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Research Article

Mozart K488 Addition Can Improve Depressive-Like Behavior in Rats: In Search of Better Management

Lisa Pangemanan[1]*, Irwanto[2], Margarita M. Maramis[3]

ABSTRACT

Background: Fluoxetine is one of the medications used for the treatment of depression with several benefits, but some patients have a poor response to the drug. Several studies reported the use of Mozart music (K448) as an alternative therapy for treating the condition, yet the combination of Mozart and fluoxetine remains underexplored. In light of this, this study aims to assess the impact of combined fluoxetine and Mozart (K448) therapy on depressive-like behavior and associated hormonal changes in a rodent model subjected to Chronic Unpredictable Mild Stress (CUMS) conditions. **Materials and Methods**: The depression-induced animal model received one of these three specified treatments: fluoxetine (F), Mozart (M), or a combination of fluoxetine and Mozart (F+M). The depressive-like behavior was assessed using a 24-hour sucrose preference test (SPT). Additionally, after 21 days of treatment, plasma corticosterone levels and hippocampal melatonin levels were assessed. Statistical analysis using either ANOVA or Kruskal-Wallis tests was then performed. **Results**: The fluoxetine-Mozart group had higher SPT compared to CUMS group. However, they do not have a better result compared to other groups in terms of corticosterone and melatonin levels with values of respectively. **Conclusion**: The combined therapy of fluoxetine and Mozart improved depressive-like behavior.

Key words: Fluoxetine, Mozart, Depressive-like behavior, Melatonin, Corticosterone, Hippocampus.

Lisa Pangemanan[1]*, Irwanto[2], Margarita M. Maramis[3]

[1]Department of Child Health, Faculty of Medicine, Widya Mandala Catholic University, Surabaya, INDONESIA.

[2]Department of Child Health, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA.

[3]Department of Psychiatry, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA.

Correspondence

Lisa Pangemanan

Department of Child Health, Faculty of Medicine, Widya Mandala Catholic University, Surabaya, INDONESIA.

E-mail: lisa-p@ukwms.ac.id

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INTRODUCTION

Fluoxetine is a commonly used antidepressant[1], and its mechanism of action, among others, is through the modulation of neurons in the hippocampus.[2] Furthermore, several studies revealed that it can reduce the high plasma cortisol levels in depression.[3] Despite this beneficial effect, some patients have a low response to this treatment.[4] Among others, increased corticosterone and decreased melatonin levels are some of the common indicators of depression.[5] A previous study reported that music can serve as an alternative and complementary therapies for the condition.[6] It also has the ability to decrease cortisol levels as well as increase melatonin levels in patients.[7] Mozart is an alternative therapy to treat depression[8], acting on various brain regions, such as the hippocampus to improve mood.

Several studies revealed that depression has a variety of manifestations and symptoms.[9,10] The animal model of depression was created to mimic the main symptoms in humans, such as anhedonia.[11] Sucrose Preference Test is often used for the assessment of anhedonia.[12] CUMS serves as a means to induce an animal model of depression.[13] Furthermore, the models were characterized by weight loss[14], increased corticosterone, and decreased melatonin levels[15], decreased serotonin and decreased BDNF.[16] A previous study revealed that Mozart music (K448) can reverse depressive-like behavior in rats. Melatonin has been reported to increase the therapeutic effect of fluoxetine in the hippocampus to improve depressive-like behavior.[17] Music can also be combined with other treatments for achieving better outcomes in depressed patients.[18] Consequently, this study seeks to investigate the combined impact of music and fluoxetine therapy on parameters such as body weight, SPT, FST, as well as plasma corticosterone and hippocampal melatonin levels.

MATERIALS AND METHODS

Conducted between January and March 2022, this research took place in the experimental animal laboratory of the Faculty of Medicine, Universitas Brawijaya, located in Malang, Indonesia. The study protocol underwent thorough review and received approval from the Animal Care and Use Committee of the Faculty of Veterinary Medicine, Universitas Airlangga, located in Surabaya, Indonesia, under reference number 2.KE.120.10.2021.

Experimental Animals and Study Design

Male Wistar rats sourced from Indoanilab (Bogor, Indonesia) comprised the sample population, randomly assigned to two groups: control (without CUMS) and treatment (subjected to CUMS). Furthermore, psychological dominant stressor modification of CUMS protocols were given to the CUMS group after one week of acclimatization.[19] Before and after the application of CUMS, a sucrose preference test was conducted to evaluate the effective establishment of a depression-induced animal model.

The experimental animals were collectively housed, with two rats accommodated in each cage, and separation was maintained by a wire mesh. The environmental conditions in the room were regulated to a temperature of 23 ± 20 °C and humidity ranging from 40% to 70%, following a 12-hour light and 12-hour dark cycle (with lights switched on at 6:00 AM). The rats had unrestricted

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access to food, water, and a 1.5% sucrose solution. The daily food ration was measured each morning before distribution, and the remaining food weight was recorded the subsequent day. New batches of water and sucrose solutions were freshly made every day, each stored in separate containers.

The criteria for inclusion involved selecting male rats at the age of fourteen weeks, demonstrating depressive-like behavior in the treatment group as determined by the Sucrose Preference Test (SPT). In contrast, exclusion criteria encompassed physical ailments and disabilities, evaluated by a veterinarian. The rats in the CUMS group were randomly assigned to four categories: CUMS (CUMS + water), fluoxetine (CUMS + fluoxetine), Mozart (CUMS + Mozart + water), and fluoxetine + Mozart (CUMS + Mozart + fluoxetine) group. The control group received standard care and 2 ml/kg of water administered through gavage feeding. Fluoxetine, dissolved in 2 ml/kg of water, was administered at a dosage of 10 mg/kg body weight via gavage feeding, with the dose selection based on a prior study.[20] Mozart music (K448) was delivered at a volume of 60-80 dB (measured by a sound level meter) from 6:00 pm to 6:00 am, positioned 30 cm from the cage, and all cages received equal exposure. A separate room was designated for groups without music exposure, and the entire treatment duration extended for 21 days. The study's design is depicted in Figure 1.

Chronic Unpredictable Mild Stress Procedure

The Chronic Unpredictable Mild Stress (CUMS) procedure was implemented following Katz protocols, with specific modifications.[21, 22] Notably, the modifications were made by eliminating food and water deprivation, emphasizing psychologically dominant stressors.[19] CUMS protocols were executed by randomly administering 1 or 2 unexpected stressors each day over a 21-day period. Consistently, the same stressor was not applied on two consecutive days throughout this process. The CUMS procedure continued consistently during the subsequent 21 days of the treatment period. The CUMS protocol encompassed a range of stressors, including cold swimming, foot shock, forced swimming, tail piercing, immobilization, absence of bedding, exposure to bright light, tail tying, isolation in a narrow dark space, predator exposure, wet bedding, and prolonged exposure to continuous light.[19]

Outcome Measures

Weekly assessments of each rat's body weight were conducted using an electronic scale, and the consumed food was determined by subtracting the leftovers from the total food provided. The rats' weekly average meal was identified as the mean amount of food they consumed during the week.

Sucrose preference tests were carried out 3 times, namely pre-animal model creation, before the treatment started, and 21 days post-treatment started. The formula utilized for the test was expressed as the sucrose percentage (%), calculated by dividing the sucrose consumption (in milliliters) by the sum of sucrose consumption (in milliliters) and water consumption (in milliliters), multiplied by 100%. A 24-hour sucrose and water consumption were also measured and recorded. Based on the procedures, no water deprivation nor fasting was performed before SPT. A Forced Swim Test (FST) based on the Porsolt method[23] was carried out 3 times, namely pre-animal model creation, before the treatment started, and day 22 post-treatment started. However, due to technical problems, FST cannot be analyzed.

All rats underwent euthanasia 24 hours after the last treatment administration, followed by blood collection to measure corticosterone plasma level using ELISA by Bioassay Technology Laboratory (BT

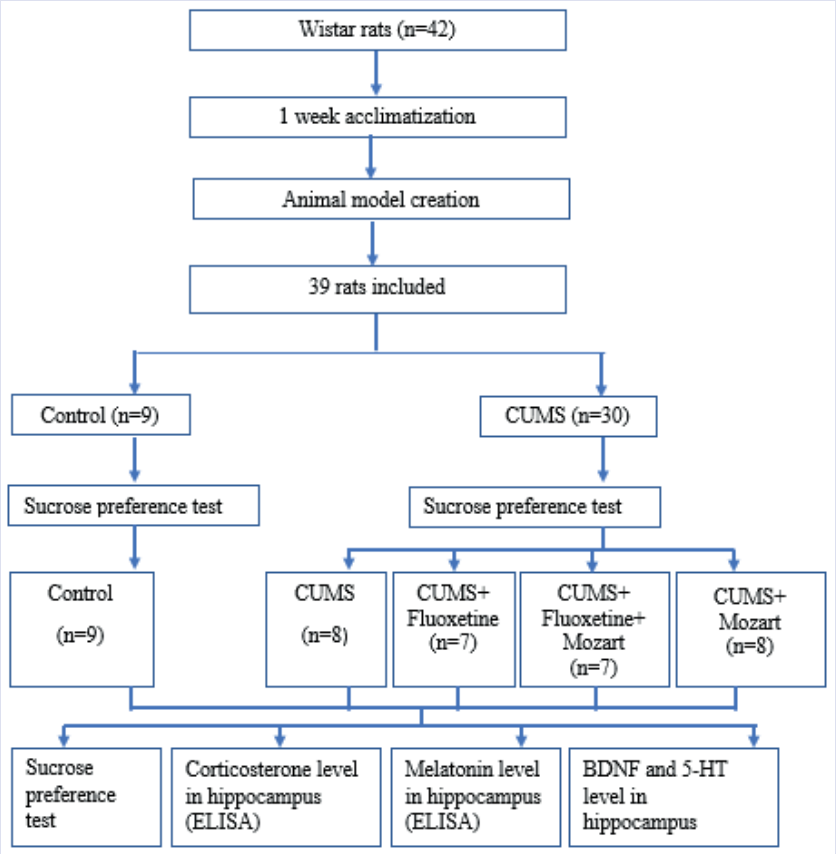

Figure 1: Study's design.[19]

Lab) (E0496Ra). Ethylenediaminetetraacetic acid was used as an anticoagulant to obtain plasma from the blood samples. Plasma mixing was carried out for 10 minutes, followed by centrifugation for 20 minutes at 2,000-3,000 RPM, and the collection of the non-sediment supernatant. The obtained supernatant was used for measuring plasma corticosterone levels following the manufacturer's instructions. Subsequently, the hippocampus was retrieved to measure melatonin levels using ELISA by BT Lab (E0601Ra). The hippocampal tissue underwent a cold PBS rinse (pH 7.4), was weighed, and subsequently homogenized. Homogenization occurred in PBS (ratio of tissue mass (g) to PBS volume (mL) = 1:9) using an ice-cold glass homogenizer, followed by sonication. Centrifugation was then conducted for 15 minutes at 12,000 RPM (4 °C), and the resulting supernatant was collected for the assessment of hippocampal melatonin levels, adhering to the provided manufacturer's guidelines. Additionally, measurements and separate reports were made for hippocampal serotonin levels and hippocampal BDNF levels.[24]

Statistical Analysis

The mean ± SD represented the data, and distinctions between groups were evaluated either via ANOVA or the Kruskal-Wallis test, contingent upon homogeneity. Statistically significant findings for this study were determined by a p-value below 0.05. IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA) was employed to conduct the data analysis.

RESULTS

A total of 42 rats were included in this study, their body weights ranging between 92 and 159 grams. The mean body weight between the groups began to show a significant difference after one week of treatment (Table 1). However, there were no significant differences at the end of the treatment, as shown in Table 1.

From the results, it is evident that the fluoxetine + Mozart group exhibited the highest body weight among the treatment groups. The weekly average meals between groups failed to show any variation in the experiment, as shown in Figure 2.

The Sucrose Preference Test revealed a notable difference in SPT after treatment among the groups, as depicted in Figure 3.

Fluoxetine + Mozart combination therapy improved SPT better compared to fluoxetine group, however Mozart therapy yield the best result. There were no significant differences among treatment groups in terms of plasma corticosterone level and hippocampal melatonin level, as shown in Figure 4.

DISCUSSION

This study revealed that after 21 days of CUMS protocols, a lower body weight was seen, compared to the control. Palucha-Poniewiera et al. reported that the effect of CUMS on weight depended on the duration

Table 1: Mean body weight between groups.

	CUMS (n=8)	CUMS+F (n=7)	CUMS+F+M (n=7)	CUMS+M (n=8)	Control (n=9)	p value
Weight (g), mean±SD						
Pre CUMS	163,250 ± 12,624	165,429 ± 37,255	174,857 ± 19,030	170,750 ± 13,594	170,556 ± 14,169	0.825[a]
Day-1	193,125 ± 15,254	192,571 ± 36,317	206,286 ± 11,026	197,875 ± 15,579	226,222 ± 24,030	0.019*[a]
Day-8	198,625 ± 17,784	191,571 ± 36,377	218,286 ± 15,660	202,750 ± 17,136	231,333 ± 24,495	0.011*[a]
Day-15	202,500 ± 19,449	193,000 ± 38,695	223,286 ± 14,603	209,125 ± 19,679	234,222 ± 22,802	0.013*[a]
Day-22	212,000 ± 21,220	205,429 ± 44,139	233,286 ± 20,822	224,625 ± 22,753	242,333 ± 22,853	0.067[a]

[a]ANOVA *Significant, p value <0.05

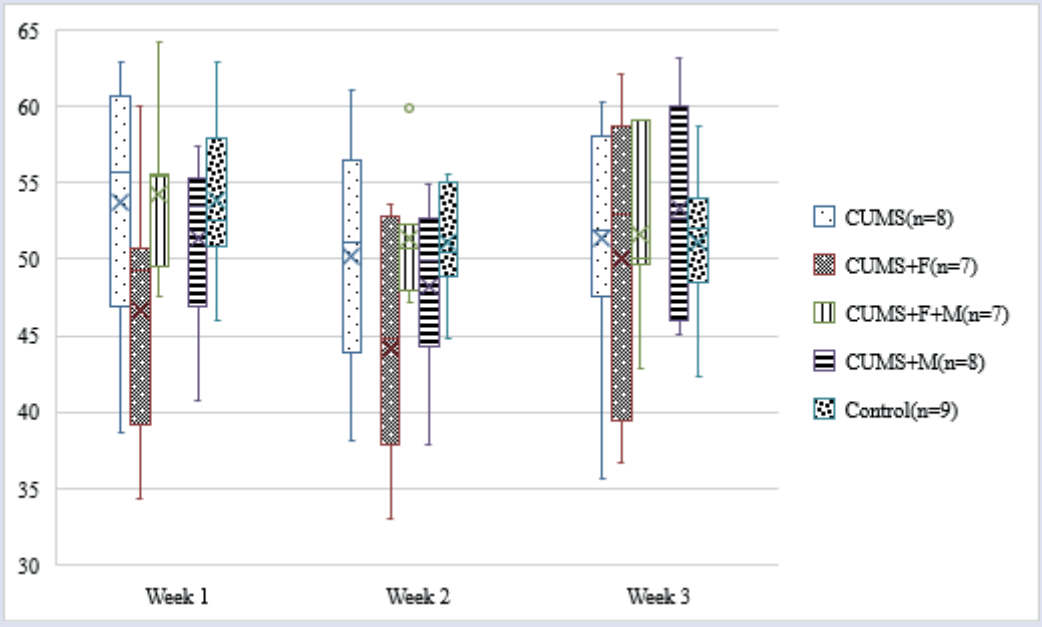

Figure 2: Weekly average meals between groups. Weekly average meals were assessed one week after treatment, two weeks after treatment, and three weeks after treatment.

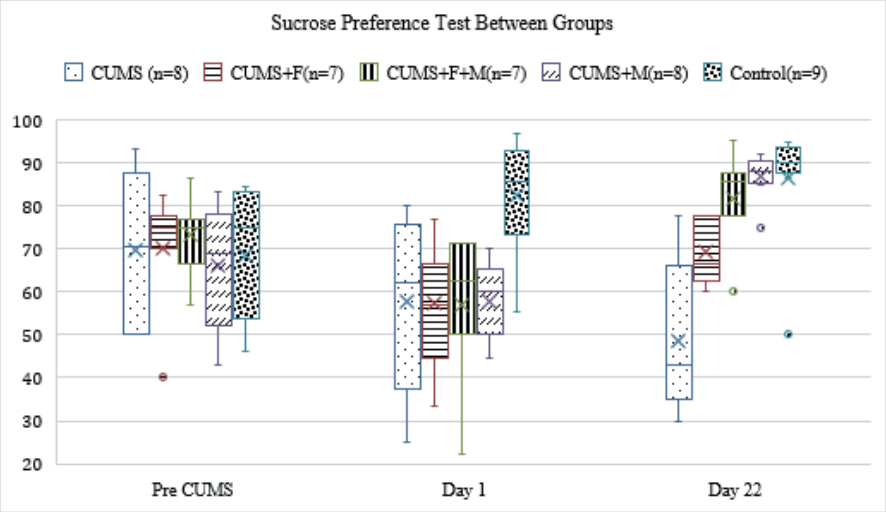

Figure 3: Sucrose preference test of the rats. Rats were administered either one of three treatments i.e., fluoxetine, fluoxetine+music, or music for 3 weeks. Stressors were still given during treatment periods. Sucrose preference test were assessed 3 times, i.e., pre-animal model creation, before the treatment started and 21-days post treatment started. *significant with p value <0.05.

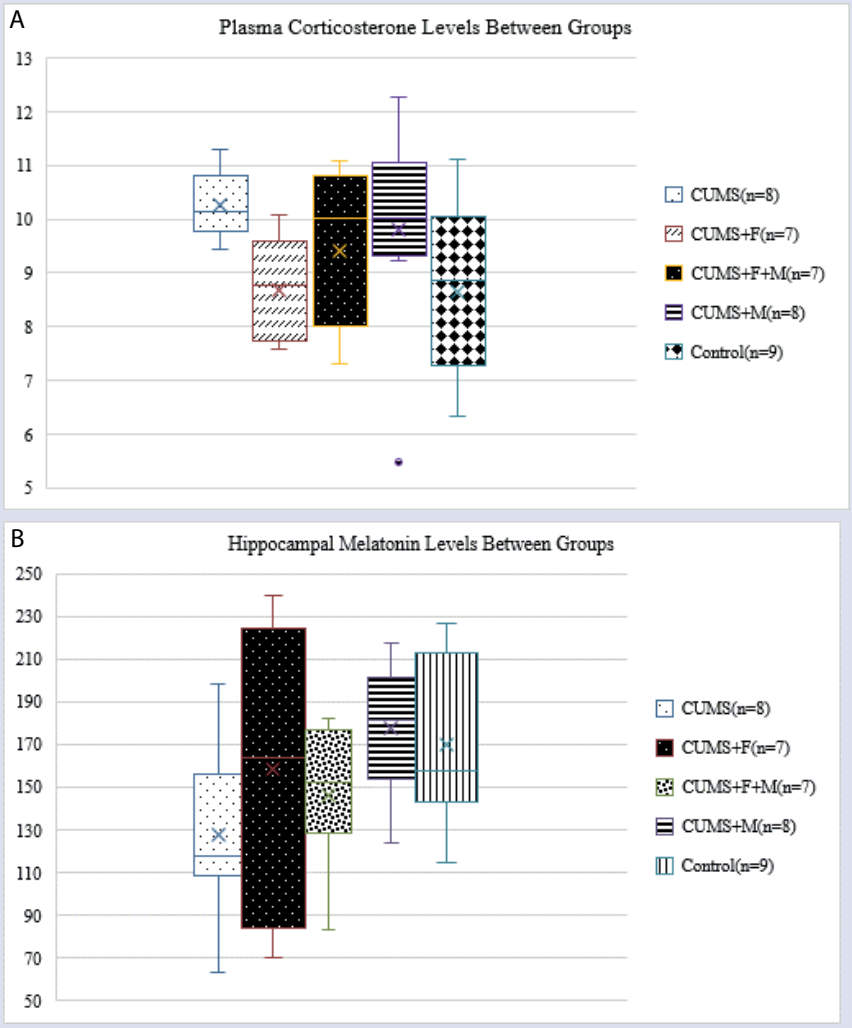

Figure 4: Plasma corticosterone levels (A) and hippocampal melatonin levels (B) of the rats. Rats were administered either one of three treatments i.e., fluoxetine, fluoxetine+music, or music for 3 weeks. Stressors were still given during treatment periods. Corticosterone and melatonin were measured 1 day after the treatments end.

of its administration.[25] Thirty-six days of CUMS protocols has been proven to cause a lower body mass index (BMI) compared to the control.[25] A previous study revealed that fluoxetine has an anorexic effect[26], and acute fluoxetine therapy led to modest weight loss, which improved in accordance with depression's symptom improvement. Lafferty et al. reported that Mozart K448 has the ability to increase body mass.[27] In this study, the fluoxetine + Mozart group reached similar body weight with the control sooner compared to the Mozart group. The results also showed that the fluoxetine-Mozart and Mozart groups revealed no significant weight difference in comparison to the control. The weight in the fluoxetine group was the lowest compared to those of other groups. These findings are consistent with Chojnacki et al. which found that the combination of fluoxetine and other treatment that can negate the fluoxetine's effect on BMI, and led to a better BMI.[26]

Environmental stress can elicit depressive-like behavior.[15] The most consistent effect observed after several weeks of CUMS administration was a decrease in sucrose consumption assessed by SPT.[28] However, this decrease was reversed with the use of antidepressant treatment.[29] Prominent depressive-like behavior characterized by lower SPT was observed among the CUMS group in this study. There are several classes of antidepressants[30] with different mechanisms of action.[31] Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant with high efficacy.[32] Despite its effectiveness, there are cases where some patients exhibit a limited response to the drug.[32] Adjunctive treatment with other methods is an option worth to be considered for the depression's treatment. Music can be used either as a single or a combined therapy with other modalities to treat depression.[33] Several studies revealed that music, such as Mozart K448 has the ability to improve depressive symptoms.[34] Papadakis et al revealed that Mozart music (K448) can attenuate this condition in rat models. The findings of this study indicate that the combined therapy of fluoxetine and Mozart improved depressive-like behavior, in terms of sucrose consumption, better than fluoxetine only.[35]

Environmental stress can cause increased corticosterone levels and decreased melatonin levels.[15] Koprdova et al. stated that the CUMS Wistar rats have significantly increased plasma corticosterone levels compared to the control.[36] A study done Musshoff found that rat hippocampus has melatonin receptors, and since that decreased peripheral melatonin levels was found in patients with depression[5, 37-39], it is interesting to see whether there is a lower hippocampal melatonin level in CUMS group. This study showed that CUMS group has higher plasma corticosterone levels as well as lower hippocampal melatonin compared to the control. Fluoxetine has the ability to increase its production in the hippocampus as well as reduce plasma corticosterone.[40] Increased melatonin levels have been reported to improve depressive symptoms[41], and this can be achieved through the use of an effective antidepressant treatment[42, 43]. Music can increase melatonin.[34, 44] It is also interesting to see the hippocampal melatonin levels in treatment groups. This study revealed that among the treatment groups, fluoxetine group has lowest mean corticosterone levels compared to the CUMS group. Among the treatment groups, the rats administered with Mozart showed the highest mean of melatonin levels compared to the CUMS group. The addition of melatonin enhanced the effects of fluoxetine on depressive-like behavior and BDNF-TrkB signaling.[17] The fluoxetine-Mozart group showed better depressive-like behavior improvement in terms of SPT than the fluoxetine group, although it did not reach statistically significant differences in corticosterone and melatonin levels. The improvement in depressive-like behavior after the administration of the fluoxetine-Mozart combined therapy may be caused by an alteration in the pathway and receptors of the hormones rather than their levels only.

This study contributes supplementary data regarding the application of combined therapy involving fluoxetine and Mozart K. 448. The addition of Mozart to fluoxetine can accelerate body weight improvement and increase SPT better than fluoxetine alone.

This study has several limitations, such as the measurement of only the plasma corticosterone, hippocampal melatonin, hippocampal serotonin, and hippocampal BDNF levels. It is worth noting that the findings on hippocampal serotonin and hippocampal BDNF levels have been published elsewhere.[24, 35, 45, 46] The assessment did not include an evaluation of the quantity of cells or the complexity of neurons in the hippocampus. Fenton et al. revealed that corticosterone levels often increase in depression-like behavior. The condition is also characterized by a decrease in cell numbers as well as neuron complexity.[47-49] Furthermore, the corticosterone and melatonin receptors were not assessed in this study. Several studies revealed that melatonin receptors hold significance in both the pathophysiology and treatment of depression.[41, 50] The melatonin pathways were also not evaluated in this study, but they have been reported to have an important role in depressive-like behavior improvement.[51] Dmitrzak-Weglarz et al. stated that the pathways have significant functions in depression.[52] An additional control group receiving fluoxetine should be added to evaluate the impact of fluoxetine on behavior.[53, 54] Acute and chronic fluoxetine administration is known to impact behavior.[55, 56]

CONCLUSION

Compared to the other treatment groups, the group that received the combined therapy of fluoxetine and Mozart for 21 days exhibited superior body weights and SPT results. The results showed that the combination of two effective treatments does not always result in positive outcomes in all aspects. The fluoxetine group showed the lowest mean corticosterone levels compared to the other treatments. Furthermore, the Mozart group showed the highest mean melatonin levels compared to other treatment groups. Based on the results, the combined therapy of fluoxetine and Mozart can improve depression.

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AUTHORS' CONTRIBUTIONS

LP, II, and MMM: Conceptualized the research design. LP: Executed the research, collected data, performed statistical analyses, conducted a literature review, and drafted, composed, and revised the manuscript. II and MMM: Provided supervision for the research and critically reviewed the manuscript. All authors have thoroughly reviewed and approved the final version of the manuscript.

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