RESEARCH PAPER

Acta Neurobiol Exp 2021, 81: 328–334
DOI: 10.55782/ane-2021-031

Morinda citrifolia Linn. fruit extract mitigates heroin seeking behavior in mice

Vijayapandi Pandy[1,2]*, Yasmin Khan[1,3], Durga Priyanka Yarlagadda[2] and Sri Pravallika Tatinada[2]

[1] *Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia,*
[2] *Department of Pharmacology, Chalapathi Institute of Pharmaceutical Sciences (Autonomous), Chalapathi Nagar, Lam, Andhra Pradesh, India,*
[3] *Department of Pharmacy, Benazir Shaheed University Lyari, Karachi, Pakistan,*
** Email: pandiphd@gmail.com; pandiphd@yahoo.co.in*

Methanolic extract of *Morinda citrifolia* unripe fruit (MMC) was tested against heroin addiction using a mouse modified runway model of drug-seeking. Habituation sessions were carried out for 10 min/d for 3 days. On day 0, the total run time of each mouse was noted (the start box to goal box) during the preconditioning test. This was followed by the conditioning session (30 min), in which the animals were conditioned with escalating doses of heroin hydrochloride (5, 10, 20, 40 and 40 mg/kg) for 5 days upon entry into the goal box. On day 6, the run time of each mouse, from start to goal box, was recorded during the post conditioning test. Extinction trials were performed for the next 5 days, in which no drug/saline was injected upon goal box entry. On day 13, a priming dose of heroin (8 mg/kg) was given to reinstate drug seeking in the mice. MMC given as oral doses (1, 3 and 5 g/kg) dose-dependently prolonged the run time to reach the goal box, indicating MMC attenuated heroin reinforcement. Moreover, MMC (5 g/kg) was found to reverse the heroin-seeking on extinction trial 1 and 2. MMC was also found to reverse heroin-induced reinstatement in mice. This study demonstrates that MMC attenuated heroin seeking at different phases of drug self-administration in a mouse modified runway model.

Key words: *Morinda citrifolia*, noni, heroin hydrochloride, modified runway model, mice, addiction

INTRODUCTION

Heroin, also known as diamorphine, is an opioid first prepared by C.R. Alder Wright in 1874 from morphine. It is the natural plant based product of *Papaver somniferum*, commonly known as opium poppy, manufactured as a white or brown powder. Heroin is primarily used to produce the euphoria effect, which means to experience, enjoy or anticipate strong feelings of well-being and happiness (Blum et al., 2013). Heroin addiction can cause serious adverse effects with all routes of drug administration. The treatments for heroin addiction include behavioral therapy such as reward, reinforcement and rehabilitation (recovery) and pharmacotherapy using buprenorphine and methadone (Ma et al., 2019). The adverse effects of buprenorphine include respiratory distress, sleepiness, adrenal insufficiency, arrhythmia, low blood pressure, allergic reactions and seizures, if already present, and the adverse reactions of methadone include digestive problems, nausea, vomiting, sleepiness, headache, dizziness and stomach pain, which limit their use in the treatment of opioid addiction (Zoorob et al., 2018; Koehl et al., 2019). Therefore, the current research is focused on complementary and alternative medicines like ayurveda, siddha, unani or homeopathy medications, which are readily available from the natural environment and considered less toxic when compared to their synthetic counterparts.

In the present study, *Morinda citrifolia* (synonyms are Indian mulberry, Great morinda, noni, Cheese

Received 7 December 2020, accepted 8 July 2021

fruit, and Beach mulberry), which belongs to the coffee family Rubiaceae (Singh and Sharma, 2020), was used. The different parts of the noni plant such as the root, leaf, stem and fruit have been used by East Asians to treat a variety of ailments such as headaches, arthritis, hypertension, diabetes, burns, tuberculosis, diabetes, drug addiction and hypertension (Almeida et al., 2019; Pandy et al., 2020). However, the fruit of *M. citrifolia* is extensively used for therapeutic purposes in the form of dry fruit powder, dry fruit powder extract, fruit puree, fruit syrup, fruit juice and probiotic fruit juice (fermented by *Lactobacillus plantarum, Lactobacillus casei* and *Bifidobacterium longum*) (Almeida et al., 2019). The unripe *M. citrifolia* fruit is a green color that turns yellowish white when it ripens. The unpalatability of ripened fruit is due to its astringent taste and rancid odor like butyric acid (Almeida et al., 2019). The various phytochemicals present in *M. citrifolia* fruit have been detailed in the literature, see review article for details (Almeida et al., 2019). Noni fruit has reportedly been used for many neuropharmacological interventions including analgesic, antidepressant, anxiolytic, antipsychotic and nootropic therapies and for anti-craving against various drugs of abuse like heroin, methamphetamine and ethanol (Basar et al., 2010; Pandy et al., 2012; 2018; 2020; Pachauri et al., 2013; Narasingam et al., 2016; 2017; Khan and Pandy, 2016; 2020; Pandy and Khan, 2016a). Moreover, a neuromodulatory effect on dopaminergic system, in *ex vivo* and *in vivo* studies, has been reported for noni fruit extract (Pandy et al., 2012; 2014) and it has been suggested that the anti-dopaminergic activity of the noni fruit extract might account for its efficacy against nausea and vomiting, psychosis and drugs of abuse.

Reinforcement in animal models is widely used to test for frequency and enhancement of behavior/memory. There are two types, positive (wanted behavior) and negative (taking away an undesirable element) reinforcement, and this model is used to study addictive/aversive drugs (Venniro et al., 2016). A straight alley runway apparatus (Akhiary et al., 2018; Nguyen et al., 2018) is used to study the goal-seeking motivated behavior in rodents, but the major drawback of this model is the frequent occurrence of quick running even in animals that were not reinforced. Therefore, a modified runway model for mice was introduced in which a "Z" shaped runway replaced the conventional straight runway, bridging the start and goal boxes, and remarkably increasing the run time (i.e., increased time duration for the transition between start and goal boxes) (Pandy and Khan, 2016b; Vijeepallam et al., 2019; Khan and Pandy, 2020). The current study aimed to investigate the effect of methanolic extract of *M. citrifolia* unripe fruit (MMC) on heroin seeking by using a modified runway paradigm in mice.

METHODS

Plant collection, extraction and phytochemical characterization and standardization

The details of plant collection, extraction and phytochemical characterization and standardization were described in our previous publication (Pandy et al., 2014). Briefly, the *M. citrifolia* fruits were collected from Malacca, Malaysia and identified taxonomically by Rimba Ilmu. For future reference, the voucher specimen of *M. citrifolia* Linn. possessing a number (KLU 47738) was documented by Rimba Ilmu and belongs to the Institute of Biological Sciences, University of Malaya, Kuala Lumpur.

Animals

All the animals were acclimated for 7 days before the start of the study. ICR male mice with a body weight of 25-30 g were used. All animals were procured from the University of Malaya's Laboratory Animal Center. Animals were divided into groups of 4-5 animals in one cage and were kept under standard laboratory conditions (20-22°C temperature; 45-60% relative humidity; 12 h/12 h: light/dark cycle). A standard pellet diet and purified drinking water were made freely available at all times. This study protocol met the National Research Council of the National Academies (USA) standards and received prior approval (No. 20131203/PHAR/R/VP) from the IACUC of the FOM (Faculty of Medicine), University of Malaya.

Drugs, chemicals and apparatus

Heroin hydrochloride samples were obtained from the Department of Chemistry, Malaysia Ministry of Health. The heroin hydrochloride drug solution prepared in normal saline was injected intraperitoneally (i.p.) at a uniform volume of 1 ml/100 g body weight of the mice. Sodium carboxymethylcellulose (CMC 1% w/v) solution was used to prepare different doses of MMC working solutions.

The modified runway apparatus and all its measurement details were reported in our previous publication (Pandy and Khan, 2016b). The runway apparatus had two square-shaped boxes (a start and

a goal box of 150 mm each) connected by a "Z" shaped runway. From the start box to the goal box, the total length of the runway apparatus was 1,800 mm. In order to minimize the visual contact of the animal with the experimenter, the apparatus was kept on a table (1,200 mm height from the floor). A total of 6 hurdles, 30 mm high, were placed throughout the length of the runway alley, which significantly prolonged the run time of animals, reaching the goal box from the start box. The start box had a black polished floor surface and its walls were affixed with horizontal black and white stripes, whereas the goal box had a white wire mesh floor and its walls were affixed with vertical black and white stripes. Guillotine doors were used to close both start and goal boxes from the alley. A Logitech webcam (C270) was fixed above the apparatus to record the animal's behavior by computer. A digital stopwatch was used to record the run time in seconds by observing the animal's behavior through a computer monitor (note: direct eye contact with animal would alter animal behavior).

Procedure

The experiment consisted of six distinct phases, which were divided into familiarization, baseline or pre-conditioning, acquisition or conditioning, post-conditioning, elimination or extinction and re-establishment or reinstatement as shown in Fig. 1. Before the start of the experiment, all animals were acclimated individually for 3 days (day -3 to day -1), during which a mouse was kept in the start box. After 90 s, the guillotine door situated in the start box was lifted to allow the animal to explore the entire runway, except for the start and goal boxes, for 10 min. On the

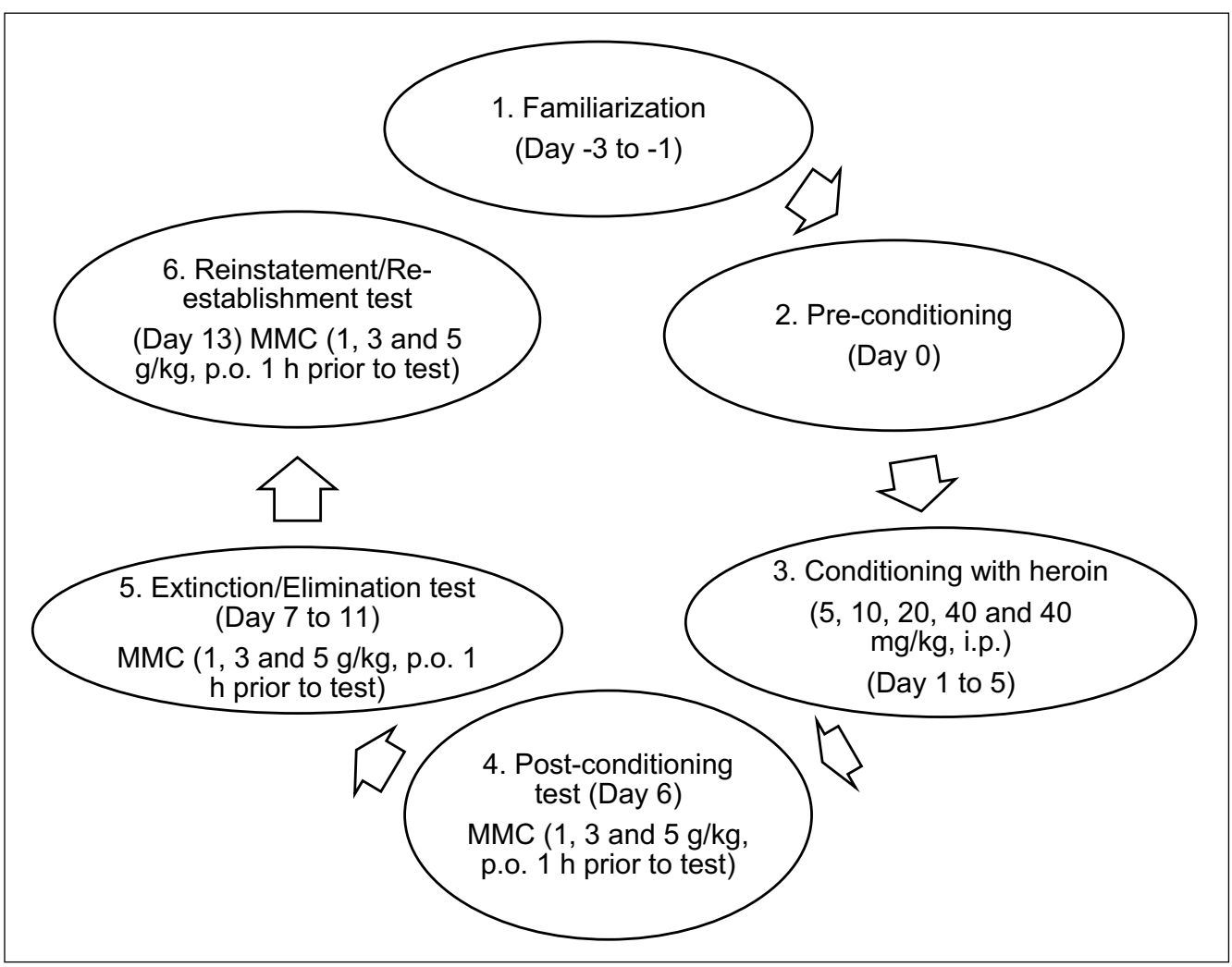

Fig. 1. Experimental study design of mouse modified runway paradigm.

pre-conditioning day (day 0), the same methodology that used for habituation was followed, with the addition of a baseline reading (time taken for a transition between start and goal boxes) for each mouse. During this session, the start box was closed after the exit of the animal from the start box to block retracing and the goal box was kept open to allow the animal to enter. Immediately after goal box entry the guillotine door was closed and the animal was taken back to the home cage.

The next 5 days (day 1– day 5), the animals were conditioned with escalating doses of heroin (5, 10, 20, 40 and 40 mg/kg, i.p.) or normal saline (1 ml/100 g, i.p.) for 30 min in the goal box. During this period, the same experimental protocol was followed as in the preconditioning trial; in addition, heroin/saline was injected upon goal box entry and conditioned for 30 min.

24 h after the final conditioning (day 6), a post-conditioning test was performed in which the animals were treated with the same protocol as during pre-conditioning but no heroin or saline was provided upon goal box entry; the test groups (8–9 animals/group) received MMC at varying oral doses (1, 3 and 5 g/kg) 1 h prior to the post-conditioning trial. The saline-control and heroin-control groups received CMC (1% w/v; 1 ml/100 g, p.o.).

In the extinction trial, new sets of saline and heroin treated animals (7–8 animals/group) were used that had previously experienced post-conditioning trials. These animals were subjected to daily extinction trials from day 7 to day 11, during which no drug (saline/heroin) was injected upon the goal box entry. However, MMC at different oral doses (1, 3 and 5 g/kg) or CMC (1% w/v) 1 h prior to extinction trials (Ext 1 to Ext 5) was administered.

Similarly, in order to test the effect of MMC on heroin reinstatement, new sets of saline-treated and heroin-treated animals (8–9 animals/group) were chosen and passed through post-conditioning and extinction trials. On day 12, a pre-reinstatement test was performed in all treatment groups. The following day, day 13, a post-reinstatement test was carried out during which a mild dose of heroin (priming dose) was injected into each subject. The priming dose of heroin was calculated as 8 mg/kg, i.p. (1/5 of the maximum conditioning dose). The priming dose was injected 15 min prior to behavioral task. The test/vehicle groups received varying oral doses (1, 3 and 5 g/kg) of MMC or CMC (1% w/v) 1 h prior to post-reinstatement testing.

Data are presented as means ± S.E.M. The results were expressed by using a two-way repeated measures analysis of variance (ANOVA) with the independent variables of group (between-subject's variable) and trial (with in-subject's variable) and subsequently Sidak multiple comparison *post hoc* test; $p<0.05$ was considered statistically significant.

RESULTS

Anti-drug seeking effect of MMC at varying oral doses (1, 3 and 5 g/kg) against heroin seeking behavior in mice using a modified straight alley runway model

The results from the preconditioning and post-conditioning run times of the different groups (Expression) are presented in Fig. 2. The study results revealed a significant effect of time ($F_{(1,38)}$=11.17; P=0.0019) but a non-significant effect of treatment ($F_{(4,38)}$=1.421; P=0.2456) and a treatment × time interaction ($F_{(4,38)}$=2.316; P=0.0749) with two-way repeated measures ANOVA. The *post hoc* Sidak multiple comparison test (preconditioning *versus* post-conditioning) showed that the heroin control group significantly decreased their run times on the post-conditioning test, which suggests drug-seeking behavior in the mice that were conditioned with heroin (Fig. 2). However, the animals pretreated with MMC at varying oral doses (1, 3 and 5 g/kg) did not exhibit significantly altered post-conditioning run times when compared with the corresponding preconditioning run times as seen in the saline control group, indicating an anti-drug-seeking effect of MMC on heroin-seeking behavior in mice.

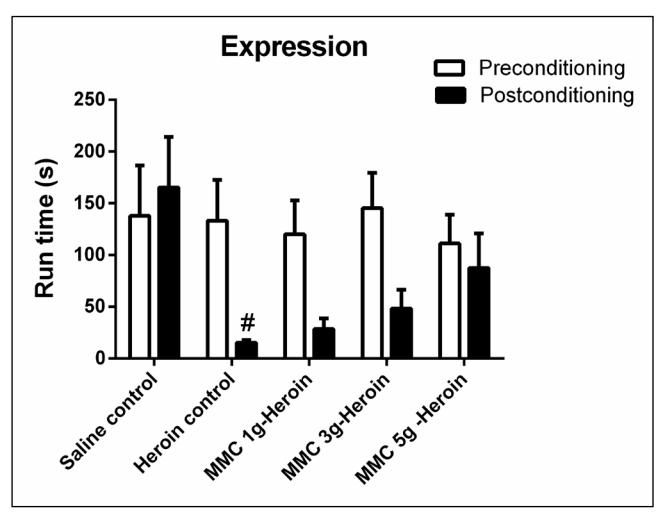

Fig. 2. Effect of MMC on expression of run times due to heroin reinforcement (mean ± SEM; n=8–9) in mice using a modified runway paradigm. Significant differences were observed at #p<0.05 (post-conditioning *versus* preconditioning run times in seconds).

Furthermore, the motivation of the test group to approach the desired box during termination attempts (Ext 1 to Ext 5) from day 7 to day 11 were compared between different treatment groups (saline control, heroin control and MMC at varying oral doses [1, 3 and 5 g/kg]), as shown in Fig. 3. The two-way repeated measures ANOVA demonstrated a significant effect of time ($F(4, 136)=4.601$; $P=0.0016$) and treatment ($F_{(4,34)}=3.795$; $P=0.0118$), however, the treatment × time interaction was not significant ($F_{(16,136)}=0.9748$; $P=0.4876$) for run time. The *post hoc* Sidak multiple comparison test revealed that the heroin-control group showed a significant ($p<0.05$) decline in run time when compared with the saline-control group during the extinction trials (Ext 1 and Ext 2), which indicates heroin-seeking behavior in heroin-extinct animals on Ext 1 and Ext 2. However, the MMC (5 g/kg)-treated heroin group did not show any significant decline in run time when compared to the saline-control group, which indicates MMC at a higher dose (5 g/kg) attenuated heroin seeking on Ext 1 and Ext 2 in mice. MMC at lower doses (1 and 3 g/kg) failed to inhibit heroin seeking in mice, as indicated by a significant decrease in run time when compared with the saline-control group (Fig. 3).

Results from the pre-reinstatement and post-reinstatement run times of the different groups are presented in Fig. 4. The results demonstrated a significant effect of time ($F_{(1,34)}=21.67$; $P=0.0001$) and treatment × time interaction ($F_{(4,34)}=4.009$; $P=0.0091$), whereas treatment failed to show a significant effect ($F_{(4,34)}=1.577$; $P=0.2027$) with two-way repeated measures ANOVA. The *post hoc* Sidak multiple comparison test (pre-reinstatement *versus* post-reinstatement) revealed that a priming dose of heroin significantly reinstated the heroin-seeking behavior in heroin-extinct mice, as indicated by fast running towards the goal box (i.e., significant decrease in run time of post-reinstatement in comparison with the corresponding pre-reinstatement). However, MMC at varying oral doses (1, 3 and 5 g/kg) treatment failed to significantly alter the post-reinstatement run times when compared with the corresponding pre-reinstatement run times as seen with the saline control group, which indicated that MMC reversed the heroin-seeking behavior in mice.

DISCUSSION

Heroin conditioning, in increasing doses (5, 10, 20, 40 and 40 mg/kg, i.p.) from day 1 to day 5, induced heroin-seeking behavior on day 6 (post-conditioning day), demonstrated by a declining run time to reach the goal box as shown in Fig. 2. A strong, rewarding effect of heroin was demonstrated in the present study in which the mice exhibited a motivational heroin-seeking behavior. Humans and animals are motivated towards performing any activity that can be rewarding (i.e., the kind of pleasurable feelings that produce positive reinforcement by which the indulged activity is repeated). The pleasurable feelings produced by heroin serve as positive reinforcement, which is mediated through the stimulation of reward

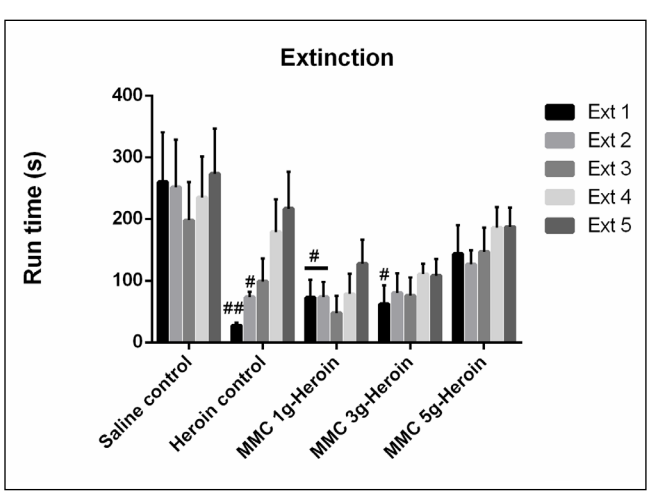

Fig. 3. Effect of MMC on extinction of heroin run times (mean ± SEM; n=7–8) in mice using a modified runway paradigm. Significant differences were noted by #p<0.05; ##p<0.01 *versus* the saline-control group.

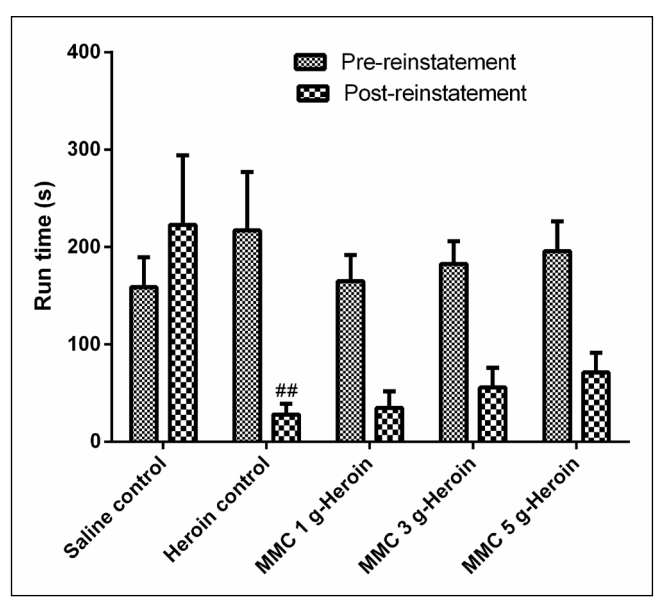

Fig. 4. Effect of MMC on reinstatement of heroin run times (mean ± SEM; n=8–9) in mice using a runway paradigm. Significant differences were noted as ##p<0.01 when compared with the corresponding pre-reinstatement run time in seconds.

pathways in the brain (Kreek et al., 2012). Heroin readily crosses the blood brain barrier to reach the brain and is then converted into morphine by deacetylation. The opioid receptors present in the ventral tegmental area, nucleus accumbens and prefrontal cortex (reward pathway regions of the brain) are activated by morphine, thereby it stimulates the release of dopamine, a motivational molecule. Activation of opioid receptors inhibits the release of GABA, which inhibits dopamine release, thus dopamine release is stimulated (Kreek et al., 2012).

Remarkably, the mice treated with (1, 3 and 5 g/kg) oral doses of MMC demonstrated an attenuating effect against heroin seeking in the mouse model of modified straight alley runway. In earlier studies, MMC was shown to exert antidopaminergic activity in *in vivo* apomorphine- and methamphetamine-induced cage climbing and stereotyped behavior, respectively, in mice and in *ex vivo* dopamine-stimulated contractility response in isolated vas deferens preparations from rats (Pandy et al., 2012; 2014; 2017). Moreover, the bioactive principles of *M. citrifolia* fruit, scopoletin and rutin, have also demonstrated antidopaminergic activity in *ex vivo* and *in vivo* studies (Pandy et al., 2014; Pandy and Vijeepallam, 2017). Therefore, we postulate that the antidopaminergic effect of MMC might play a role in the anti-motivational properties of MMC against heroin self-administration in the modified runway paradigm. Scopoletin and rutin, major bioactive principles of MMC, could be responsible for the anti-motivational effects of MMC on heroin self-administration.

Drugs of abuse can cause conditioned sensitization due to their motivational/reinforcing properties. Faster running to receive a drug of abuse in the runway model is mediated through the development of conditioned sensitization (Bevins et al., 2001). Nevertheless, the conditioned sensitization might be altered due to the influence of locomotion and memory. In earlier studies, MMC failed to change locomotor activity (spontaneous) and improved learning and memory in mice (Pandy et al., 2018). Thus, the anti-drug seeking effect of MMC against heroin was not simply mediated through changes in locomotion and cognitive function.

In this study, the effect of MMC on the extinction phase of heroin self-administration in mice was also studied. Heroin-seeking behavior was observed on the first two days of extinction trials (Ext 1 and Ext 2). Notably, MMC at 5 g/kg significantly reversed the heroin-seeking behavior on Ext 1 and Ext 2 in mice. This result highlighted the efficacy of MMC against heroin seeking during the extinction phase of drug self-administration in the modified runway model and suggests a possible therapeutic benefit of MMC in maintaining abstinence during heroin withdrawal.

The present study also investigated the effect of MMC on reinstatement of heroin self-administration due to mild stimuli (a priming dose of heroin) following an extinction period in mice. It was found that a small-dose heroin (8 mg/kg, i.p.) injection (priming), following extinction trials, significantly reinstated the motivation of mice to attain the goal box. Interestingly, MMC-treated mice failed to express priming dose heroin-induced reinstatement in the modified straight alley runway model in mice, indicating a potential use for MMC in treating relapse of heroin self-administration.

CONCLUSION

In sum, the present results for run time at different phases of a modified runway model reveal anti-motivational properties of *M. citrifolia* fruit against heroin seeking in mice and reveal the therapeutic potential of *M. citrifolia* fruit for treating opioid addiction. Further preclinical and clinical studies are necessary to develop phytotherapy to combat heroin addiction.

ACKNOWLEDGEMENT

The author, VP, expresses his sincere gratefulness to the Science and Engineering Research Board (SERB), India for the support of a core research grant (CRG/2018/000813).

REFERENCES

Akhiary M, Purvis EM, Klein AK, Ettenberg A (2018) Methamphetamine self-administration in a runway model of drug-seeking behavior in male rats. Pharmacol Biochem Behav 175: 27–32.

Almeida ÉS de Oliveira D, Hotza D (2019) Properties and applications of Morinda citrifolia (Noni): A Review. Compr Rev Food Sci Food Saf 18: 883–909.

Basar S, Uhlenhut K, Högger P, Schöne F, Westendorf J (2010) Analgesic and anti-inflammatory activity of Morinda citrifolia L. (Noni) fruit. Phytother Res 24: 38–42.

Bevins RA, Besheer J, Pickett KS (2001) Nicotine-conditioned locomotor activity in rats: dopaminergic and GABAergic influences on conditioned expression. Pharmacol Biochem Behav 68: 135–145.

Blum J, Gerber H, Gerhard U, Schmid O, Petitjean S, Riecher A (2013) Acute effects of heroin on emotions in heroin-dependent patients. Am J Addict 22: 598–604.

Khan Y, Pandy V (2016) Methanolic extract of Morinda citrifolia L. (Noni) unripe fruit attenuates ethanol-induced conditioned place preferences in mice. Front Pharmacol 7: 352.

Khan Y, Pandy V (2020) Morinda citrifolia Linn. (Noni) fruit extract attenuates ethanol seeking behavior in mouse runway paradigm. J Res Pharm 24: 632–639.

Koehl JL, Zimmerman DE, Bridgeman PJ (2019) Medications for management of opioid use disorder. Am J Health Syst Pharm 76: 1097–1103.

Kreek MJ, Levran O, Reed B, Schlussman DS, Zhou Y, Butelman RE (2012) Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. J Clin Invest 122: 3387–3393.

Ma B, Mei D, Wang F, Liu Y, Zhou W (2019) Cognitive enhancers as a treatment for heroin relapse and addiction. Pharmacol Res 141: 378–383.

Narasingam M, Vijeepallam K, Mohamed Z, Pandy V (2017) Anxiolytic- and antidepressant-like activities of a methanolic extract of Morinda citrifolia Linn. (noni) fruit in mice: Involvement of benzodiazepine-$GABA_A$ergic, serotonergic and adrenergic systems. Biomed Pharmacother 96: 944–952.

Narasingam M, Pandy V, Mohamed Z (2016) Noni (Morinda citrifolia L.) fruit extract attenuates the rewarding effect of heroin in conditioned place preference but not withdrawal in rodents. Exp Anim 65: 157–164.

Nguyen D, Nesarajah Y, Erb S, Ito R (2013) Repeated cocaine exposure attenuates the desire to actively avoid: a novel active avoidance runway task. Front Behav Neurosci 12: 108.

Pachauri SD, Verma PR, Dwivedi AK, Tota S, Khandelwal K, Saxena JK, Nath C (2013) Ameliorative effect of Noni fruit extract on streptozotocin-induced memory impairment in mice. Behav Pharmacol 24: 307–319.

Pandy V, Bonam SR, Raya AR, Nadendla RR (2020) Morinda citrifolia Linn. (Noni) fruit, antioxidant effects, and neuroprotection. In: Colin R. Martin and Victor R. Preedy (eds.) Oxidative Stress and Dietary Antioxidants in Neurological Diseases. Burlington: Academic Press; 291–307.

Pandy V, Khan Y (2016a) Noni (Morinda citrifolia Linn.) fruit juice attenuates the rewarding effect of ethanol in conditioned place preference in mice. Exp Anim 65: 437–445.

Pandy V, Khan Y (2016b) Design and development of a modified runway model of mouse drug self-administration. Sci Rep 6: 21944.

Pandy V, Narasingam M, Kunasegaran T, Murugan DD, Mohamed Z (2014) Effect of noni (Morinda citrifolia Linn.) fruit and its bioactive principles scopoletin and rutin on rat vas deferens contractility: an ex vivo study. Sci World J 2014: 909586.

Pandy V, Narasingam M, Mohamed Z (2012) Antipsychotic-like activity of noni (Morinda citrifolia Linn.) in mice. BMC Complement Altern Med 12: 186.

Pandy V, Narasingam M, Vijeepallam K, Mohan S, Mani V, Mohamed Z (2017) The ethyl acetate fraction of a methanolic extract of unripe noni (Morinda citrifolia Linn.) fruit exhibits a biphasic effect on the dopaminergic system in mice. Exp Anim 66: 283–291.

Pandy V, Vijeepallam K (2017) Antipsychotic-like activity of scopoletin and rutin against the positive symptoms of schizophrenia in mouse models. Exp Anim 66: 417–423.

Pandy V, Wai YC, Roslan NFA, Sajat A, Jallb AHA, Vijeepallam K (2018) Methanolic extract of Morinda citrifolia Linn. unripe fruit attenuates methamphetamine-induced conditioned place preferences in mice. Biomed Pharmacother 107: 368–373.

Singh B, Sharma RA (2020) Indian Morinda species: A review. Phytother Res 34: 924–1007.

Venniro M, Caprioli D, Shaham Y (2016) Animal models of drug relapse and craving: From drug priming-induced reinstatement to incubation of craving after voluntary abstinence. Prog Brain Res 224: 25–52.

Vijeepallam K, Pandy V, Murugan DD, Naidu M (2019) Methanolic extract of Mitragyna speciosa Korth leaf inhibits ethanol seeking behaviour in mice: involvement of antidopaminergic mechanism. Metab Brain Dis 34: 1713–1722.

Zoorob R, Kowalchuk A, Mejia de Grubb M (2018) Buprenorphine therapy for opioid use disorder. Am Fam Physician 97: 313–320.