text{Recognition index} = \frac{T_n}{\text{Total time spent with both objects}}$$

T-maze task

T-maze task is a reward-based alteration task (Fig. 1b) that helps to evaluate the spatial working memory in rodents. The apparatus consists of a start arm, two goal arms and a manually operated door placed 10 cm from the starting point creating a box to place the animal. The goal arms consists a small circular well at the end of the arm to place the food pellets. The procedure includes habituation, acquisition and retention test.

(a) **Habituation:** Animals were partially fasted and placed in a maze to explore target arms with food pellets. The animals were allowed to eat all the pellets. Acclimatization was done for 2 days.

(b) **Acquisition:** In the acquisition phase, animals were allowed to explore a maze with food in alternative arms. There were 6 trials per day, the animals had to take turns to receive the reward. The number of correct choices, that is, the number of choices that led to the rewarded branch, was recorded for further analysis. The maze was cleaned with 70% v/v alcohol every 2 trials to remove odor cues. The time between tests was 30 seconds. The acquisition was completed within 6 days.

(c) **Retention test:** After a 2-day break procedure, on day 11, the animal was tested with 6 trials with a 30 second inter-trial interval. The number of correct choices, that is, the number of choices that led to the rewarded branch, was recorded for further analysis. After every 2 trials, the maze was cleaned with 70% v/v alcohol[29].

Statistical analysis of the data

The videos recorded during the behavioural experiments were coded to avoid bias. Data were analysed using GraphPad Prism 5 statistical software. Data was analysed using ANOVA followed by Tukey's posthoc test. The data were presented as mean ± standard error of mean, with statistical significance defined as $p<0.05$.

Results

Indian classical music reduced anxiety in stressed animals

When compared to the control group, stressed animals in the EPM test had less open arm entries. When stressed animals were exposed to music, their number of open arm entries increased (Fig. 2a; $p<0.001$; $F_{3,28}=11.90$), and closed arm entries decreased (Fig. 2b; p=ns; $F_{3,28}=1.452$) when compared to both control and stressed animals.

In comparison to the control group, CUMS animals spent greater time in the closed arms (Fig. 2d; $p<0.001$; $F_{3,28}=10.43$) and less time in the open arms (Fig. 2c; $p<0.001$; $F_{3,28}=7.526$). The animals exposed to music exhibited a reversal of anxiety-like

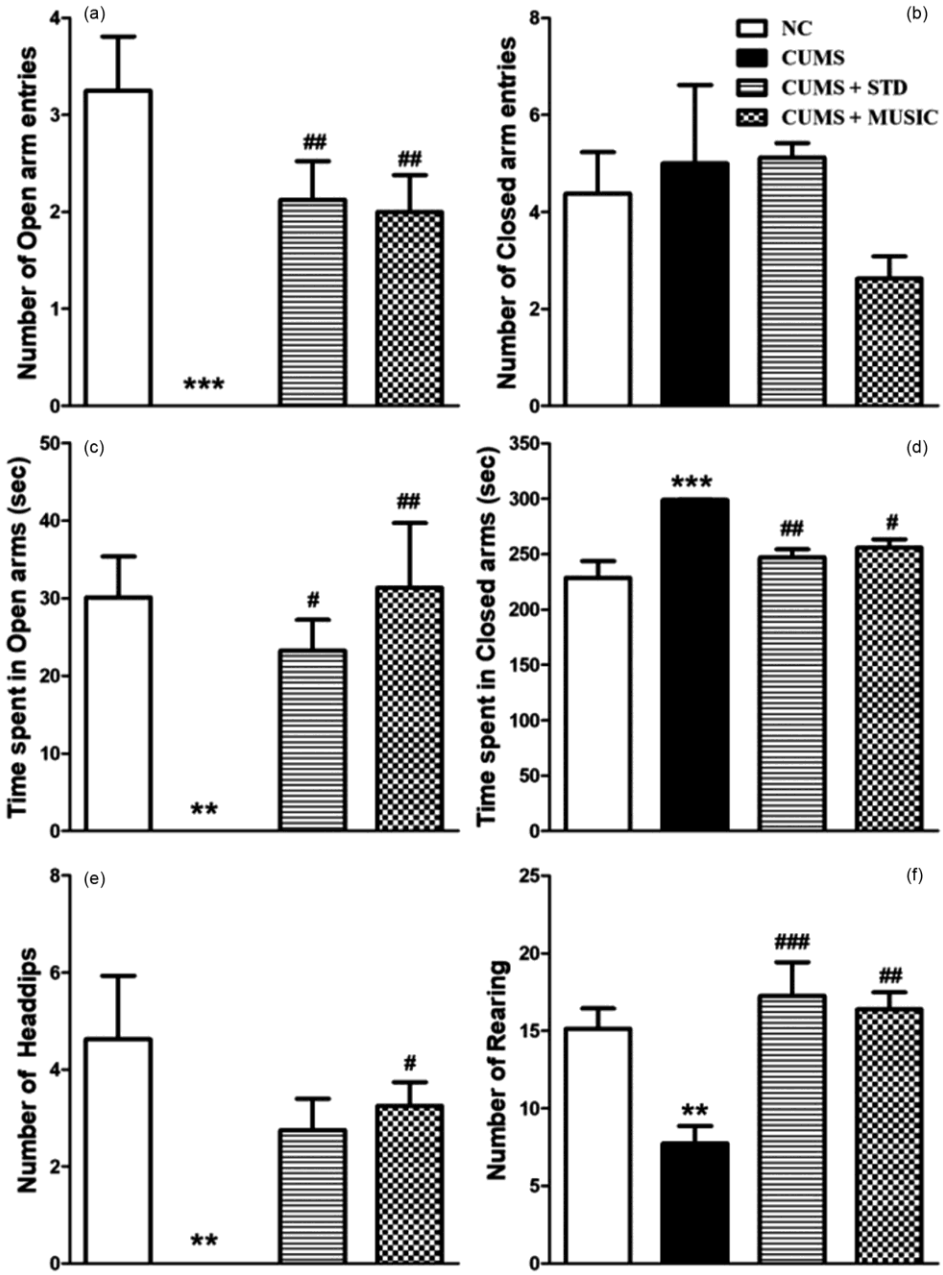

Fig. 2 — Effect of Indian classical music on CUMS induced anxiety in the elevated plus maze (EPM); (a) Number of open-arm entries, (b) Number of closed-arm entries, (c)Time spent in the open arms; (d) Time spent in the closed arms, (e) Number of head dips, (f) Number of rearing. NC: Normal control (n=8); CUMS: Chronic unpredictable mild stress (8); CUMS + STD: Fluoxetine HCl, 10 mg/kg p.o. (8); CUMS + MUSIC: Music exposure for 1 h (8). Data were expressed as Mean ± SEM. Statistical analysis was done using One-way ANOVA followed by Tukey's posthoc test. **p<0.01, ***p<0.001 as compared to normal control; $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.01as compared to the CUMS group

behaviour. As seen in (Fig. 2c ($p<0.001$; $F_{3,28}=7.526$), they spent more time in the open arms and less time in the closed arms than the stressed animals (Fig. 2d; $p<0.001$; $F_{3,28}=10.43$).

Chronic stress hindered the exploratory behaviour of the animal in the elevated plus maze activity. The number of head-dips and rearing in stressed animals were lesser, whereas the animals exposed to Indian classical *Mohana Raga* showed higher number of head-dips (Fig. 2e; $p<0.01$; $F_{3,28}=6.346$) and rearing (Fig. 2f**;** $p<0.001$; $F_{3,28}=8.403$) which shows the alleviation of anxiety-like behaviour caused by chronic

stress.

$$\text{Recognition index} = \frac{T_n}{\text{Total time spent with both objects}}$$

Music exposure restores anhedonia in animals subjected to CUMS

The disease control group showed a significant decrease in the % of sucrose water consumed (Fig. 3; Day 1: $p<0.001$; $F_{3,28} = 24.38$; Day 2: $p<0.001$; $F_{3,28} = 10.81$; Test: $p<0.001$; $F_{3,28} = 7.15$) compared to the control group. This shows that chronic stress leads to depression-like behaviour. This condition was restored by exposing the stressed animals to music exposure. The sucrose preference was increased significantly in music-exposed animals (Fig. 3; Day 1: $p<0.001$; $F_{3,28} = 24.38$; Day 2: $p<0.001$; $F_{3,28} = 10.81$; Test: $p<0.001$; $F_{3,28} = 7.15$). The restoration of anhedonic behaviour shows that Indian classical music helps treat depression-like behaviour in stressed conditions.

Effect of Indian classical music on CUMS induced behavioural despair

Animals subjected to chronic unpredictable mild stress displayed a notable rise in the duration of immobility, suggesting depressive behaviour (Fig. 4; $p<0.001$; $F_{3,28} = 54.01$). It is worth noting that exposure to music helped to alleviate the behavioural despair induced by chronic stress, resulting in a significant decrease in immobility time (Fig. 4; $p<0.001$; $F_{3,28} = 54.01$) compared to stressed animals in the forced swim test.

Music exposure on recognition memory

NORT is based on the natural tendency of exploratory behaviour of rats. It was observed that the exploration time of stressed animals with the familiar object was longer (Fig. 5a; $p<0.001$; $F_{3,28} = 51.61$) than the novel object (Fig. 5b; $p<0.001$; $F_{3,28} = 22.01$)

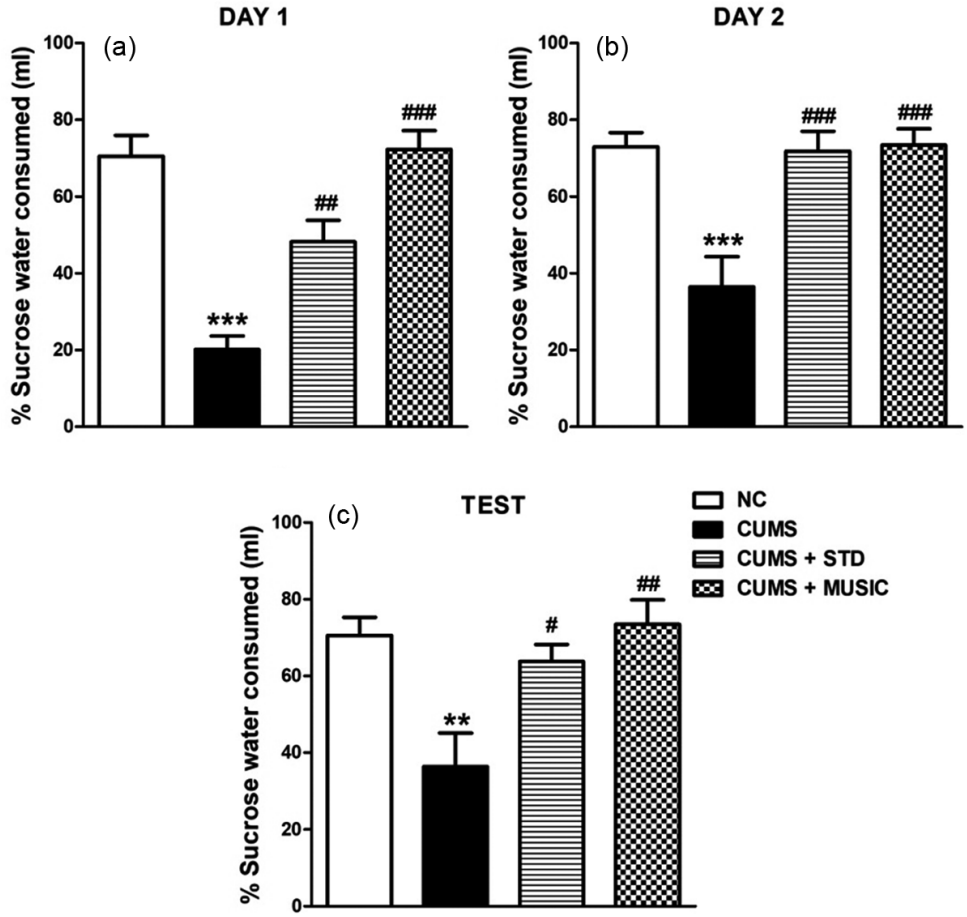

Fig. 3 — Effect of Indian classical music on CUMS induced anhedonia in sucrose preference test. (a) Day 1; (b) Day 2; (c) Day 3 of the sucrose preference test protocol. NC: Normal control (n=8); CUMS: Chronic unpredictable mild stress (8); CUMS + STD: Fluoxetine HCl, 10 mg/kg p.o. (8); CUMS + MUSIC: Music exposure for 1 h (8). Data were expressed as Mean ± SEM. Statistical analysis was done using One-way ANOVA followed by Tukey's posthoc test. **p<0.01, ***p<0.001 as compared to normal control; $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.01as compared to the CUMS group

compared to the normal rats. This resulted in a significant decrease in the recognition index (Fig. 5c; $p<0.001$; $F_{3,28} = 68.21$) and discrimination index (Fig. 5d; $p<0.001$; $F_{3,28} = 68.21$) indicating hindered recognition memory. The exposure to Indian classical music reversed the impaired memory with better exploration of novel objects (Fig. 5b; $p<0.001$; $F_{3,28} = 22.01$), which resulted in a significant increase in recognition (Fig. 5c; $p<0.001$; $F_{3,28} = 68.21$) and discrimination index (Fig. 5d; $p<0.001$; $F_{3,28} = 68.21$).

Spatial learning and memory improved on listening to Indian classical music

The T-maze alteration task was performed to investigate spatial learning and memory formation in rats. Rats under stress exhibited lower performance during both the training process (Fig. 6a; $p<0.001$; $F_{3,145} = 12.15$) and the retention test (Fig. 6c; $p<0.001$; $F_{3,28} = 19.19$) in comparison to non-stressed rats. On the 5th day and 6th day (Fig. 6b), the % of correct choices was decreased. In the assessment of retention memory, the % correct choice was reduced in stressed

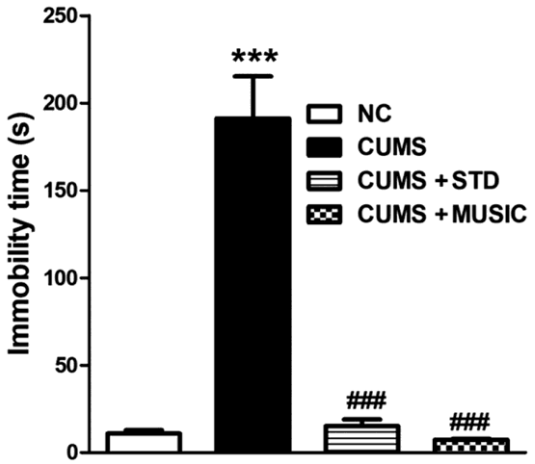

Fig. 4 — Effect of Indian classical music on CUMS induced behavioural despair in forced swim test. NC: Normal control (n=8); CUMS: Chronic unpredictable mild stress (8); CUMS + STD: Fluoxetine HCl, 10 mg/kg p.o. (8); CUMS + MUSIC: Music exposure for 1 h (8). Data were expressed as Mean ± SEM. Statistical analysis was done using One-way ANOVA followed by Tukey's posthoc test. ***p<0.001 as compared to normal control; ###p<0.01as compared to the CUMS group

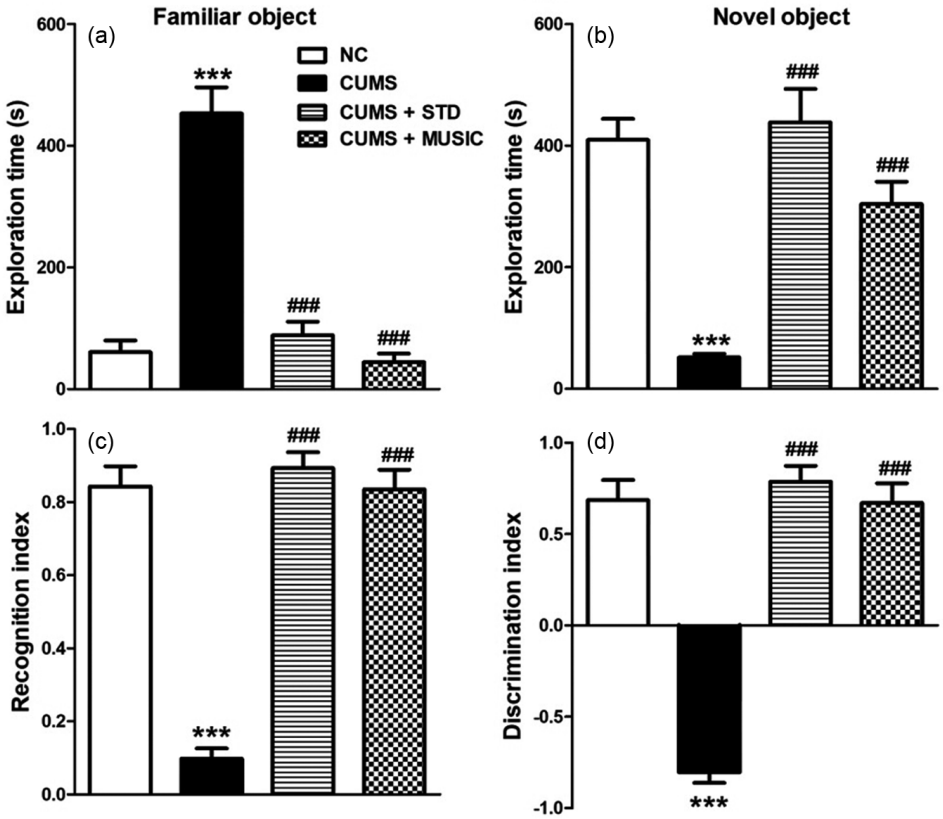

Fig. 5 — Effect of Indian classical music on CUMS induced recognition memory impairment in novel object recognition test. (A) Exploration time with familiar object; (B) Exploration time with novel object; (C) Recognition index; (D) Discrimination index. NC: Normal control (n=8); CUMS: Chronic unpredictable mild stress (8); CUMS + STD: Fluoxetine HCl, 10 mg/kg p.o. (8); CUMS + MUSIC: Music exposure for 1 h (8). Data were expressed as Mean ± SEM. Statistical analysis was done using One-way ANOVA followed by Tukey's posthoc test. ***p<0.001 as compared to normal control; ###p<0.01as compared to the CUMS group

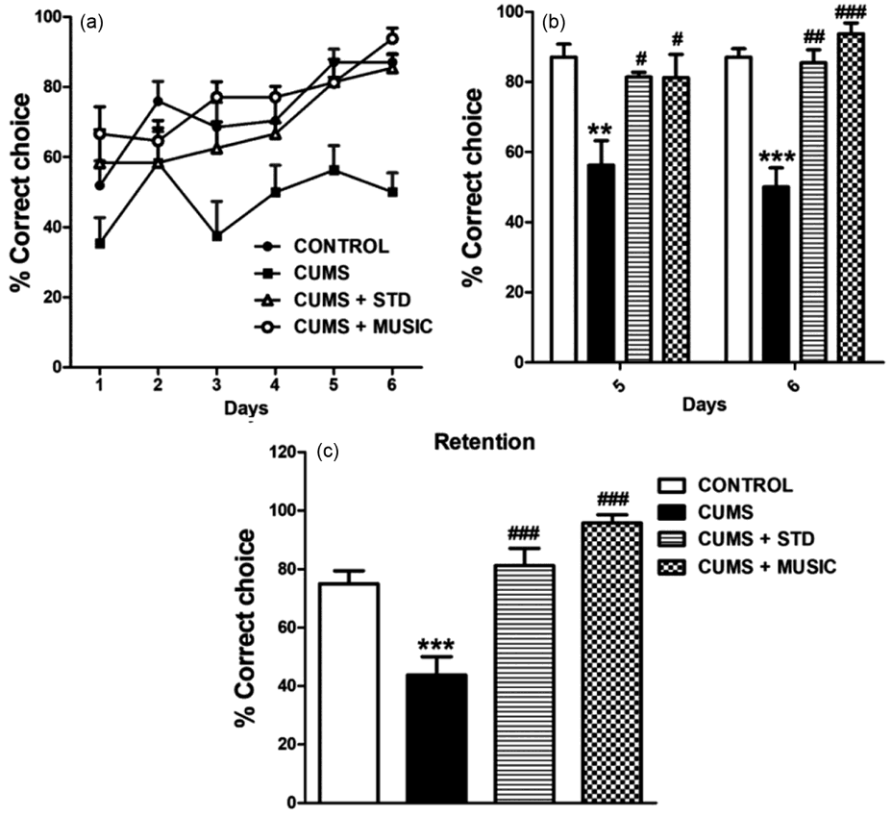

Fig. 6 — Effect of Indian classical music on CUMS induced memory impairment in T-maze alteration task. (a) Learning behaviour during training; (b) Correct choices on the 5th and 6th day of the training; (c) Correct choices during the retention test. NC: Normal control (n=8); CUMS: Chronic unpredictable mild stress (8); CUMS + STD: Fluoxetine HCl, 10 mg/kg p.o. (8); CUMS + MUSIC: Music exposure for 1 h (8). Data were expressed as Mean ± SEM. Statistical analysis was done using One-way ANOVA followed by Tukey's posthoc test. ***$p<0.001$ as compared to normal control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.01$as compared to the CUMS group

conditions. This revealed that the capacity to take the right decision was diminished when the animals were exposed to CUMS. Interestingly, the hampered spatial learning and memory were improved when the stressed rats were exposed to *Mohana Raga* for 1 h per day for 3 weeks. During the training period, % of correct choices was increased on the 5th and 6th day compared to the stressed rats. Also, the animals exposed to music showed improved retention memory in the retention test.

Discussion

The current study examined how *Mohana Raga*, an Indian classical song, can mitigate cognitive abnormalities brought on by CUMS. The animals underwent a 28-day CUMS protocol exposure, and then they spent 21 days listening to music for one hour every day. The effects of music exposure on cognitive deficiencies caused by CUMS were examined using the EPM, SPT, FST, NORT, and T-maze alteration tasks. Animals exposed to CUMS in the current study exhibited more anxiety-like behaviours, including shorter times spent and fewer admissions into the EPM's open arms. Additionally, they displayed anhedonic behaviour, as evidenced by a decreased preference for sucrose in SPT and increased immobility during FST, which suggests behavioural despair. Reduced working memory and recognition memory in the NORT and T-maze alteration tasks were also caused by CUMS.

In the previous study, animals exposed to 42 days CUMS protocol resulted in depression-like behaviour, neuronal damage, and oxidative stress[30]. In this animal model, various unmanageable physical, psychological, and circadian stressors were applied unpredictably and randomly for several weeks[31]. 1) restrained stress, 2) overnight illumination, 3) food deprivation, 4) water deprivation, 5) wet bedding, 6) cage tilting, and 7) social stress or isolation were used in the present study[20,32,33]. Chronic stress exacerbated

EPM anxiety-like behaviour[34]. After six weeks of chronic mild stress and six more weeks of social isolation, it was shown that CUMS caused behavioural changes that were comparable to those seen in depression. Additionally, it decreased levels of peripheral vascular endothelial growth factor, which promotes neurogenesis and improves memory and learning, as well as neurogenesis in the dentate gyrus[35].

Music stimulates emotional factors and also serves as a form of environmental enrichment. Exposing the subjects to musical enrichment counteracted the adverse impacts of being separated from their mothers, which induces sustained stress such as reduced social interaction, heightened feelings of anxiety, and behaviour depression, and also alters the brain's ability to change and adapt[36]. Music therapy improves post-stroke motor function and promotes neuronal repair, and the possible mechanism could be stimulating brain-derived neurotropic factor and glial fibrillary acidic protein secretion[23]. A clinical study involving 148 healthy volunteers between the age group of 18-21 showed a noticeable enhancement in memory after exposure to *Raag Darbari*. Exposure to Indian classical music has significantly improved word recall and story recall[37].

According to a research study, Indian classical music is considered a cost-effective method for alleviating the negative impacts of stress-induced cognitive impairments. This study compared the effects of Western and Indian classical instrumental music on learning and memory in young rats under stress[38]. Recently, the outbreak of the coronavirus has caused a surge in anxiety and stress in the population. In response to this, a research study was carried out to investigate the effects of listening to *Raga Thodi* on anxiety levels in young women. The results showed that just 15 min of daily exposure to this instrumental music on the sitar decreased anxiety. Mental health experts now suggest incorporating *Raga Thodi* into strategies for managing stress and anxiety[39]. Exposure to music has a beneficial impact on mood and contributes to the management of chronic pain, anxiety, and depression[40]. Remarkably, we observed that music exposure alleviated anxiety in the stressed animals. We could see that the entries and time spent in the open arms was increased showing better performance than the stressed animals in EPM. The results also showed that raga Mohana was effective in reducing depression-like behaviour which was observed by the increased sucrose consumption of stressed animals and also increased immobility time.

Exposing unborn chicks to music during the prenatal stage leads to improved spatial learning and memory after they hatch. This prenatal exposure to auditory stimulation, starting from day 10 in incubation until hatching, resulted in enhanced spatial learning abilities in newly hatched chicks[41]. Previous exploratory study conducted by Ahuja *et al.*[42] indicated that an increased attentional effort after listening to music, the accuracy on the auditory P300 task increased and the reaction time decreased for the patients with schizophrenia. Previous case study used *Mohana Raga* to reduce schizophrenia symptoms including delusions, hallucinations, fear and negative emotional outbursts[43]. Previously it was shown that exposure to instrumental Raaga Shivaranjani and *Mohana Raga* for 30 days improved concentration and academic performance[44]. Raag Bhoopali showed beneficial effects in listeners[45,46].

In our study, we could see the positive effect of Indian classical music on both recognition memory and spatial learning and working memory. The animals with music exposure had better recognition and discrimination index in NORT and also these animals performed much better throughout the learning process as well as retention test in the T-maze alteration task.

There are some limitations of the present study. While existing research has provided valuable insights into the therapeutic effects of music, there are still many areas that require deeper exploration to fully understand the nuances of how music influences the brain, emotions, and behaviour across different populations. Further studies include, estimation of cortisol levels, neurotransmitter levels, Brain-derived neurotrophic factor (BDNF), cytokine profiling and histological studies in the hippocampus, amygdala and prefrontal cortex.

Conclusion

To conclude, the behavioural study indicates that being exposed to music leads to a significant improvement in anxiety and depression symptoms, as well as cognitive issues related to chronic stress. Indian classical instrumental music can be reliable in alleviating chronic stress-induced cognitive impairment. Future studies can be planned which involve the study of the mechanism behind the positive effect of music exposure on the cellular and

molecular level. Further studies can lead to effective interventions and side effect-free therapies for cognitive deficits.

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

BV and TK contributed to the concept and design. The data acquisition was done by TK. Data analysis and interpretation, and manuscript writing done by BV and TK. Both authors read and approved the final manuscript.

Ethics Approval

The protocol was submitted to the Institutional Animal Ethics Committee, KLE College of Pharmacy, Bengaluru and approval (07/BVR/2022) was granted for the usage of animals.

Data Availability

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

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