ORIGINAL ARTICLE

Antidepressant Effects of Mitragyna speciosa Korth Extract on Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus is most common associated with neurological complications, including depressive symptoms, so this study investigated whether *mitragyna* may provide benefits in reducing depressive symptoms in animal models of diabetes. This study aims to evaluate the effect of *mitragyna* as a potential antidepressant agent in animal models of diabetes mellitus using the Force Swimming Test (FST).
Methods: In this study, diabetes mellitus rats were induced by administering streptozotocin and then divided into four groups: control group (Control), Group Diabetes (DM), *Mitragyna* treatment group (DM+EMS 15mg) and (DM+EMS 30mg). After the treatment period, the rats were then tested with the FST, which is used to measure immobility behavior which can be used as an indicator of depressive symptoms.
Results: The results showed that the treatment group that received *mitragyna* showed shorter immobility times compared to the control group ($P<0.01$), indicating an increased active response in facing FST stressors.
Conclusion: These results indicate that *mitragyna* has potential as an antidepressant agent in reducing depressive *symptoms* in rats models of diabetes mellitus.

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Introduction

Depression is a common mental disorder worldwide and can occur alongside other medical conditions, including diabetes.[1] Diabetes mellitus is a chronic disease characterized by high levels of glucose in the blood and significantly affected quality of life patient.[2] Diabetics have a higher risk of developing depression compared to the general population. Treatment of depression usually involves taking antidepressants, but these medications often have undesirable side effects. *Mitragyna speciosa Korth* (otherwise known as Kratom) is a plant from Southeast Asia and has been used traditionally as a herbal medicine to treat various health problems, including depression.[3] Several studies have demonstrated the potential of *Mitragyna speciosa* in treating symptoms of depression, but no studies have specifically explored its antidepressant effects in individuals suffering from diabetes.[4]

Force Swimming test (FST) is a method has been used in experimental study. FST used for evaluated behavioral and measure the level of depression in mouse. This test involves forcing rats to swim in a pool of water for a certain period of time and measuring their behavior during the swimming test.[5]

This study aims to evaluate the antidepressant effect of *Mitragyna speciosa Korth* extract on rats suffering from type 2 diabetes by testing the swimming method. Data from this study is expected to provide new insight into the potential use of *Mitragyna speciosa* as an alternative treatment for depression in individuals with underlying medical conditions such as diabetes.

Methods

This is a research experimental study, with the research design control group (Post Test Only Control Group Design), by taking measurements after the treatment is given.

Extraction and fractions methods

The extraction method used in this research is maceration. A total of 3 kg of dried *Mitragyna speciosa Korth* simplicia powder was extracted using 96% methanol solvent. Change the solvent every 1x24 hours and macerate for 7x24 hours. The maserate is concentrated using a rotary evaporator and water bath to obtain a thick extract.

Experimental animals

The experimental animals used were *Mus musculus* purchased from PUSVEPMA. A total of 20 male rats were separated according to research groups, namely control group (K), DM group, DM group and 15 mg dose of *Mitragyna speciosa Korth* extract (DM+EMS1), and DM group and 30 mg *Mitragyna speciosa Korth* extract (DM+MS2). Before testing, the rats were adapted (acclimatized) for one week in the UNUSA Faculty of Medicine Research Laboratory. Before treatment, the weight of the test animals was weighed and marked. The test animals used are those that comply with the criteria for the use of test animals and have passed the ethical review. Then, grouped according to treatment.

Streptozotocin induction

Streptozotocin (STZ) induction uses a dose of 75 mg/kg BW by injection via the intraperitoneal route for 3 consecutive days.

Forced Swimming Test (FST)

Forced Swim Test (FST) was carried out according to Yankelevitch-Yahav et al. (2015) with modifications. The test was carried out by placing rats in a tube filled with water at a certain depth so

that the rats's hind legs did not touch the bottom of the tube and their front legs could not hold on to the edge of the tube. The water temperature is adjusted to room temperature because water temperature that is too cold can trigger more active swimming behavior. The duration of forced swimming was 6 minutes and the time when the rats showed signs of immobility was recorded.

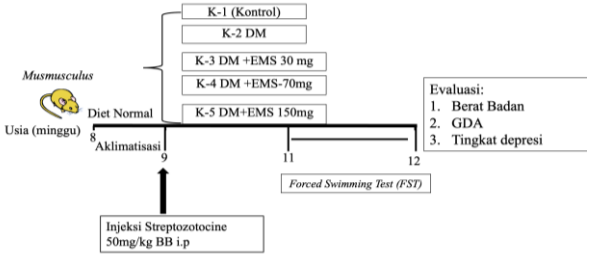

Figure 1. Design studies

Blood Glucose examination

After 14 days of treatment, blood glucose levels were evaluated.

Data Analysis

Research data are presented as mean ± standard error. By analyzing with the ANOVA test. If it does not meet the ANOVA test then use a non-parametric test, namely the Kruskal Wallis Test. Then proceed with the Mann-Whitney test.

Results

Effect of *Mitragynine* on immobility time Forced swim test (FST)

The forced swim test (FST) is a behavioral test commonly used in preclinical research to assess depression-like behavior and the potential antidepressant effects of a substance. Animals subjected to FST (usually rodents) are placed in a container filled with water so that they cannot escape. The time they spend immobile is considered an indicator of hopeless or depression-like behavior. *Mitragynine*, as one of the main active compounds in kratom, has been the subject of research to understand its effects on behavior and physiology.

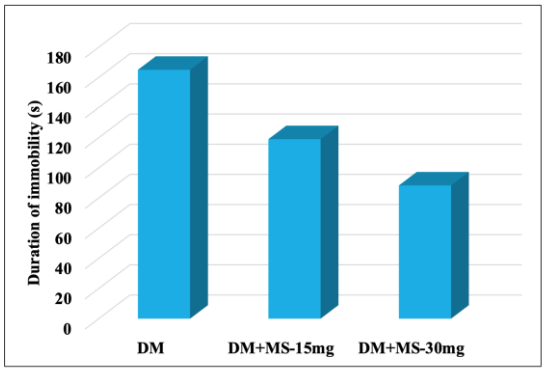

Figure 2. Effect of *Mitragynine* on FST immobility

This study showed that after 30 minutes of treatment, mitragynine significantly reduced ($P < 0.05$) the duration of immobility time at 15 mg/kg and 30 mg/kg respectively compared with the diabetes mellitus group.

Discussion

Comorbidity of diabetes and depression represents a significant clinical challenge, and new treatment options are needed. *Mitragynine*, which is one of the herbal plants that has potential as an antidepressant, is a promising candidate. The results of this study suggest that Mitragyna speciosa Korth, commonly known as kratom, exhibits significant antidepressant effects in diabetic rats, a finding that aligns with previous research demonstrating the psychotropic potential of kratom alkaloids (Singh et al., 2019).[9] Notably, the administration of kratom extract resulted in a marked improvement in the behavioral symptoms associated with depression in diabetic models, as evidenced by increased exploration in the open field test and a reduced immobility time in the

forced swim test (Hassan et al., 2017).[10] The findings of this study suggest that *Mitragyna speciosa* Korth, commonly known as kratom, has notable antidepressant effects in diabetic rats. These effects are particularly significant given the dual challenge of managing diabetes and depression concurrently. Kratom's efficacy could be attributed to its active alkaloids, such as mitragynine, which have been previously noted for their impact on mood regulation through interaction with opioid receptors (Singh et al., 2019).[9] The observed reduction in immobility time in the FST in diabetic rats treated with *Mitragynine* supports the hypothesis that *Mitragynine* may reduce depressive-like behavior in this population. These effects can be attributed to its interactions with various neurotransmitter systems.[6]

Behavioral assessments, including the open field test and the forced swim test, indicated improved activity levels and reduced signs of despair in rats after treatment with kratom extract. These behavioral changes are consistent with prior studies indicating the potential of kratom extracts in alleviating depressive symptoms through neurotransmitter modulation (Hassan et al., 2017).[10-12] Additionally, the observed improvement in glycemic control among the treated rats suggests a possible synergistic effect of kratom's antidiabetic properties, which could further enhance its antidepressant potential. [6,13]

The interaction between kratom's analgesic and antidepressant properties is particularly relevant in diabetic populations, where chronic pain is a prevalent and debilitating symptom.[14,15] The ability of kratom to address pain, a common comorbid condition, may contribute to its overall effectiveness in improving mood.[16,17,18] However, while the analgesic properties of kratom are well-documented, their direct contribution to its antidepressant effects warrants further investigation.

Despite these promising findings, the use of kratom is not without concerns. The potential for dependency and the variability in alkaloid content across different batches of kratom pose significant challenges. These factors complicate its clinical use and necessitate standardized production practices to ensure consistent therapeutic outcomes.[19]

The results showed that diabetic rats treated with *Mitragynine* exhibited significantly reduced immobility time in the FST compared with diabetic control rats. This suggests that *Mitragynine* may exert antidepressant-like effects in diabetic rats, potentially reducing the comorbidity of depression in diabetes.[7] *Mitragynine's* mechanism of action includes modulation of opioid receptors, adrenergic receptors, and serotonin receptors, all of which are involved in the pathophysiology of depression.[8] Further research is needed to elucidate the precise mechanism through which *Mitragynine* exerts its antidepressant effects in diabetic rats.

In light of these results, kratom presents a potential natural alternative for treating depression in diabetic patients. However, extensive clinical trials are necessary to fully understand its mechanisms, therapeutic potential, and safety profile. Future research should focus on the pharmacokinetics, long-term effects, and optimal dosing of kratom to establish its efficacy and safety in clinical settings.[20]

Conclusion

These results indicate that *Mitragyna* has potential as an antidepressant agent in reducing depressive *symptoms* in rats models of diabetes mellitus. This suggests that *Mitragynine* potentially reducing the comorbidity of depression by mechanism modulation of opioid receptors, adrenergic receptors, and serotonin receptors, all of which are involved in the pathophysiology of depression.

Limitations and Further Research

However, the study's limitations include a lack of comparison with non-diabetic rats and other standard antidepressants, which could provide additional insights into the specific antidepressant effects of mitragynine in the context of diabetes. Future research should also address the long-term effects and safety profile of mitragynine, especially given the chronic nature of diabetes and depression. Further pharmacokinetic and pharmacodynamic studies are necessary to explore how mitragynine interacts with other common medications in diabetic populations, which is critical for its potential use as an adjunct therapy. Additionally, transitioning from animal models to human clinical trials is essential to validate these findings and consider any translational implications.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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