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Original Article

Antidepressant-like Effects of Intra-cerebroventricular Microinjection of Kaempferol in Male Rats: Involvement of 5-HT2 Receptors

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Abstract

Background and Objective: Kaempferol (KM) is a flavonoid found in plant-derived foods and medicinal plants. Recently, it has been well established that KM plays a protective role against the development of Alzheimer's disease. This study evaluated the effect of intracerebroventricular microinjection of KM on depression and identified the potentially related serotonergic mechanisms in rats.

Materials and Methods: Male rats were assigned to control, vehicle (dimethyl sulfoxide), KM, fluoxetine, cyproheptadine, KM (20 µg/rat) + cyproheptadine (1 µg/rat), and KM (20 µg/rat) + cyproheptadine (4 µg/rat) groups. All the groups received their respective treatments for 30 days. Depression was evaluated by both forced swimming and tail suspension tests. Monoamine oxidase-A (MAO-A), as a neurochemical parameter, was also evaluated in the liver and brain of animals.

Results: Treatment with KM significantly decreased immobility time in both forced swimming and tail suspension tests, compared to the vehicle. In the forced swimming test, remarkable effects in immobility time were induced by KM + cyproheptadine after a single dose during weeks 2, 3, and 4 of treatment, compared to the cyproheptadine group. In the tail suspension test, both fluoxetine and KM indicated remarkable effects in the immobility time during weeks 3 and 4. In addition, in both the brain and liver, MAO-A activity was decreased after treatment with KM.

Conclusions: These results indicated the antidepressant-like effects of KM through the involvement of 5HT2 receptors in male rats.

Keywords: Depression, Flavonoids, Intraventricular, Monoamine oxidase

Background

Depression (clinical depression or crucial depressive disorder) is a typical but consequential mood disorder. This condition provokes severe symptoms that affect how a person feels, thinks, and handles daily activities, such as eating, sleeping, or working. In addition, in clinical practice, depression is the 2nd most frequent chronic condition [1], and in 2020, it was the world's 2nd major public health problem and disability [2]. The current treatments help about two-thirds of anxious and depressed populations; however, the severity of enhancement is still frustrating [3].

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is the depletion of the neurotransmitters serotonin, norepinephrine, or dopamine in the central nervous system. The "serotonin hypothesis" of clinical depression dates back to 50 years ago. At its most basic level, the hypothesis proposes that decreased serotonin pathway activity is a causative factor in the pathogenesis of depression [4]. This was focused on the antidepressant effects of monoamine oxidase inhibitors and tricyclic antidepressants and the depressogenic impacts of amine-depleting agents, such as reserpine [5].

Despite the fact that there are numerous effective antidepressants on the market today, current treatments are frequently ineffective, with unsatisfactory results in roughly one-third of all treated subjects. This requires the construction of safer and more efficient antidepressants derived from medicinal herbs with proven psychotherapeutic ability in a range of animal models [6].

Flavonoids are phytochemicals that fall into one of many categories, including anthocyanins, flavones, isoflavones, flavanols, and flavanones [7]. The results of pharmacological and epidemiological trials

have shown that the use of flavonoids constituents is linked to the reduction of coronary disorders and a variety of benefits, including anti-cancer, anti-oxidative, anti-inflammatory, and antiviral activity [8-10].

Numerous edible plants (e.g., tea leaves, broccoli, strawberries, and grapes), as well as plants or botanical items widely used in herbal medicine, produce the flavonoid kaempferol (KM) (e.g., *Moringa oleifera* and *Sophora japonica*) [11, 12]. The findings a number of studies have found a correlation between the intake of KM-rich foods and a lower risk of developing a variety of diseases, including cardiovascular diseases and cancers. Kaempferol and several of its glycosides provide a broad variety of pharmacological functions, such as anti-inflammatory, anti-oxidant, anti-cancer, anti-microbial, cardioprotective, antidiabetic, neuroprotective, anxiolytic, analgesic, anti-osteoporotic, antidepressant (intraperitoneally form), and anti-allergic activities, according to various preclinical reports [13, 14]. Moreover, based on the results of studies, the serotonin system (especially 5-Hydroxytryptamine$_2$ [5-HT$_2$] receptors) was involved in the antidepressant-like activity of flavonoids [15].

Regardless of the fact that KM has a variety of clinically proven pharmacological practices, there is no empirical evidence that demonstrates its central anti-depression effects.

Objectives

The present research was conducted to ascertain the possible effects of KM on depression through the serotonergic system in male rats.

Materials and Methods

Animals

In the present study, 42 male Wistar rats weighing 220-250 g at the time of abscission were used (animal-house of Hamadan University of Medical Sciences, Hamadan, Iran). Almost all rodents were given at least a week to conform to the lab conditions prior to surgery and were treated for five min per day during that period. The rats were acclimatized in an animal house at room temperature (22±2°C) and on a 12-hour light/12-hour dark schedule. They had easy entrance to food and water. The rats after handling 2-3 times, were divided into groups before tests as follows: 1. Control, 2. dimethyl sulfoxide/vehicle, 3. KM (10, 20, and 40 µg/rat), 4. Fluoxetine, 5. cyproheptadine (Ch; a 5-HT$_2$ receptors antagonist; 1 and 4 µg/rat), 6. KM (20 µg/rat) + Ch (1 µg/rat), and 7. KM (20 µg/rat) + Ch (4 µg/rat). It is mentioned that seven intact experimentally male rats were presented in each group. Furthermore, not only were the protocols for treating the rodents accepted by the Hamadan University of Medical Sciences (Research and Ethics Committee; IR-UMSHA-REC-1396-618) but they were also in line with the National Institutes of Health (NIH) Declaration [85-23, 1985].

Drugs

Cyproheptadine, pentobarbital sodium, fluoxetine, and KM were purchased from Sigma-Aldrich. [USA]. Before intracerebroventricular microinjection, all drugs were dissolved in dimethyl sulfoxide for 20 min.

Surgical procedures

All surgical procedures were conducted under ketamine-xylazine (50 mg/kg ketamine+5 mg/kg xylazine) anesthesia [16, 17]. Stainless steel, 22-gauge guide cannulas were implanted (bilaterally) 1 mm above the intended site of injection according to the Paxinos and Watson atlas [18].

Stereotaxic coordinates

The incisor bar (-3.3 mm), 0.8 mm posterior to the bregma, 1.4 mm lateral to the sagittal suture, and 3.4 mm from the top of the skull were used for the lateral ventricles. Dental acrylic was used to secure cannulas to jewelers' screws. The animals were gently restrained by hand and injected with 22-gauge injection needles for drugs infusion (1 mm below the tip of the pilot cannulas). Polyethylene tubing was used to inject each injection unit into a 50-l Hamilton syringe (Model 705 RN SYR). The lateral ventricles were infused with drugs for 3-4 min. To allow diffusion, the injection needles were left in place (for an additional 30 sec), and then the styles were reinserted into the pilot cannulas [19].

Forced swimming test

The Forced Swimming Task (FST) [20, 21] was used to evaluate the antidepressant effect [20, 21]. To start, the rats who had not yet been treated were forced to swim for 15 min in a glass tank (22.5×40 cm) filled with fresh water (25°C). The tests were conducted after a single procedure as well as 1, 2, 3, and 4 weeks after the therapy. During the test, a blinded observer qualified to make the measurements reported the immobility and climbing times. When the back legs were not moving and the rats were slightly hunched over, they were called immobile. During the 5-minute test, the overall time of immobility was assessed. The rats were cleaned with a towel after being removed from the water and returned to their home cage.

Tail suspension test

It is also another tool that may be used to evaluate the behavioral impact of antidepressants or other therapeutic and genetic ruses that are important in depression. Using scotch tape, the rats were independently suspended by their tails from a horizontal bar (50 cm from the floor). Commonly, rats displayed a variety of escape-oriented habits intercut with increasing periods of immobility. During 6-minute test sessions, the length of immobility (in seconds) was documented [22].

Spontaneous locomotor activities

An open-field test was employed to assess the impact of KM on specific locomotor behaviors to verify that the antidepressant-like behavior and cognitive-enhancing effect described above were not false positives due to the effect of KM on motor actions. For 5 min, both animals were evaluated for brushing, rearing, and licking activity. The number of these activities was counted and the frequency was registered [23, 24].

Monoamine oxidase-A evaluation

After the behavioral checks, the animals were anesthetized with an intraperitoneal injection of pentobarbital sodium (50 mg/kg of body weight). The livers and brains (striatum and cortex) were partitioned and homogenized with a glass Potter-Elvehjem homogenizer in ice-cold 100 mM potassium phosphate buffer (pH 7.4). The cumulative monoamine oxidase (MAO)-A operation was calculated using the same method as before, with a slight modification (Boonruamkaew et al., 2017; Herraiz et al., 2018). To inhibit MAO-B operation, the homogenates were incubated with 500-lM tyramine and 500-nM pargyline.

The chromogenic sample was used to make the assay containing aminoantipyrine, vanillic acid, and horseradish peroxidase. At 490 nm, the absorbance was taken spectrophotometrically. The MAO-A content was assayed in micromoles per minute per gram of tissue [25, 26].

Statistical analysis

Data were presented as mean ± SEM and processed by commercially available software GraphPad Prism® 8.0.2. The data were analyzed using a one-way and/or two-way analysis of variance (ANOVA) followed by post hoc analysis (Bonferroni's multiple comparisons test). The level of $p < 0.05$ was considered statistically significant.

Results

Antidepression-like activity of KM: involvements of serotoninergic mechanism

Means (±SD) of the parameters investigated in the FST are shown in Figure 1 (a, b). A two-way ANOVA regarding immobility times revealed the significant effect of treatment ($F [5, 30]=230.9$; $P<0.001$). Further analysis using Bonferroni's post-test exhibited significant changes in immobility times after a single dose of KM (20 µg/rat) during 4 weeks of treatment, compared to vehicle ($P<0.05$). The results of a two-way ANOVA for climbing times showed the significant effect of treatment ($F [5, 180]=1066$; $P<0.001$). Moreover, after a single dose of KM (20 µg/rat), remarkable changes in the climbing time were induced during weeks 3 and 4 of treatment, compared to vehicle ($P<0.01$). In comparison to vehicle, fluoxetine remarkably reduced the immobility time, however, improved the climbing time through weeks 1, 2 ($P<0.05$), 3, and 4 ($P<0.01$).

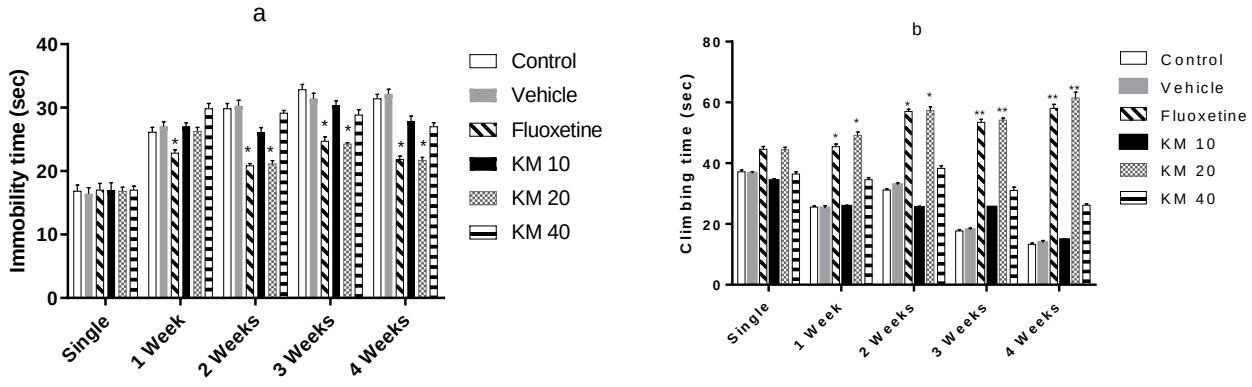

Figure 1. Immobility time (a) and climbing time (b) as indices of anti-depressant of rats subjected to the forced swimming test with different doses of kaempferol (10, 20, and 40 g/rat)
Data are shown as a mean ± SD (n=7 each). *P<0.05. vs vehicle-treated group

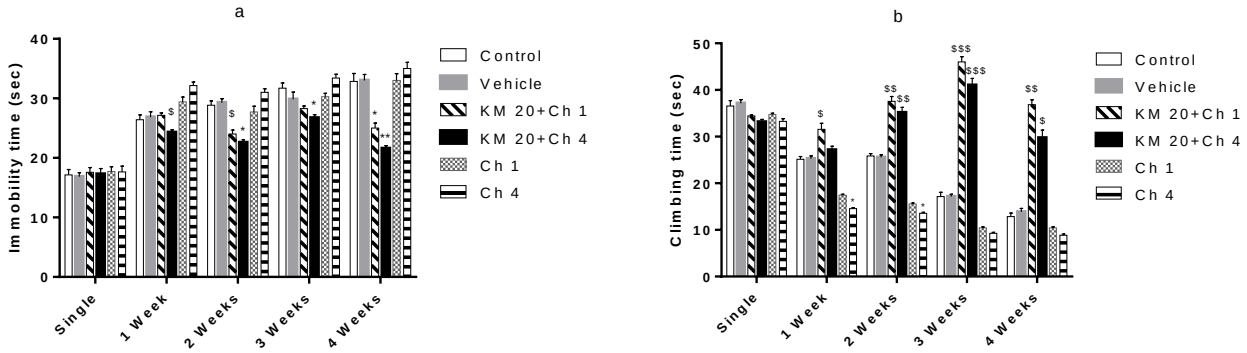

Figure 2. Effect of kaempferol (20 and 40 g/rat) + cyproheptadine (1 and 4 g/rat) on immobility time (a) and climbing time (b) as indices of anti-depressant in rodents who were forced to swimming task (a) and climbing time (b) of rats subjected to the forced swimming test
The information is displayed as a mean ± SD (n=7 each). *P<0.05 vs vehicle-treated group; $P<0.05, $$P<0.01, $$$P<0.001 vs cyproheptadine 4-treated group

According to Figure 2 (a, b), two-way ANOVA revealed the significant effect of treatment regarding immobility times (F [5, 179]=361.4; P<0.001). Additionally, significant changes in immobility time were induced by a single dose of KM (20 µg/rat) + Ch (4 µg/rat) during weeks 2 (P<0.05), 3 (P<0.05), and 4 (P<0.01) of treatment. Furthermore, significant changes in immobility time were induced by a single dose of KM (20 µg/rat) + Ch (1 µg/rat) at week 4 of treatment (P<0.05). The results of a two-way ANOVA about climbing times revealed the significant effect of treatment (F [5, 180]=3819; P<0.001).

In addition, the treatment of rats with KM (20 µg/rat) + Ch (1 µg/rat) significantly increased climbing time during weeks 1 (P<0.05), 2 (P<0.01), 3 (P<0.001), and 4 (P<0.01), compared to Ch (4 µg/rat) alone. It was also found that the treatment of the rats by KM (20 µg/rat) + Ch (4 µg/rat) significantly increased climbing time during weeks 2 (P<0.01), 3 (P<0.001), and 4 (P<0.05), compared to Ch (4 µg/rat) alone.

In the tail suspension test (TST), a two-way ANOVA about immobility times revealed the significant effect of treatment (F [5, 180]=2689; P<0.001). Adjuvant analysis using Bonferroni's posttest exhibited that both fluoxetine and KM (20 µg/rat) significantly changed the immobility time during weeks 3 and 4 (P<0.05), compared to control (Figure 3.a). Moreover, the results of a two-way ANOVA showed the significant effect of treatment (F [5, 180]=3469; P<0.001).

In addition, the treatment of the rats with KM (20 µg/rat) + Ch (1 µg/rat) significantly increased immobility time during weeks 2 and 4, compared to Ch (4 µg/rat) alone (P<0.05). Treatment of the rats by KM (20 µg/rat) + Ch (4 µg/rat) significantly increased climbing time in week 3, in comparison to Ch (4 µg/rat) alone (P<0.05) (Figure 3b).

Effect on spontaneous motor activities

It was found that KM had an effect on spontaneous motor activities, such as rearing, grooming, and licking (figures 4a, b, c). At all doses, the vehicle and KM failed to display major improvements in all the above-mentioned random motor activities.

Suppression of MAO-A activity by KM

The impact of KM on brain MAO-A is depicted in Figure 5. The administration of KM (20 µg/rat),

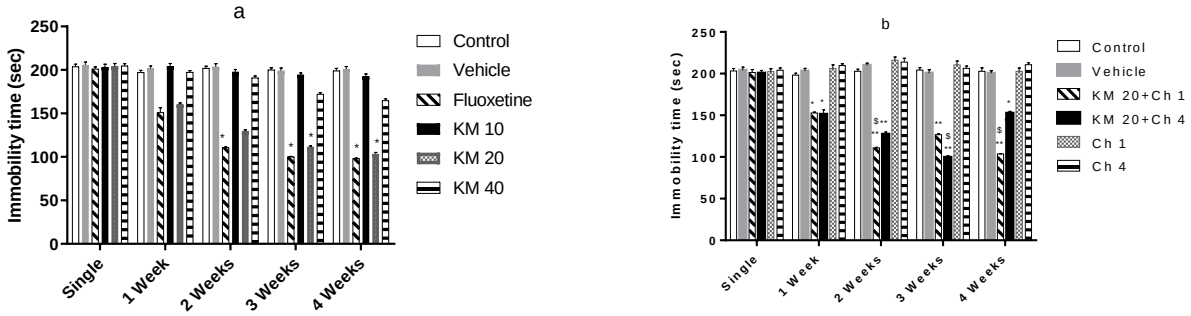

Figure 3. Anti-depressant effect of kaempferol (10, 20, and 40 µg/rat) (a) and kaempferol (20 µg/rat) + cyproheptadine (1 and 4 µg/rat) (b) on the tail suspension test (immobility time of rats)
The information is displayed as a mean ± SD (n=7 each). *P<0.05, **P<0.01 vs vehicle-treated group; $P<0.05 vs cyproheptadine 4-treated group

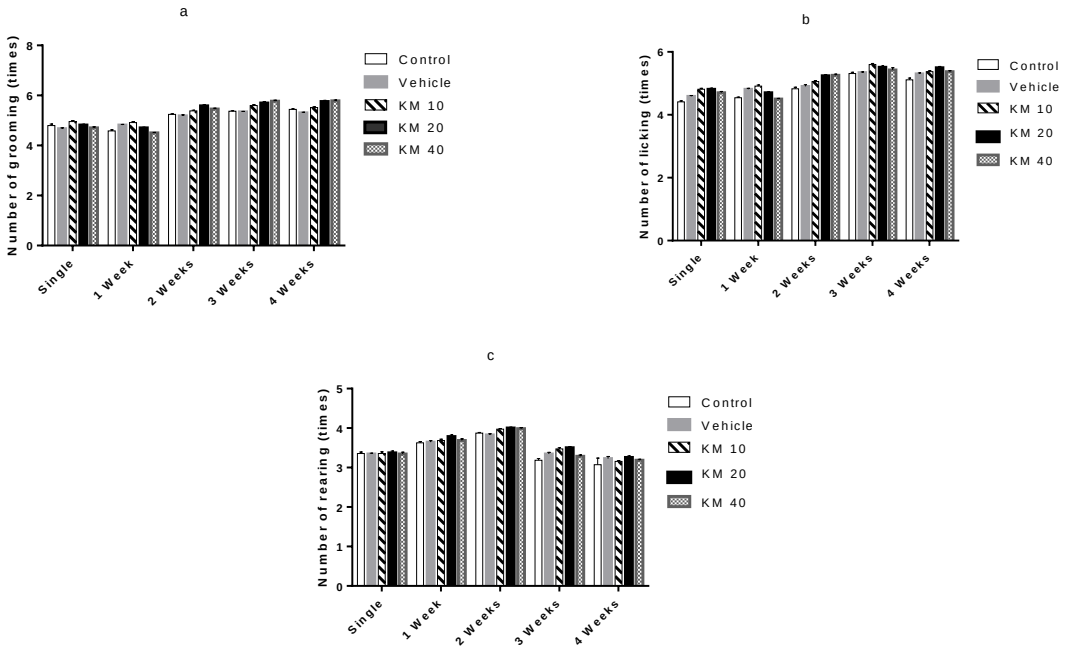

Figure 4. Effect of kaempferol (10, 20, and 40 µg/rat) on the frequency ranges of rats subjected to grooming (a), licking (b), and rearing (c)
The data is displayed as a mean ± SD (n=7 each).

fluoxetine, and KM (20 µg/rat) + Ch (4 µg/rat) markedly decreased MAO-A activity in the rats' cerebral cortex, compared to the control (P<0.05). Besides, in the rats' striatum, the administration of KM (20 and 40 µg/rat), fluoxetine, and KM (20 µg/rat) + Ch (1 µg/rat) significantly diminished MAO-A activity, compared to the control (P<0.05). According to Figure 6, the administration of KM (20 and 40 µg/rat; P<0.05), fluoxetine (P<0.01), and KM (20 µg/rat) + Ch (1 µg/rat) markedly decreased MAO-A activity in the rats' liver, in comparison with the control.

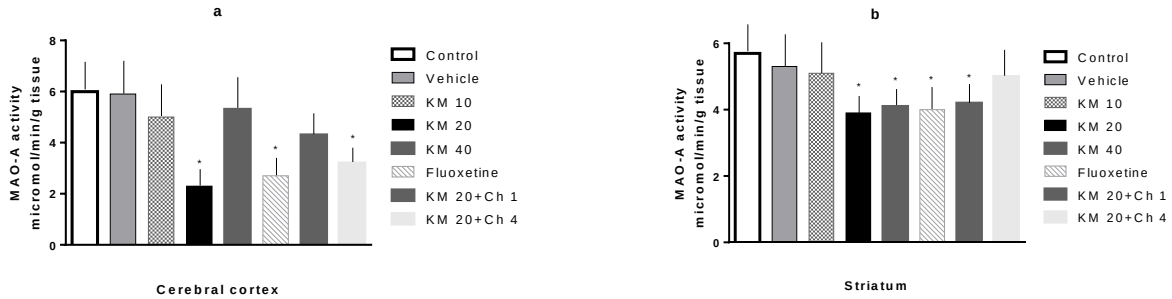

Figure 5. Effect of kaempferol (10, 20, and 40 µg/rat) and kaempferol (20 µg/rat) + cyproheptadine (1 and 4 µg/rat) on the MAO-A action in the cortex (a) and striatum (b) of the brain
The information is displayed as a mean ± SD (n=7 each). *P<0.05 vs control

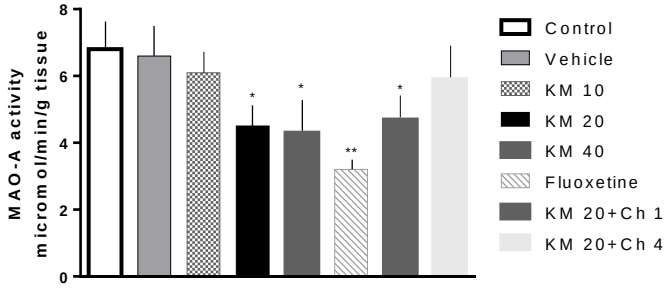

Figure 6. Effect of kaempferol (10, 20, and 40 µg/rat) and kaempferol (20 µg/rat) + cyproheptadine (1 and 4 µg/rat) on the MAO-A action in the liver
Data are represented as mean ± SD (n=7 each). *P<0.05 and **P<0.01 vs control group

Discussion

The most important finding of the present study was the antidepressant effect of KM through the serotonergic system. The FST and TST, which are the most popular assessment measures for evaluating the period of immobility when rats are subjected to an inescapable condition, were used to screen for antidepressant-like behavior, and the antidepressant impact was measured by the decreased immobility time [27, 28]. In both the FST and the TST, we observed that fluoxetine had antidepressant-like activity. Similarly, the application of KM reduced depression after a single dose for up to 4 weeks. Nevertheless, the decline in immobility time was not dose-dependent in either behavioral experiment.

The central nervous system function of monoamines, such as 5-HT, as well as dopamine theory of depression, speculated that monoamine concentrations were poor; even though there was no data concerning the procedure of monoamine deprivation [29, 30]. The monoamine hypothesis of depression predicts that the underlying pathophysiologic basis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system. This hypothesized pathophysiology appears to be supported by the mechanism of action of antidepressants: agents that elevate the levels of these neurotransmitters in the brain have all been shown to be effective in the alleviation of depressive symptoms. However, intensive investigation has failed to find convincing evidence of a primary dysfunction of a specific monoamine system in patients with major depressive disorders. Hence, the recent effective strategies for controlling depression are to increase serotonin and/or noradrenaline neurotransmitters [31, 32]. Monoamine oxidase-A is necessary for the metabolization of monoamine neurotransmitters in general; therefore, a rise in MAO-A enzyme levels in all brain areas is thought to be the primary trigger of monoamine loss in depression [33]. The findings revealed that the antidepressant-like symptoms of KM were most likely regulated by the serotonergic system. The significant decline in MAO-A behavior in the rats' brains in the KM experimental group supported this result.

It is well established that the administration of cyproheptadine (antagonist of 5-HT_2 receptors) can reverse antidepressant activity and treat serotonin syndrome [34]. Several antidepressants are also effective 5-HT_2 receptor antagonists (e.g. amitriptyline and clomipramine) and all established antidepressants share the ability to decrease 5-HT_2 receptor binding after repeated administration. Further evidence relevant to this hypothesis is provided from the systematic examination of other 'atypical' neuroleptics with respect to their clinical profile of action across diverse psychiatric syndromes. For example, ziprasidone is even more selective for the 5-HT_{2A} receptor vs. dopamine D_2 or 5-HT_{2C} receptors than is risperidone or olanzapine. Unlike most other neuroleptics, ziprasidone is a 5-HT_{1A} partial agonist that also blocks monoamine transport with sub-mM potency. This medication is relatively weak at displacing binding to histamine H_1 receptors, compared to other 'atypical' neuroleptics. A further difference of other 'atypical' compounds is the high potency that ziprasidone possesses for the 5-HT_{1D} receptor, and the blockade of the 5-HT_{1D} autoreceptor enhances the effects of selective serotonin reuptake inhibitors on extracellular 5-HT levels. An appreciation of the opposing effects of different 5-HT receptor subtypes in mediating the therapeutic effects of medications will be important in better defining the neurocircuitry involved in the pathogenesis of these disorders and developing treatments with more rapid onset and greater efficacy [35]. Our results indicated that the administration of cyproheptadine not only increased immobility time but also attenuated climbing time in the tests. Moreover, the intracerebroventricular administration of KM could decrease immobility and increase climbing time, which showed the antidepressant effects of KM treatment through the serotonergic system.

None of the KM doses were shown to be related to the random motor activities of the open field test. In each of the behavioral experiments, however, each subject was only tested once. The findings of the FST and TST could vary if the same rodents were used to examine locomotion in the open field test, and afterward, their immobility time was tested in the FST. Following the open field study, the TST and FST were employed to validate the efficacy of the behavioral experiments. In our research, there was no substantial variation in terms of KM on the open field behavior of the rodents, suggesting that a depression model was successfully developed [36].

Foods rich in phytochemicals, especially those high in Flavonoids (FV), have been found to have particularly strong effects on depression treatment [37]. For instance, Yi et al. (2010) showed that flavonoid naringenin had antidepressant-like behaviors and these antidepressant effects were dependent on the monoaminergic systems [38]. Another experiment in which antidepressant activity of flavonoids was determined was the one conducted by An et al. in 2008. In their investigation, the role of serotonin in the antidepressant-like effect of a flavonoid extract of

Xiaobuxin-Tang was demonstrated [39]. In our study, intracerebroventricular microinjection of KM induced remarkable antidepressant-like activity in rats.

Conclusions

In summary, the current experimental research not only verified that KM had antidepressant-like effects in the FST and TST tests but also indicated that this antidepressant-like effect might interact with the serotonergic system. Furthermore, our findings revealed that KM induced a strong antidepressant-like reaction in rats, involving biochemical modifications that decreased MAO-A levels in the cerebral cortex, striatum, and liver.

Compliance with ethical guidelines

The Committee of Hamadan University of Medical Sciences approved all experimental procedures and assessment conditions, which were carried out in compliance with the NIH Guide for the Treatment and Use of Laboratory Animals.

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Authors' contributions

Study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content: Saeed Mohammadi, Mohammad Zarei, Alireza Komaki, and Zoleikha Golipour Choshali; Acquisition of data, statistical analysis, and drafting of the manuscript: Saeed Mohammadi, Mohammad Zarei; Administrative, technical, and material support: Mohammad Zarei; Study supervision: Mohammad Zarei.

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Conflicts of Interest

There are no conflicts of interest to declare.

References

1. Garber J, Weersing VR, Hollon SD, Porta G, Clarke G, Dickerson JF, et al. Prevention of depression in at-risk adolescents: moderators of long-term response. Prevention Science. 2018;19(1):6-15.[DOI: 10.1007/s11121-015-0626-z.] [PMID]
2. Schultz JL, Killoran A, Nopoulos PC, Chabal CC.Evaluating depression and suicidality in tetrabenazine users with Huntington disease. Neurology. 2018;91(3):202-207 [DOI:10.1212/WNL. 0000000000005817.] [PMID]
3. Hammen C. Risk Factors for Depression: An Autobiographical Review. Annual review of clinical psychology. 2018; 14:1-28. [DOI: 10.1146/annurev-clinpsy-050817-084811] [PMID]
4. Steinberg L, Underwood M, Bakalian, MJ, Kassir S, Mann JJ.S83. 5-HT1A, 5-HT2A, and SERT Binding in Auditory Cortex in Major Depressive Disorder. Biological Psychiatry. 2018; 83(9):S379. [DOI:10.1016/j.biopsych.2018.02.974]
5. Mann, JJ, Sublette ME, Oquendo MA,Miller J. 173. PET Imaging Matching Major Depression Pathophysiology and Antidepressant Treatment Target. Biological Psychiatry, 2018; 83(9): 70. [DOI:10.1016/j.biopsych.2018.02.191]
6. Kasch KL, Rottenberg J, Arnow BA, Gotlib IH.Behavioral activation and inhibition systems and the severity and course of depression. Journal of abnormal psychology. 2002;111(4):589-97. [DOI: 10.1037//0021-843x.111.4.589.] [PMID]
7. Srinivas NR. Recent trends in preclinical drug–drug interaction studies of flavonoids—Review of case studie, issues and perspectives. Phytotherapy research. 2015; 29(11): 1679-1691. [DOI:10.1002/ptr.5447.] [PMID]
8. Nijveldt RJ, Van Nood. Flavonoids: a review of probable mechanisms of action and potential applications–. The American journal of clinical nutrition. 2001;74(4):418-425. [DOI: 10.1093/ajcn/74.4.418] [PMID]
9. Le Marchand L. Cancer preventive effects of flavonoids—a review. Biomedicine & pharmacotherapy. 2002; 56(6): 296-301. [DOI: 10.1016/s0753-3322(02)00186-5.] [PMID]
10. Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as nutraceuticals: a review. Tropical Journal of Pharmaceutical Research. 2008; 7(3):1089-1099. [DOI: 10.4314/tjpr.v7i3.14693]
11. Kashyap D, Sharma A, Tuli HS, Kartin S, Punia S, Mukherjee TK. Kaempferol–A dietary anticancer molecule with multiple mechanisms of action: Recent trends and advancements. Journal of Functional Foods, 2017; 30:203-219.[DOI: 10.1016/j.jff.2017.01.022.] [PMID]
12. Neveux S, Smith NK, Roche A, Blough BE, Pathmasiri W, Coffin AB. Natural Compounds as Occult Ototoxins? Ginkgo biloba Flavonoids Moderately Damage Lateral Line Hair Cells. Journal of the Association for Research in Otolaryngology. 2017;18(2):275-289. [DOI: 10.1007/s10162-016-0604-6.] [PMID]
13. Calderyn-Montaco JM, Burgos-Moryn E, Pйrez-Guerrero C, Lypez-Lбzaro MA review on the dietary flavonoid kaempferol. Mini reviews in medicinal chemistry. 2011; 11(4):298-344.[DOI: 10.2174/138955711795305335.] [PMID]
14. Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. Food chemistry. 2013; 138(4):2099-2107. [DOI: 10.1016/j.foodchem.2012.11.139] [PMID]
15. Khan H, Perviz S, Sureda A, Nabavi SM, Tejada S. Current standing of plant derived flavonoids as an antidepressant. Food and Chemical Toxicology. 2018; 119:176-88. [DOI: 10.1016/j.fct.2018.04.052] [PMID]
16. Mohammadi S. Golshani Y. Neuroprotective Effects of Rhamnazin as a Flavonoid on Chronic Stress-Induced Cognitive Impairment. Journal of Advanced Neuroscience Research. 2017; 4:30-37. [DOI:10.15379/2409-3564.2017.04.02.03]
17. Zarei M, Mohammadi S, Jabbari S, Shahidi S. Intracerebroventricular microinjection of kaempferol on memory retention of passive avoidance learning in rats: involvement of cholinergic mechanism (s). International Journal of Neuroscience. 2019; 129(12):1203-1212. [DOI: 10.1080/00207454.2019.1653867.] [PMID]
18. Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates in Stereotaxic Coordinates. 2007; Elsevier.
19. Mohammadi S, Oryan S, Komaki A, Eidi A, Effects of hippocampal microinjection of irisin, an exercise-induced myokine, on spatial and passive avoidance learning and memory in male rats. International Journal of Peptide Research and Therapeutics. 2020;26(1):357-367. [DOI:10.1007/s10989-019-09842-2]
20. Honda I, Araki K, Honda S, Soeda F, Shin MC, Misumi S, et al.Deletion of GIRK2 subunit containing GIRK channels of neurons expressing dopamine transporter decrease immobility time on forced swimming in mice. Neuroscience letters, 2018; 665:140-146. [DOI: 10.1016/j.neulet.2017.11.028] [PMID]
21. Golshani Y, Mohammadi S, Golshan M. Effects of Rhus Coriaria essential oil on depression and anxiety in male rats. KAUMS Journal (FEYZ). 2019; 23(5):476-484.
22. Pałucha-Poniewiera A, Podkowa K, Lenda T, Pilc A. The involvement of monoaminergic neurotransmission in the antidepressant-like action of scopolamine in the tail suspension test. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2017; 79:155-161.[DOI: 10.1016/j.pnpbp.2017.06.022.] [PMID]
23. Zarei M, Ahmadimoghaddam D, Mohammadi S. Artemisia biennis Willd.: Anti-Nociceptive effects and possible mechanisms of action. Journal of Ethnopharmacology. 2020;113604. [DOI: 10.1016/j.jep.2020.113604.] [PMID]
24. Ahmadimoghaddam D, Sadeghian R, Ranjbar A,

Izadidastenaei Z, Mohammadi S.Antinociceptive activity of Cnicus benedictus L. leaf extract: a mechanistic evaluation. Research in Pharmaceutical Sciences. 2020; 15(5):463 472. [DOI: 10.4103/1735-5362.297849.] [PMID]
25. Fallahzadeh A, Mohammadi S Assessment of the Antinociceptive, Anti-Inflammatory, and Acute Toxicity Effects of Solanum Dulcamara Essential Oil in Male Mice. Journal of Babol University of Medical Sciences. 2020; 22(1):162-168.
26. Golshani Y, Mohammadi S, Antinociceptive and Acute Toxicity Effects of Erigeron acer L. In Adult Male Rats. Journal of Medicinal Plants, 2017; 2(62):85-93.
27. Castagnй V, Moser P, Roux S, Porsolt RD. Rodent models of depression: forced swim and tail suspension behavioral despair tests in rats and mice. Current Protocols in Pharmacology. 2010;49(1): 15-22. [DOI: 10.1002/0471142301.ns0810as55.] [PMID]
28. Dunn AJ, Swiergiel AH. Effects of interleukin-1 and endotoxin in the forced swim and tail suspension tests in mice. Pharmacology Biochemistry and Behavior, 2005; 81(3):688-693. [DOI: 10.1016/j.pbb.2005.04.019]
29. Delgado PL. Depression: the case for a monoamine deficiency. The Journal of clinical psychiatry, 2000; 6:7-11.
30. Elhwuegi AS. Central monoamines and their role in major depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2004; 28(3):435-451. [DOI: 10.1016/j.pnpbp.2003.11.018] [PMID]
31. Deakin J. Depression and antisocial personality disorder: two contrasting disorders of 5HT function in Neuropsychopharmacology. 2003; 64:79-93.[DOI: 10.1007/978-3-7091-6020-6_5.] [PMID]
32. Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, Mcguffin P, et al.Gene–environment interaction analysis of serotonin system markers with adolescent depression. Molecular psychiatry, 2004; 9(10):908.
33. Mohammadi S, Oryan S, Komaki A, Eidi A, Zarei M. Effects of intra-dentate gyrus microinjection of myokine irisin on long-term potentiation in male rats. Arquivos de neuro-psiquiatria, 2019; 77(12):881-887. [DOI: 10.1590/0004-282X20190184.] [PMID]
34. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. The Journal of clinical psychiatry, 1991; 52(4): 22-30.[PMID]
35. Marek GJ, Carpenter LL, McDougle CJ, Price LH, Synergistic action of 5-HT 2A antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. Neuropsychopharmacology, 2003;28(2):402-12. [DOI: 10.1038/sj.npp.1300057.] [PMID]
36. Katz RJ, Roth KA, Carroll BJ. Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. Neuroscience & Biobehavioral Reviews, 1981; 5(2):247-251.[DOI: 10.1016/0149-7634(81)90005-1] [PMID]
37. Rahimi R, Nikfar S, Abdollahi M. Efficacy and tolerability of Hypericum perforatum in major depressive disorder in comparison with selective serotonin reuptake inhibitors: a meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33(1):118-127. [DOI: 10.1016/j.pnpbp.2008.10.018.] [PMID]
38. Yi LT, Li CF, Zhan X, Cui CC, Xiao F, Zhou LP, et al. Involvement of monoaminergic system in the antidepressant-like effect of the flavonoid naringenin in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2010; 34(7):1223-1228. [DOI: 10.1016/j.pnpbp.2010.06.024.] [PMID]
39. An L, Zhang YZ, Yu NJ, Liu, XM, Zhao N, Yuan Li. Role for serotonin in the antidepressant-like effect of a flavonoid extract of Xiaobuxin-Tang. Pharmacology Biochemistry and Behavior, 2008; 89(4):572-580. [DOI: 10.1016/j.pbb.2008.02.014.] [PMID]