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Identification and Evaluation of the Antidepressant Activity of *Manilkara zapota* L.

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Abstract

Background: Depression is widespread and severe, affecting millions worldwide and representing a major cause of morbidity and mortality. However, conventional antidepressants are frequently ineffective and have various serious side effects. Thus, alternative treatment options are of growing interest. Herbal medicines, such as *Manilkara zapota* L., are promising due to their complex composition of phytochemicals.

Methods: *Manilkara zapota* L. antidepressant effects were evaluated in albino mice using the Forced Swim Test and Tail suspension Test, in comparison to standard antidepressant medication. Two different animal groups received two different dosages of 5ml per kg and 10ml per kg of *Manilkara zapota* L. The animals in the control group received normal saline, while the Standard group received imipramine. The animals were given drugs orally, and thirty minutes later, behavioral tests were conducted.

Results: *Manilkara zapota* L., at a dose of 10 ml per kg, significantly ($p<0.05$) reduced the length of immobility in the Forced Swim Test and Tail Suspension Test.

Conclusion: There is no discernible difference between our usual antidepressant medicine (imipramine) and *Manilkara zapota* L., at a dose of 10 ml per kg.

Keywords: *Manilkara zapota* L., Antidepressant, Forced swim test, Tail suspension Test, immobility time.

1. Introduction

Depression is a prevalent mental health condition experienced as persistent sadness, lack of interest in enjoyable activities, and multiple physical and emotional symptoms persisting for at least a fortnight (Farahzadi, 2017). This condition manifests as a major cause of disability and death across the globe, with developing countries such as Pakistan having high cases of anxiety and depression. Some of the core factors blamed for the increased prevalence in such regions include political and economic instability, job-related stress, genetic susceptibility, and other environmental factors. Moreover, patients with depression also present with co-occurring anxiety disorders, which makes diagnosis and treatment challenging (Oluwatosin et al., 2021). Although conventional antidepressant medicines work for certain patients, they have low response rates, lengthy therapy periods, and side effects. This calls for the alternative and safe treatment methods available. One such method is the use of natural remedies such as fruits and vegetables, as they contain effective substances known as antioxidants and phytochemicals. This paper evaluates *Manilkara zapota* L., commonly known as sapodilla, chiku fruit, or *Manilkara* leaf, and its ability to treat depression. *Manilkara zapota* L. has previously indicated its value in terms of its antidepressant properties, meaning it has several health advantages. Its fruit is especially well recognized for its antioxidant and anti-inflammatory properties, and many plant components, including the leaves, bark, and seeds, have historically been utilized medicinally (Tiller, 2013). Research findings indicate that *Manilkara zapota* L. has analgesic, hypocholesterolemic, antihyperglycemic, and antimicrobial properties. The fruit contains numerous known and recognized medicinal chemicals (Wong & Licinio, 2001). Such chemicals have shown to be beneficial in treating respiratory disorders, diarrhea, fever, and depression. Possible therapeutic substances comprise tannin, saponins, and quercetin, which help to alleviate muscle discomfort, digestive issues, and possibly cancer. To conclude, the benefit of fruits like *Manilkara zapota* L. in the direction of depression can be best understood by their routine use, which may enhance and restore well-being. More clinical experience is needed to investigate the possibility of its full use (Dhamija et al., 2017).

2. Materials and Methods

2.1 Plant material and extract preparation

The taxonomist recognized the fresh cheekus as *Manilkara zapota* L. after they were gathered from the neighborhood market in Karachi, Pakistan. The leaves were dried in a hot air oven at 40 °C for 14 days. The dried leaves were then crushed using a commercial blender to get fine powder. The powder 400 g was continuously extracted with methanol using soxhlet apparatus. The dried powder 2000 mL of soxhlet chamber was added 65 ± 5 °C methanol for 2 h was concentrated to dryness. The methanolic leaf extracts obtained were dried at 40 °C in a hot air oven till constant weight obtained and stored under refrigerated condition. The percentage yield of methanolic extract 8.98% w/w (Yong et al., 2020).

2.2 Animals Housing, Grouping and Treatment administration

The albino mice were divided into four groups, with seven mice in each group. The first group of mice was called the control group that were administered with 0.9% normal saline. The second and third groups of mice received 5 ml/kg and 10 ml/kg of *Manilkara zapota* L. respectively for 49 days, while the fourth group received a regular dose of imipramine (25mg/kg), a standard antidepressant medicine.

2.3 Forced Swim Test (FST)

The forced swim test is a behavioral test used to assess the effectiveness of antidepressant medications, and experimental treatments intended to induce or avoid depressive-like states. The escape-related mobility behavior of mice kept in an unavoidably transparent, water-filled tank is measured (Yankelevitch-Yahav et al., 2015). The mouse was dropped and left for six minutes within a glass cylinder measuring 20 cm in height and 14 cm in diameter, with water that was 15 cm deep and between 24 and 25°C. Following the first two to three minutes of intense activity, the animals exhibited a period of inertia during which they float motionless. When the mouse stopped fighting and just remained floating in the water, with only the motions required to maintain its head above the water, it was considered immobile. Measured was the length of immobility behaviors during the swimming test's last 4-minute interval. An antidepressant effect can be detected by a reduction in the amount of time spent immobile (Mahmoudi et al., 2015).

2.4 Tail Suspension Test (TST)

We employed an adapted version of the TST that was approved for use with NMRI mice before (Steru et al. 1985). As a result, 30 minutes after injection, each mouse was suspended by its tail from a 20-cm-high aluminum hook by means of adhesive tape that was inserted two centimeters from the tail tip. The mice were arranged so that the horizontal plane was parallel

to the base of their tails. Mice typically exhibited behavior focused on escaping, punctuated by increasingly extended periods of immobility. A professional observer videotaped the six-minute test sessions and scored the results. (Berrocoso et al., 2013)

2.5 Statistical Analysis

The observed data was put through multiple comparison tests (Post hoc Tuckey test) and One way ANOVA using SPSS software. When the level of significance (P-value) is less than 0.05, it is considered significant; when it is less than 0.01, it is highly significant and P values greater than 0.05 were considered insignificant.

2.6 Ethical issues

This experiment was approved by the IBC (Institutional Bioethical Committee) of University of Karachi. All methods were carried out in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, so as to minimize suffering to the smallest possible extent.

3. Results

3.1 Forced Swim Test

Table I indicated that there was a significant mean difference of -17.714 for the standard to the control with p =.000 and 95% CI of -26.51 to -8.92, indicating that the standard was significantly better. There was also a significant difference with the *Manilkara zapota* L. dose 1 with mean -13.429, p =.002, and 95% CI: -22.23 to -4.63. Similarly, the standard showed significantly better results than the *Manilkara zapota* L. dose 2 with mean -10.714, p =.013; and 95% CI: -19.51 to -1.92. The comparisons between the control group and *Manilkara zapota* L. treatments did not reveal any significant differences. The mean difference between the control group and *Manilkara zapota* L. dose 1 and *Manilkara zapota* L. dose 2 were 4.286 and 7.000 respectively. There was also a significant difference between *Manilkara zapota* L. dose 1 and the standard with mean 13.429; p =.002, and 95% CI: 4.63 to 22.23. The difference between *Manilkara zapota* L. dose 1 and 2 was not significant. There was a significant difference between *Manilkara zapota* L. dose 2 and the standard medications, p =.013, mean was 10.714; 95% CI was 1.92 to 19.51. However, there was no significant difference between *Manilkara zapota* dose 2 and *Manilkara zapota* L. dose 1.

Table I: Multiple comparison post Hoc Tukey test on Immobility time of drugs among Control, Standard drug Imipramine and *Manilkara zapota* L. dose 1 and M. Zapota dose 2 by using Forced swim Test.

(I) **Treatment of the drug**	(J) **Treatment of the drug**	**Mean Difference (I-J)**	**Std. Error**	Sig.	**95% Confidence Interval**	
					Lower Bound	**Upper Bound**
Standard	Control	-17.714*	3.189	.000	-26.51	-8.92
	Manilkara zapota dose1	-13.429*	3.189	.002	-22.23	-4.63
	Manilkara zapota dose2	-10.714*	3.189	.013	-19.51	-1.92
Control	Standard	17.714*	3.189	.000	8.92	26.51
	Manilkara zapota dose1	4.286	3.189	.545	-4.51	13.08
	Manilkara zapota dose2	7.000	3.189	.153	-1.80	15.80
***Manilkara zapota* dose1**	Standard	13.429*	3.189	.002	4.63	22.23
	Control	-4.286	3.189	.545	-13.08	4.51
	Manilkara zapota dose2	2.714	3.189	.829	-6.08	11.51
***Manilkara zapota* dose2**	Standard	10.714*	3.189	.013	1.92	19.51
	Control	-7.000	3.189	.153	-15.80	1.80
	Manilkara zapota dose1	-2.714	3.189	.829	-11.51	6.08
The mean difference is significant at the 0.05 level.						

3.2 Tail Suspension Test

The results of the immobility periods between the Standard group and Control group as well as between the Standard and *Manilkara zapota* L. 5ml show a significant difference when the immobility time of the Standard group is compared with Control, *Manilkara zapota* L. 5ml, and *Manilkara zapota* L. 10ml measurements. However, there isn't much of a difference between the *Manilkara zapota* L. 10ml and the Standard.

Table II shows that the standard drug has significantly differed from the control with the mean difference of 24.714, p.000 to 95% CI: 10.342- 39.086. These results imply that compared to the control, standard drug has reduced immobility time by being significantly different. However, comparing standard drug to *Manilkara zapota* L. dose 1, there was also a significant difference, t =.841, mean difference = 19.571, p =.005, 95% CI: 5.199- 33.943. This means that when compared to *Manilkara zapota* L. dose 1, standard drug has done significantly better. On the other hand, when *Manilkara zapota* L. dose 2 is compared to the standard drug, the difference was not significant, t =.841, mean difference = 13.000, p =.086, 95% CI: -1.372- 27.372. However, when the control group was compared to the treatment groups of *Manilkara zapota* L., no significant differences have been noticed. The mean differences for *Manilkara zapota* L. dose 1 and dose 2 have been observed to the control were t =.841, mean difference = -5.143, p =.758, 95% CI: -19.515- 9.229. When *Manilkara zapota* L. dose 1 and dose 2 were compared to the control, the results showed t =.841, mean difference = -11.714, p =.139, 95% CI: -26.086- 2.658. Furthermore, when *Manilkara zapota* L. dose 1 was compared to the standard drug, there was a significant difference t =.841, mean difference = -19.571, p =.005, 95% CI: -33.944- -5.199, which means that standard drug is significantly more efficient. No significant difference has been found when comparing *Manilkara zapota* L. dose 1 and dose 2 differences, t =.841, mean difference = -6.571, p =.595, 95% CI: -20.944- 7.801. Lastly, comparing *Manilkara zapota* L. dose 2 to the standard drug, there was no significant difference, t =.841, mean difference = -13.000, p =.086, 95% CI: -27.372- 1.372. Additionally, when comparing the difference between *Manilkara zapota* L. dose 2 and dose 1, also no significant difference has been noticed.

Table II: Multiple comparison post Hoc Tukey test on Immobility time of drugs among Control, Standard drug Imipramine and *Manilkara zapota* dose1 and M. Zapota dose 2 by using Tail Suspension Test**.**

(I) Treatment of the drug	(J) Treatment of the drug	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Standard	Control	24.71429*	5.20988	.000	10.3423	39.0863
	Manilkara zapota dose1	19.57143*	5.20988	.005	5.1994	33.9435
	Manilkara zapota dose 2	13.00000	5.20988	.086	-1.3720	27.3720
Control	Standard	-24.71429*	5.20988	.000	-39.0863	-10.3423
	Manilkara zapota dose1	-5.14286	5.20988	.758	-19.5149	9.2292
	Manilkara zapota dose 2	-11.71429	5.20988	.139	-26.0863	2.6577
Manilkara zapota L. dose1	Standard	-19.57143*	5.20988	.005	-33.9435	-5.1994
	Control	5.14286	5.20988	.758	-9.2292	19.5149
	Manilkara zapota dose 2	-6.57143	5.20988	.595	-20.9435	7.8006
Manilkara zapota L. dose 2	Standard	-13.00000	5.20988	.086	-27.3720	1.3720
	Control	11.71429	5.20988	.139	-2.6577	26.0863

	Manilkara zapota dose1	6.57143	5.20988	.595	-7.8006	20.9435
*. The mean difference is significant at the 0.05 level.						

4. Discussion

Depression impacts about 5% of the global population, which is 121 million people internationally (Santomauro et al., 2021). Lifetime prevalence rates suggest that 5.8% of men and 9.5% of women would suffer from a depressive episode, which might result in suicide. Psychomotor retardation, melancholia, mood swings, and a lack of interest in the environment are all symptoms of depression, mirroring the disorder's affective nature. The high morbidity and mortality associated with depression have led to the development of numerous synthetic antidepressants. However, their efficacy is relatively low, only 50% of patients make a recovery, and the necessary period for this is more than 5-8 weeks (Kessler, 2012). This necessitated the creation of more efficient and capable antidepressant methods from novel substances, particularly herbal treatment involves evaluation with animal models, such as tail suspension test opportunities and drowned behavior.

One of the herbal products is *Manilkara zapota* L., commonly called Sapodilla. It is abundant in necessary minerals, sugars, acids, proteins, amino acids, and diverse classes of bioactive molecules, depsides, phenolic acids, ellagitannins, gallotannins, and flavonoids with related therapeutical value due to polyphenolic and antioxidant characteristics (Priyanka et al., 2024). This anti-oxidant potential enables this research study to assess the antidepressant effect of *Manilkara zapota* L. This is supported by a study conducted by Li-Tao Yi et. al., who published a study on "antidepressant effects in mice of Naringin." Naringin therapy resulted in notable confined times in drowned activity and the tail suspension test, indicating depression rate decline (Yi et al., 2014). Bangar et al. findings from their study "Phytochemical profile and therapeutic potential of Manilkara zapota" confirm the extensive phytochemical properties of Sapodilla and its potential (Punia Bangar et al., 2022).

The purpose of this study was to evaluate the antidepressant properties of *Manilkara zapota* L. using the same paradigms. As indicated previously, there was a significant difference in

the immobility time between the standard drug and the control and both doses of *Manilkara zapota* L. Based on the independent sample t-test, the difference in the outcome measures was significant compared to the control, *Manilkara zapota* L. 1; and *Manilkara zapota* L. 2. Hence, the standard was superior to *Manilkara zapota* L. at the tested doses. On the other hand, the results of the difference between the outcomes of the measurements of the control and *Manilkara zapota* L. were not significant. Moreover, the differences between the two doses were not significant. Therefore, none of the doses in the measurements produced excessive antidepressant activity as tested in the models. These results are supported by the study conducted by Mahmoudi et al., in their report entitled, "Evaluation of the antidepressant-like effects of St. John's Wort in the tail suspension test and forced swimming test". The findings indicate the performance of the active antidepressant drug was not efficient as imipramine (Mahmoudi et al., 2015).

5. Conclusion

In conclusion, it is possible to state that the integration of *Manilkara zapota* L., a herbal remedy with proven antidepressant-like effects, with conventional medication, such as imipramine, may provide a synergic effect on the enhancement of the effectiveness of depression treatment. Nevertheless, focusing on its own, it is not likely that *Manilkara zapota* L. will manage to overtake the effectiveness of synthetic medications. It is necessary to conduct additional investigations to determine the most optimal combinations of herbal remedies as well as the underlying mechanisms conducive to their positive effects.

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