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The Investigation of Antidepressant and Anxiolytic Effects of *Euterpe oleracea* and Its Mechanisms of Action In Rats

Sıçanlarda Euterpe Oleracea'nın Antidepresan ve Anksiyolitik Etkilerinin ve Etki Mekanizmalarının Araştırılması

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ABSTRACT

Euterpe oleracea (EO) contains a wide variety of polyphenolic compounds, including phenolics, flavonoids, and anthocyanins, which exhibit strong antioxidant properties. EO has been proposed to alleviate oxidative stress and inflammation in brain cells. Since exposure to extreme environmental stressors-such as natural disasters, infectious disease outbreaks, and mass trauma- can trigger anxiety, depression, and cognitive decline, this study aimed to investigate the potential antidepressant and anxiolytic effects of EO. Sixty-four male Wistar albino rats (300–350 g) were randomly divided into eight groups: control, EO (30, 100, and 300 mg/kg), amitriptyline (20 mg/kg), fluoxetine (20 mg/kg), diazepam (5 mg/kg), and ketamine (5 mg/kg). All treatments were administered orally, and behavioral tests were conducted 1.5 hours after drug administration. Antidepressant-like activity was evaluated using the forced swimming test (FST), while anxiolytic-like effects were assessed through the elevated plus maze (EPM). Locomotor activity was also measured using an activity meter to rule out nonspecific motor effects. Statistical analysis was performed using the Kruskal–Wallis test, and $p < 0.05$ was considered statistically significant. All EO doses significantly reduced immobility time in the FST and time spent in closed arms in the EPM compared to the control group. The 100 mg/kg EO group showed effects similar and comparable to those of amitriptyline, ketamine, and diazepam. In contrast, fluoxetine showed no significant effects, possibly due to the limitations of acute administration. These findings suggest that EO, particularly at 100 mg/kg, may possess antidepressant and anxiolytic properties similar to standard pharmacological agents.

Keywords: Euterpe oleracea, anxiety, antidepression, locomotor activity, rat

ÖZET

Euterpe oleracea (EO), fenolikler, flavonoidler ve antosiyaninler dâhil olmak üzere geniş bir polifenolik bileşik yelpazesi içermekte olup, güçlü antioksidan özellikler göstermektedir. EO'nun beyin dokusunda oksidatif stresi ve nöroenflamasyonu azaltabileceği öne sürülmüştür. Doğal afetler, enfeksiyon salgınları ve toplu travmalar gibi aşırı çevresel stres etkenlerine maruz kalmanın anksiyete, depresyon ve bilişsel bozulmayı tetikleyebileceği göz önüne alındığında, bu çalışma EO'nun olası antidepresan ve anksiyolitik etkilerini araştırmayı amaçlamıştır.

Toplam 64 erkek Wistar albino sıçan (300–350 g), rastgele sekiz gruba ayrılmıştır: kontrol, EO (30, 100 ve 300 mg/kg), amitriptilin (20 mg/kg), fluoksetin (20 mg/kg), diazepam (5 mg/kg) ve ketamin (5 mg/kg). Tüm uygulamalar ağızdan yapılmış ve davranış testleri ilaç uygulamasından 1,5 saat sonra gerçekleştirilmiştir. Antidepresan benzeri aktivite zorunlu yüzme testi (FST) ile, anksiyolitik benzeri etkiler ise yükseltilmiş artı labirent testi (EPM) ile değerlendirilmiştir. Spesifik olmayan motor etkilerin dışlanması için lokomotor aktivite ayrıca aktivite ölçer ile analiz edilmiştir. İstatistiksel analizlerde Kruskal–Wallis testi kullanılmış ve $p < 0.05$ anlamlı kabul edilmiştir.

Tüm EO dozları, kontrol grubuna kıyasla FST'de hareketsizlik süresini ve EPM'de kapalı kollarda geçirilen süreyi anlamlı şekilde azaltmıştır. 100 mg/kg EO dozu, amitriptilin, ketamin ve diazepam ile karşılaştırılabilir düzeyde etkiler göstermiştir. Buna karşılık, fluoksetin akut uygulamanın sınırlılıkları nedeniyle anlamlı bir etki göstermemiştir. Bu bulgular, özellikle 100 mg/kg dozunda EO'nun, standart farmakolojik ajanlara benzer antidepresan ve anksiyolitik özelliklere sahip olabileceğini düşündürmektedir.

Anahtar kelimeler: Euterpe oleracea, anksiyete, antidepresif etki, lokomotor aktivite, sıçan

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Introduction

Euterpe oleracea (EO), commonly known as açaí, has attracted increasing scientific attention due to its potent antioxidant and anti-inflammatory properties. Depression is a complex psychiatric disorder that alters behavior and cognition, particularly in response to stress. Epidemiological studies suggest that individuals exposed to environmental stressors, such as heavy vehicular traffic, are at higher risk for developing depression, anxiety, and cognitive impairment [1]. According to the World Health Organization (2017), more than 300 million people are affected by depression worldwide, with an 18% increase in prevalence observed between 2005 and 2015. Anxiety and depression are among the most prevalent psychiatric disorders, particularly within the spectrum of stress-related conditions [2].

Currently, the pharmacological management of these disorders primarily involves monoamine oxidase inhibitors, benzodiazepines, selective serotonin reuptake inhibitors, and tricyclic antidepressants. Although effective in symptom relief, these agents are often associated with significant adverse effects, including sexual dysfunction, weight gain, and cardiovascular complications [3].

EO extract has been widely studied for its nutritional and phytochemical composition, which includes a variety of bioactive compounds such as flavonoids (31%), phenolic compounds (23%), lignoids (11%), and anthocyanins (9%) [4,5] . These constituents have demonstrated potent antioxidant and anti-inflammatory effects [6]. Preclinical studies have shown that EO extract can reduce oxidative stress and inflammation in brain cells [7] . Furthermore, polyphenolic flavonoids in EO have been reported to cross cellular membranes and attenuate intracellular oxidative damage linked to inflammatory processes [8]. These antioxidant properties are attributed to their capacity to scavenge free radicals and prevent oxidative cellular damage, thereby contributing to disease prevention [9]. The antioxidant and anti-inflammatory effects of EO have also been supported by studies conducted in human models [10].

Despite its well-established biological activity, the potential effects of EO extract on depressive and anxiety-like behaviors have not yet been investigated. Therefore, the present study aimed to evaluate the antidepressant- and anxiolytic-like effects of EO extract in rats, in comparison with standard pharmacological treatments.

Materials and Methods

Animals

Sixty-four (250 ± 25 g) male Wistar albino rats were used for this study. The rats were obtained from the Institutional Animal Care Facility (TICAM) in Eskişehir Osmangazi University. They were kept under ambient conditions at 22°C–24°C and a 12-h light–12-h dark cycle for 1 week before the experiment. Pellet diets (Rodent Diet CE-2, Turkey, Inc.) and tap water were given to the experimental animals ad libitum. The experiments were approved by the Animal Care Committees of Eskişehir Osmangazi University (Date: October 27th, 2016, no:102-552) .

Drugs and chemicals

E. oleracea was purchased from Mountain Fresh Herbal Capsules, Inc., (United Kingdom). Euterpe oleracea (EO) extract has been studied extensively as it has nutritional and phytochemical compositions. Chemically ~90 substances have been described, which approximately consists of flavonoids (31%), phenolic compounds (23%), lignoids (11%), and anthocyanins (9%). . It has been proved that these compounds have potent anti-inflammatory, cardioprotective, antitumoral, and antioxidant effects. Amitriptyline, Fluoxetine, Diazepam, Ketamine, and Xylazine were obtained from TICAM. All chemical substances were dissolved in 0.9% serum solutions.

Assessment of locomotor activity

Locomotor activity was assessed using automate apparatus (AMS 02 Animal Activity Monitoring system). Animals were placed individually in clear Perspex cages (40 cm × 40 cm × 40 cm), and the number of compliance transit cages was recorded for the subsequent 5-min period. The locomotor activity was calculated on the sixth day, 85 min after the drug was injected for all the experimental groups.

The stereotypic movements and distance were recorded. The results at the $P < 0.05$ level were accepted as statistically significant.

Forced swimming test (FST)

The forced swimming test that is used for assessing the antidepressant effect was performed as Porsolt and friends' described [11]. Two sessions were assessed 24 h apart. The first session was the pretest stage (15 min) and the second was the test stage (5 min). Rats were moved to the experimental environment for adaptation at least 30 min before the behavioral test. Water depth was adjusted according to the size of the rat. Cylinders filled with tap water at 23°C ± 1°C. Each rat was placed in a water filled cylinder container for 15 min. After 15 min were elapsed, we removed the rat from the container and placed it in the transient drying cage with a heat lamp and heat pad above and under it, respectively. The rat was closely and continuously monitored while recovering in the cage. We changed the water after every session to avoid any influence on the next rat. Twenty-four hours later, the rats were acclimatized for at least 30 min prior to the behavioral test.

The Forced Swim Test as a Model of Depressive-like Behavior which is one of the most commonly used assays for the study of depressive-like behavior in rodents [12]. The video camera was switched on and the rat was placed in the water filled cylinder container for 5 min in the same container as the previous day.

After 5 min had elapsed, we turned the camera off, removed the rat from the container, and placed it in the transient drying cage with the heat lamp and heat pad above and under it, respectively. The rat was closely and continuously monitored while recovering in the cage, and the water was changed after every session to avoid any influence on the next rat [13].

Elevated plus maze test (EPMT)

The elevated plus maze test that is used for assessing the anxiolytic effect was performed as Pellow and friends described in 1985 [14]. Rats were placed at the junction of the four arms of the maze, facing an open arm, and entries/duration in each arm were recorded by a video-tracking system and observer simultaneously for 5 min. Other ethological parameters (i.e., rears, head dips and stretched-attend postures) were also be observed. An increase in open arm activity (duration and/or entries) reflected antianxiety behavior. In our laboratory, rats were exposed to the plus maze on one occasion. Thus, the results were obtained in 5 min in each rat [15]. Before starting the behavioral test, a 1-week acclimation period was carried out. Rat elevated plus maze is made of medium-density fiberboard with a matte black acrylic surface and consists of four arms (two open without walls and two enclosed by 30-cm high walls) 50-cm long and 10-cm wide. Each arm of the maze is attached to sturdy plastic legs, such that it is elevated 50-cm off a base that it is on [16].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences program for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA). The results were statistically analyzed with the Kruskal–Wallis test and $p < 0.05$ was accepted as statistically significant. The 0.25-0.75(Q1-3) percentile and median values of the data were used. Data are given as "mean ± standard error of the mean." Pairwise comparison of single use of EO and combination use of was evaluated with Student's t test.

Results

All doses of EO significantly reduced the immobility time in forced swimming and time spent in closed arms in elevated plus maze tests, compared to the control. The effects of 100-mg/kg EO on these tests were similar to 20-mg/kg amitriptyline, 5-mg/kg ketamine, and 5-mg/kg ve diazepam. On the contrary, 20-mg/kg fluoxetine did not reduce the immobility time and time spent in closed arms compared to all groups, including the control group. The rats were anesthetized with xylazine (15 mg/kg) and ketamine (60 mg/kg). Antidepressant effect was evaluated with immobility the time data results. In comparison with the control group, EO 100, fluoxetine, amitriptyline, and ketamine have shown an antidepressant effect. However, while it was observed in amitripty-

line and ketamine, no anxiolytic effect was observed in fluoxetine and diazepam doses. This result shows that, as an SSRI reuptake inhibitor, the fluoxetine acute effect was on its natural impact. We think that the result we see for diazepam is different according to the type, weight, breed, and experiment season of the experimental animal.

Comparing total movement with the control group and all groups of EO, we observed that there are no differences notable for all doses of E. oleracea in the locomotor activity test (Fig.1). When we evaluated the total movement for the control group, EO 100, amitriptyline, fluoxetine, ketamine, diazepam, EO100+ amitriptyline, EO100+ fluoxetine, EO100+ diazepam, and EO100+ ketamine. Results at $p< 0.01$, compared to control, were considered statistically significant (Fig. 2). There were no statistically significant differences between the control, EO 100, amitriptyline, fluoxetine, ketamine, diazepam, EO100+ amitriptyline, EO100+ fluoxetine, and EO100+ ketamine ($p> 0.05$) (Fig. 2). According to the assessments of the FST between control, EO 30, EO 100, and EO 300 groups, the antidepressant effects of all doses EO in FST; EO100 shows that $p< 0.001$ compared to the control group (Fig. 3).

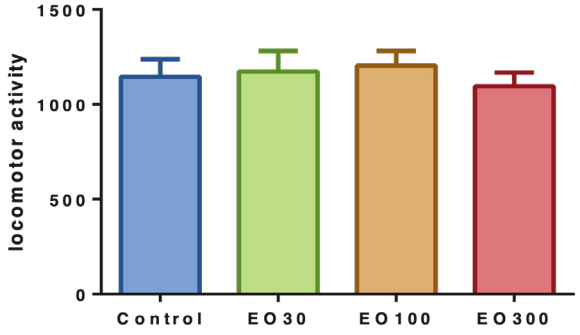


Figure 1. Total movement of all doses of EO and control group were comparable in locomotor activity test. EO: Euterpe oleracea.

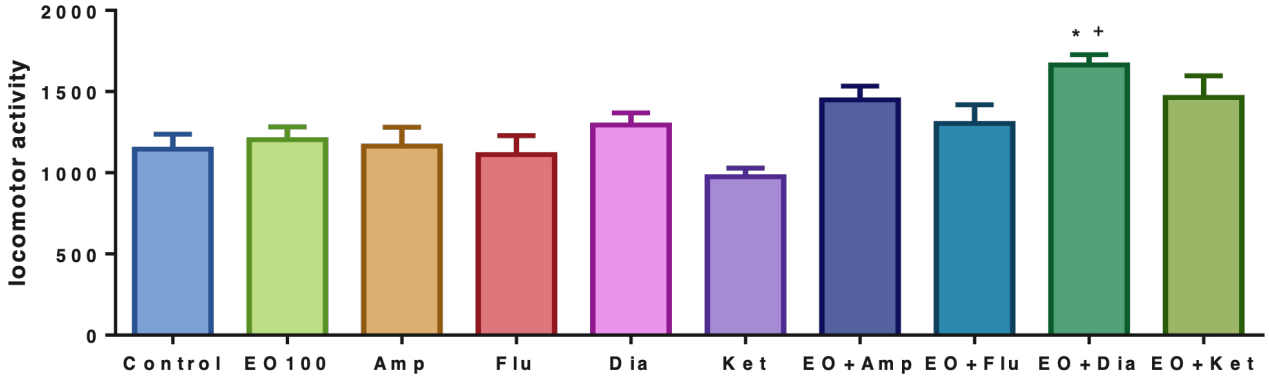


Figure 2. Total movement of EO 100 mg/kg, other groups and combinations of EO 100 mg/kg dose in locomotor activity test. ** p< 0.01 compared to control. EO: Euterpe oleracea, AMP: Amitriptyline, FLU: Fluoxetine, KET: Ketamine, DZP: Diazepam.

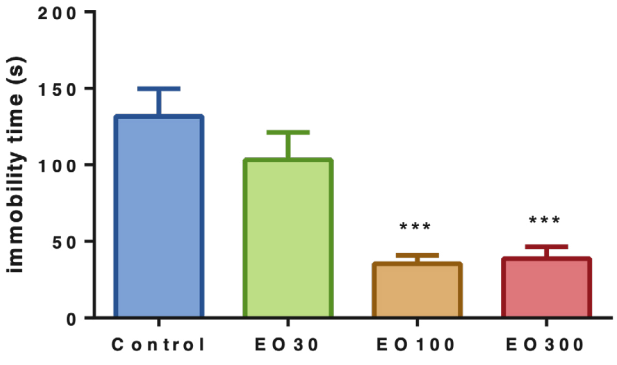


Figure 3. The antidepressant effects of all doses EO in forced swimming test *** p< 0.001 compared to control EO: Euterpe oleracea.

Comparing EO100 and other groups in the FST for the antidepressant effects, the results show that ketamine $p< 0.01$, amitriptyline $p< 0.001$, and EO100 have $p< 0.0001$. Compared to the control group, diaz-

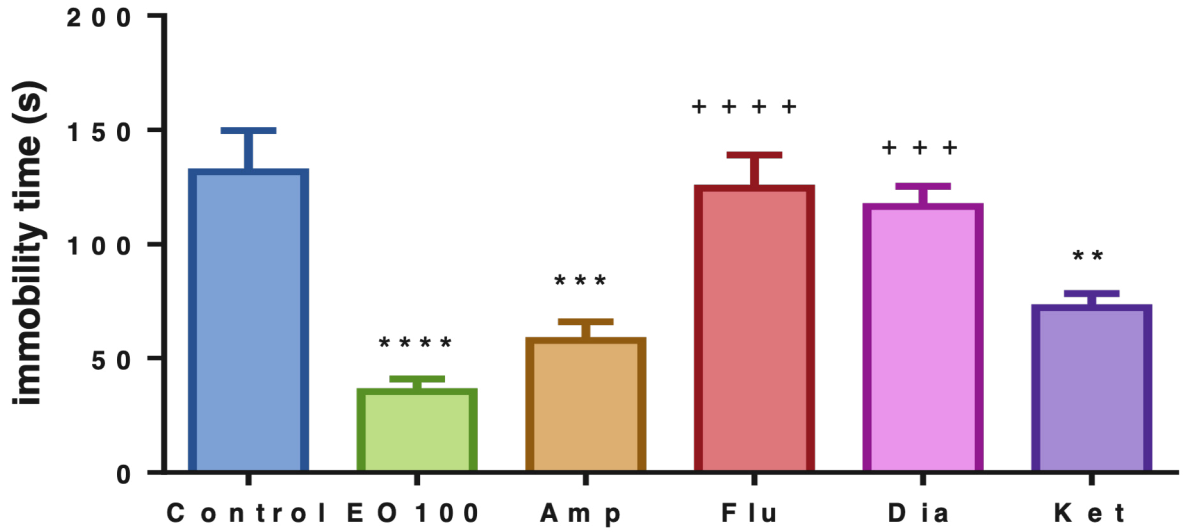


Figure 4. The antidepressant effects of EO100 and others groups in force swimming test. **p< 0.01, *** p< 0.001, **** p< 0.0001 compared to control, +++ p< 0.001, ++++ p< 0.0001 compared to EO100 mg/kg. EO: Euterpe oleracea, AMP: Amitriptyline, FLU: Fluoxetine, KET: Ketamine, DZP: Diazepam.

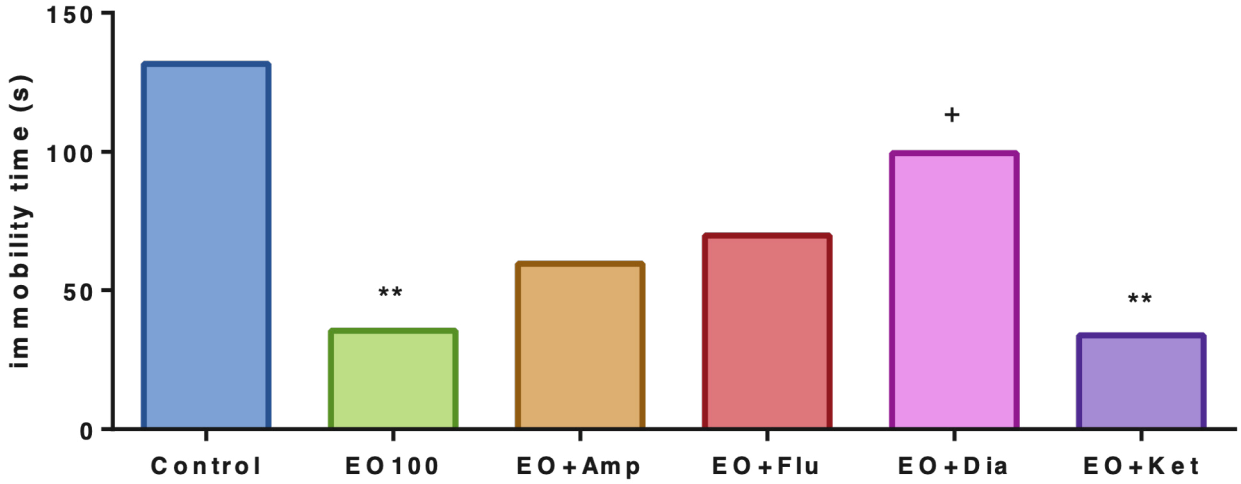


Figure 5. Antidepressant effects of combinations of EO 100 mg/kg and EO 100 mg/kg dose in force swimming test. ** p< 0.01 compared to control. + p< 0.05 compared to EO 100 mg/kg. EO: Euterpe oleracea, AMP: Amitriptyline, FLU: Fluoxetine, KET: Ketamin, DZP: Diazepam.

epam $p < 0.001$, and fluoxetine $p < 0.0001$ compared to EO100 mg/kg. Hence, EO is significantly reduced immobility time in forced swimming compared with both control and other antidepressant drugs (Fig. 4). When we evaluated the antidepressant effects of following combinations, we compared between EO 100 mg/kg and EO 100 mg/kg + ketamine $p < 0.01$ compared to control, EO 100 mg/kg + diazepam $p < 0.05$, compared to EO 100 mg/kg dose in force swimming test. However, while it was observed in amitriptyline and ketamine, no anxiolitic effect was observed in fluoxetine and diazepam doses. This result shows that, as an SSRI reuptake inhibitor, the fluoxetine acute effect was on the natural impact. We believe that the result we see for diazepam differs based on the type, weight, breed, and experiment season of the experimental animal. When we evaluated the antidepressant effects of combinations EO 100 mg/

kg and EO 100 mg/kg + ketamine $p < 0.01$ compared to control, EO 100 mg/kg+ diazepam $p < 0.05$, compared to EO 100 mg/kg (Fig 5) dose in force swimming test. When we evaluated the combinations, the antidepressant effect of amitriptyline disappeared in combination with EO100. When fluoxetine and diazepam were used together with EO 100, a significant effect was observed in terms of antidepressant effect (Fig. 4–5). In combination with ketamine and EO 100, in terms of the antidepressant effect, the effect did not change compared to individual use and can be used together (Fig. 4–5).

Based on the time spent in closed arms in EPMTs compared to control, the anxiolytic effects of all doses EO in the EPMT. The results show that EO 30 and EO 100 $p < 0.001$ compared to control (Fig. 6). The anxiolytic effects of EO 100 mg/kg and other groups in EPMT. Amitriptyline $p < 0.05$, diazepam $p < 0.01$, EO 100 mg/kg $p < 0.0001$ were compared to control, and ketamine and fluoxetine $p < 0.001$ were compared to EO 100 mg/kg (Fig. 7). The anxiolytic effects of combinations of EO 100 mg/kg dose in elevated plus maze test. Even though EO100, amitriptyline, and diazepam's anxiolytic effects were observed compared to the control group, we did not observe an anxiolytic effect based on the fluoxetine and ketamine doses (Fig 7). However, when we compare the EO100 with all of drugs, it has a stronger effect than other drugs known to have anxiolytics effect. Comparing EO 100 mg/kg and EO100 mg/kg + amitriptyline $p < 0.001$ to the control group, the effects of 100-mg/kg EO on these tests were similar to amitriptyline 20 mg/kg, ketamine 5 mg/kg, and diazepam 5 mg/kg. Particularly, when we compare the amitriptyline combinations' anxiolytics effect with the control group, combined with EO 100, it appears further strengthened to the amitriptyline alone effect (Fig. 7–8). However, despite the anxiolitic effect of diazepam and anxiolitic effect of EO100 when used alone, it was eliminated in the EO 100 combination with diazepam in the study. Therefore, when two anxiolitics are used together, they eliminate each other's effect. This is also an important finding in terms of drug–nutrient interactions. Conversely, fluoxetine 20 mg/kg did not reduce immobility time and time spent in closed arms compared to all groups, including the control group. No difference was noted in the anxiolitic effect of fluoxetine and ketamine in combination with EO 100. Although it is a finding that a relative anxiolytic effect can be seen in the combination of EO100 and fluoxetine, it was not statistically significant. The same situation has been observed with the use of ketamine alone and EO + ketamine use (Fig 7–8).

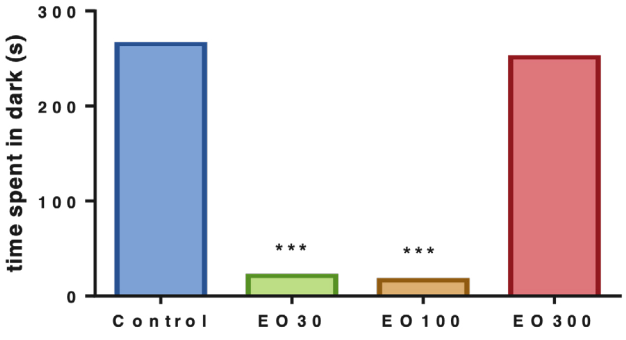


Figure 6. Anxiolytic effects of all doses EO in elevated plus maze test. *** $p < 0.001$ compared to control. EO: Euterpe oleracea.

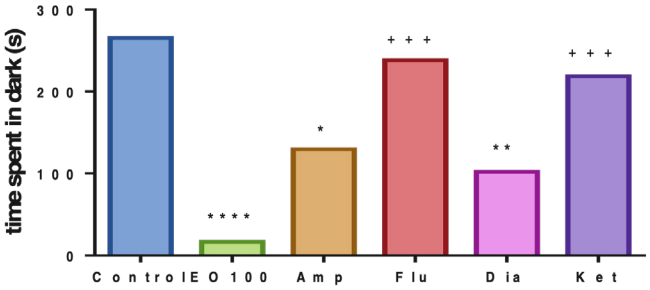


Figure 7. Anxiolytic effects of EO 100 mg/kg and other groups in elevated plus maze test. *$p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$ compared to control, +++ $p < 0.001$ compared to EO 100 mg/kg. EO: Euterpe oleracea, AMP: Amitriptyline, FLU: Fluoxetine, KET: Ketamine, DZP: Diazepam.

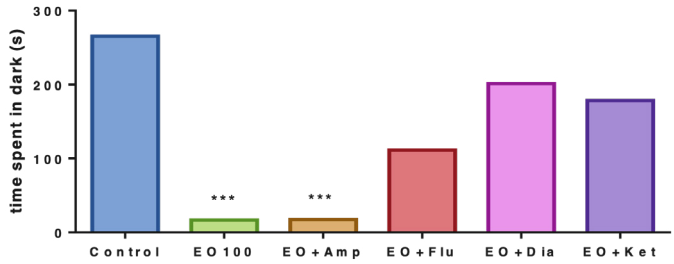


Figure 8. Anxiolytic effects of combinations of EO 100 mg/kg dose in elevated plus maze test. *** p< 0.001 compared to control. EO: Euterpe oleracea, Amp:, FLU: Fluoxetine, KET: Ketamine, DZP: Diazepam.

Discussion

Evaluation of the Effects of E. Oleracea and Antidepressants

This study investigated the anxiolytic and antidepressant-like effects of EO in stressed rats, using both behavioral and biochemical approaches. Our results demonstrated that EO exhibited significant anxiolytic effects, as assessed by the Elevated Plus Maze Test (EPMT), and antidepressant effects, as determined by the Forced Swim Test (FST). The EPMT is a valid tool for screening anxiolytic drugs in animal models, while the FST is commonly employed to evaluate the efficacy of various antidepressant treatments in rodents [14]. It has been well documented that individuals residing and working in areas with high vehicle traffic are more susceptible to developing anxiety, depression, and cognitive impairments [17].

The relationship between oxidative stress and depression has gained significant attention in recent research, particularly regarding the mechanisms through which antidepressants exert their effects. Antioxidants play a crucial role in reducing oxidative stress, which is often elevated in individuals suffering from major depressive disorder (MDD). This synthesis aims to explore the antioxidant mechanisms associated with various antidepressants and their implications for treatment efficacy.

Antioxidants counteract oxidative stress by neutralizing reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidant enzymes. For example, studies have demonstrated that antidepressants such as fluoxetine significantly increase serum antioxidant enzyme activities in the brain, potentially contributing to their antidepressant effects [18]. Moreover, hydrogen sulfide (H_2S) has been identified as a potent antioxidant capable of scavenging oxidants and reactive aldehydes, exhibiting antidepressant- and anxiolytic-like effects in diabetic rat models by reducing oxidative stress in the hippocampus [19,20]. This suggests that the enhancement of antioxidant defenses is a critical mechanism through which certain antidepressants function.

Additionally, the antioxidant properties of specific compounds have been linked to their antidepressant effects. For instance, the aqueous extract of Albizia adianthifolia has shown potential in alleviating anxiety and depression while reducing oxidative stress markers such as malondialdehyde (MDA) in the amygdala [21]. Similarly, flavonoids, including quercetin, have been reported to exert neuroprotective effects through their antioxidant and anti-inflammatory properties, which may alleviate depressive symptoms [22,23]. The role of antioxidants in the pathophysiology of depression is further supported by findings indicating that decreased antioxidant status correlates with elevated oxidative stress markers in depressed individuals [24].

Clinical evidence also supports the notion that antioxidant treatments can enhance the efficacy of traditional antidepressants. For instance, adjunctive therapies using antioxidants like N-acetylcysteine (NAC) have shown promising results in improving treatment outcomes for patients with bipolar disorder and major depressive disorder [25]. Given the significant role of oxidative stress in the neurobiological mechanisms underlying mood disorders, restoring antioxidant capacity could represent a viable therapeutic strategy [26]. In this context, the efficacy of EO in treating depression and anxiety was assessed in this study. Depression affects over 300 million individuals globally [1], and clinical and epidemiological studies suggest a high comorbidity between depression and anxiety. According to the World Health Organization (2012) more than 75% of individuals with depressive disorders also suffer from anxiety disorders. Several studies indicate that

oxidative stress is implicated in a variety of mental disorders, including depression, anxiety disorders, schizophrenia, and bipolar disorder [27].

In this study, we observed significant changes in the total movement of the control group, EO100, amitriptyline, fluoxetine, ketamine, diazepam, EO100 + amitriptyline, EO100 + fluoxetine, EO100 + diazepam, and EO100 + ketamine groups. Specifically, EO100 demonstrated decreased immobility time and increased struggling time, indicating an acute antidepressant effect. When comparing EO100 with the other groups in the FST, the results showed that ketamine ($p< 0.01$), amitriptyline ($p< 0.001$), EO100 ($p< 0.0001$), diazepam ($p< 0.001$), and fluoxetine ($p< 0.0001$) all showed significant effects compared to the control. Notably, EO100 significantly reduced immobility time compared to both the control and other antidepressant drugs (Fig. 4).

Further evaluation of the antidepressant effects of combinations of EO100 (100 mg/kg) with other treatments (e.g., amitriptyline, fluoxetine, ketamine, and diazepam) indicated that EO100 combined with ketamine or diazepam showed a significant reduction in immobility time compared to the control, with EO100 + ketamine ($p< 0.01$) and EO100 + diazepam ($p< 0.05$) showing the most significant changes. However, no anxiolytic effect was observed with fluoxetine or diazepam, suggesting that fluoxetine's effects are primarily related to its selective serotonin reuptake inhibition (SSRI) mechanism. Differences in responses to diazepam may be attributed to factors such as the animal's type, weight, breed, and experimental conditions.

Additionally, the antidepressant effect of amitriptyline was diminished when combined with EO100. In contrast, combinations of EO100 with fluoxetine or diazepam led to significant antidepressant effects (Fig. 4-5). When combined with ketamine, EO100 did not exhibit any enhanced effect compared to its individual use, suggesting that these treatments can be used together without altering the overall antidepressant outcome.

Amitriptyline, a tricyclic antidepressant widely used for over fifty years, not only treats depression but also relieves chronic pain, including diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and migraine. Its mechanism of action involves inhibiting the reuptake of neurotransmitters such as serotonin and norepinephrine, thereby increasing their availability in the synaptic cleft and enhancing mood regulation and other physiological processes [28]. Despite its long half-life, which allows for convenient once-daily dosing, amitriptyline's efficacy extends beyond its antidepressant effects, making it valuable for patients with comorbid conditions [29]. Although generally well-tolerated, it is important to monitor specific patient populations, such as the elderly, pregnant women, and those with cardiac or neurological conditions, for potential adverse effects.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is renowned for its role in treating depression and anxiety disorders. It primarily increases synaptic serotonin levels, facilitating enhanced communication in brain regions crucial for emotional regulation and memory processing, such as the hippocampus [30]. Chronic fluoxetine treatment can lead to significant neuroadaptive changes, which contribute to its therapeutic effects [30]. Fluoxetine is commonly used to treat major depressive disorder, obsessive-compulsive disorder, bulimia nervosa, and panic disorder [31]. Additionally, fluoxetine has been shown to enhance neurogenesis in the hippocampus, further supporting its antidepressant effects [32,33].

Ketamine, an NMDA receptor antagonist, has garnered attention for its rapid antidepressant and anxiolytic effects, especially in treatment-resistant depression [34]. Unlike traditional antidepressants that target the monoaminergic system, ketamine works through the glutamatergic system, offering rapid relief for some individuals who do not respond to conventional treatments [35].

Evaluation of the Effects of EO and Anxiolytics

When comparing EO100 to other known anxiolytic drugs, it demonstrated a stronger effect. Specifically, the effects of 100 mg/kg EO100 were comparable to those of amitriptyline (20 mg/kg), ketamine (5

mg/kg), and diazepam (5 mg/kg). Furthermore, when combining EO100 (100 mg/kg) with amitriptyline, the effect was significantly enhanced compared to amitriptyline alone ($p< 0.001$), as observed in the control group (Fig. 7–8). Research suggests that amitriptyline's influence on neurotransmitters such as serotonin and norepinephrine plays a key role in its anxiolytic effects. One study found a correlation between monoamine oxidase inhibition by amitriptyline and improvements in somatization, psychological, and panic-phobic anxiety symptoms, though no correlation was found with improvements in depression [36]. Other studies have examined amitriptyline's effects on anxiety in animal models [37], but further research is necessary to fully understand its impact on various anxiety disorders in humans.

It is important to note that amitriptyline may have side effects, and its use should be carefully monitored by a healthcare professional. In younger individuals (under 24 years old), there is an increased risk of suicidal thoughts and behaviors, necessitating close supervision [38]. Despite its anxiolytic effects, the combination of EO100 and diazepam in this study resulted in the elimination of the anxiolytic effect, highlighting the potential interaction between these drugs. Diazepam, a benzodiazepine commonly used to treat anxiety, muscle spasms, and seizures, works by enhancing the effects of GABA, a neurotransmitter that inhibits brain activity, leading to a calming effect [39]. However, benzodiazepines like diazepam, while effective in treating panic disorders, may not be suitable for everyone, particularly those with certain medical conditions. It is crucial to consult a healthcare provider before using diazepam, especially if you have pre-existing health concerns.

The study found that when two anxiolytic drugs were used together, their effects were diminished, an important consideration for drug-nutrient interactions. Conversely, fluoxetine (20 mg/kg) did not reduce immobility time or the time spent in closed arms compared to the control group, nor did it show significant changes when combined with EO100 or ketamine. While a relative anxiolytic effect was observed with the combination of EO100 and fluoxetine, it was not statistically significant. Notably, acute administration of fluoxetine can paradoxically induce anxiety-like behaviors, as evidenced by studies demonstrating increased anxiety in animal models following short-term treatment [40]. This duality highlights the importance of treatment duration and dosage in determining the drug's effects on anxiety. Moreover, fluoxetine's impact on neuroplasticity could increase anxiety in certain contexts, particularly if it disrupts the integration of anxiety and aversive memories [41]. The complex interplay between fluoxetine's effects on neuroplasticity and anxiety is further influenced by genetic factors and the specific anxiety model employed in research [42].

Similarly, the effects of ketamine, both when used alone and in combination with EO100, did not significantly alter immobility time or time spent in closed arms (Fig. 7–8). Ketamine, a well-known NMDA receptor antagonist, has shown rapid, albeit transient, improvements in mood and anxiety symptoms. Ongoing research is exploring optimal dosing strategies and routes of administration to maintain therapeutic benefits in the long term [34]. However, ketamine's potential side effects, including dissociation, hallucinations, and changes in blood pressure and heart rate, should be considered [43]. Ketamine's blockade of NMDA receptors increases glutamate release, which activates AMPA receptors and promotes the release of brain-derived neurotrophic factor (BDNF), a protein associated with synaptic function and resilience to stress, thereby contributing to its anxiolytic effects [44,45]. Additionally, ketamine's influence on the locus coeruleus, a key area regulating arousal and stress responses, further elucidates its potential to mitigate anxiety [46].

Antioxidants play a crucial role in mitigating oxidative stress, a contributing factor in various neuropsychiatric disorders, including anxiety. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, leading to cellular damage and dysfunction. This imbalance has been linked to the pathophysiology of anxiety disorders, particularly in regions of the brain such as the amygdala and

prefrontal cortex, which are vital for emotional regulation [47]. The administration of antioxidants has been shown to reduce oxidative stress markers, such as malondialdehyde (MDA), and alleviate anxiety-like behaviors in animal models. For instance, Adiantum capillus-veneris extract was found to decrease MDA levels and enhance antioxidant capacity, correlating with a reduction in anxiety behaviors [48].

Moreover, specific antioxidants have demonstrated anxiolytic properties. St. John's Wort, for example, has been reported to significantly attenuate lipid peroxidation and restore glutathione levels, suggesting its potential as an effective antioxidant for alleviating anxiety symptoms [49]. Similarly, Piper sylvaticum has been evaluated for its anxiolytic and antioxidant activities, showing promising results in reducing anxiety-like behaviors in both in vivo and in vitro studies [50]. These findings underscore the therapeutic potential of natural antioxidants in managing anxiety disorders.

The mechanisms by which antioxidants exert their effects on anxiety typically involve modulation of key signaling pathways. For instance, melatonin, a well-known antioxidant, has been shown to protect neurons from oxidative stress-induced damage, which can contribute to anxiety and depression [51]. Additionally, phosphodiesterase 2 inhibitors, which possess antioxidant and anti-apoptotic properties, have been linked to improvements in anxiety-like behaviors, suggesting that enhancing antioxidant defenses in the brain can have significant therapeutic implications for anxiety treatment [52]. Antioxidants also play a role in restoring the balance of neurotransmitter systems, such as gamma-aminobutyric acid (GABA), which is essential for regulating anxiety [53].

In conclusion, antioxidants play a pivotal role in ameliorating anxiety symptoms through various mechanisms. By reducing ROS levels, enhancing antioxidant enzyme activity, and restoring neurochemical balance, antioxidants represent a promising avenue for the development of novel anxiolytic therapies.

Conclusions

In this study, we propose that Euterpe oleracea (EO), particularly at a dose of 100 mg/kg, exhibits both antidepressant and anxiolytic effects, comparable to the reference antidepressant and anxiolytic drugs used. However, the ineffectiveness of fluoxetine (FLU) on depression and anxiety tests may be attributed to its acute administration. When combining drugs with nutritional supplements, some drug effects may be potentiated, while others may be inhibited. Specifically, EO100 appears to neutralize the effects of amitriptyline (AMP), suggesting that these should not be used together for the treatment of depression. Although not statistically significant, the combination of EO100, FLU, and diazepam (DZP) showed some joint effects on depression, albeit with no clear enhancement.

Regarding the antidepressant effects of EO100 in combination with ketamine (KET), no significant changes were observed, indicating that this combination can be used safely without altering the antidepressant effect. On the other hand, combining EO with AMP enhanced AMP's anxiolytic effect, whereas the combination of EO and diazepam reduced diazepam's anxiolytic effect. Therefore, EO should not be used with diazepam, as this combination negates its effects.

Although the combination of EO and FLU reduced FLU's efficacy, this effect was not statistically significant. EO did not significantly alter the anxiolytic effect of ketamine, and no changes in efficacy were observed. The use of EO in combination with selective serotonin reuptake inhibitors (SSRIs) like FLU and NMDA antagonists such as KET appears to be safe, without significant drug–nutrient interactions. EO itself is anxiolytic and can enhance the effect of melatonin (MT).

In terms of antidepressant and anxiolytic effects, KET and EO can be used either individually or in combination with similar outcomes, with no increase or decrease in effect. There are no issues with combining EO with FLU or diazepam in terms of antidepressant effects. However, in terms of anxiolytic effects, the combination of diazepam and EO leads to the loss of diazepam's effectiveness due to a drug–nutrient interaction.

The following abbreviations are used in this manuscript:

Abbreviations

SSRI	Selective Serotonin Reuptake Inhibition
ROS	Reactive Oxygen Species
GABA	Gamma-Aminobutyric Acid
EPM	Elevated Plus Maze
EPMT	Elevated Plus Maze Test
FST	Forced Swimming Test
EO	Euterpe oleracea
AMP	Amitriptyline
KET	Ketamine
DZP	Diazepam
FLU	Fluoxetine
MT	Melatonin
MDA	Malondialdehyde
NAC	N-acetylcysteine

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References

1. Donkelaar, A. van; Martin, R.V.; Brauer, M.; Boys, B.L. Use of Satellite Observations for Long-Term Exposure Assessment of Global Concentrations of Fine Particulate Matter. Environ. Heal. Perspect. 2015, 123, 135–143, doi:10.1289/ehp.1408646.

2. Whiteford, H.A.; Harris, M.G.; McKeon, G.; Baxter, A.; Pennell, C.; Barendregt, J.J.; Wang, J. Estimating Remission from Untreated Major Depression: A Systematic Review and Meta-Analysis. Psychol. Med. 2013, 43, 1569–1585, doi:10.1017/s0033291712001717.

3. Masand, P.S.; Gupta, S.; Schwartz, T.L.; Virk, S.; Lockwood, K.; Hameed, A.; King, M.; Kaplan, D.S. Paroxetine in Patients With Irritable Bowel Syndrome: A Pilot Open-Label Study. Prim. Care Companion CNS Disord. 2002, 4, 12–16, doi:10.4088/pcc.v04n0105.

4. Yamaguchi, K.K. de L.; Pereira, L.F.R.; Lamarão, C.V.; Lima, E.S.; Veiga-Junior, V.F. da Amazon Acai: Chemistry and Biological Activities: A Review. Food Chem. 2015, 179, 137–151, doi:10.1016/j.foodchem.2015.01.055.

5. Costa, C.A. da; Ognibene, D.T.; Cordeiro, V.S.C.; Bem, G.F. de; Santos, I.B.; Soares, R.A.; Cunha, L.L. de M.; Carvalho, L.C.R.M.; Moura, R.S. de; Resende, A.C. Effect of Euterpe Oleracea Mart. Seeds Extract on Chronic Ischemic Renal Injury in Renovascular Hypertensive Rats. J. Med. Food 2017, 20, 1002–1010, doi:10.1089/jmf.2017.0011.

6. Jensen, G.S.; Wu, X.; Patterson, K.M.; Barnes, J.; Carter, S.G.; Scherwitz, L.; Beaman, R.; Endres, J.R.; Schauss, A.G. In Vitro and in Vivo Antioxidant and Anti-Inflammatory Capacities of an Antioxidant-Rich Fruit and Berry Juice Blend. Results of a Pilot and Randomized, Double-Blinded, Placebo-Controlled, Crossover Study. J. Agric. Food Chem. 2008, 56, 8326–8333, doi:10.1021/jf8016157.

7. Wong, D.Y.S.; Musgrave, I.F.; Harvey, B.S.; Smid, S.D. Açaí (Euterpe Oleraceae Mart.) Berry Extract Exerts Neuroprotective Effects against β-Amyloid Exposure in Vitro. Neurosci. Lett. 2013, 556, 221–226, doi:10.1016/j.neulet.2013.10.027.

8. Schauss, A.G.; Wu, X.; Prior, R.L.; Ou, B.; Huang, D.; Owens, J.; Agarwal, A.; Jensen, G.S.; Hart, A.N.; Shanbrom, E. Antioxidant Capacity and Other Bioactivities of the Freeze-Dried Amazonian Palm Berry, Euterpe Oleraceae Mart. (Acai). J. Agric. Food Chem. 2006, 54, 8604–8610, doi:10.1021/jf0609779.

9. Wani, S.; Kumar, P. Antioxidants and Its Properties as Affected by Extrusion Process: A Review. Recent Pat. Food, Nutr. Agric. 2015, 7, 108–114, doi:10.2174/2212798407666150708111213.

10. Schauss, A.G. Bioactive Foods in Promoting Health. Sect. C: Actions Individ. Fruits Dis. Cancer Prev. Treat. 2010, 479–490, doi:10.1016/b978-0-12-374628-3.00032-3.

11. Porsolt, R.D.; Anton, G.; Blavet, N.; Jalfre, M. Behavioural Despair in Rats: A New Model Sensitive to Antidepressant Treatments. Eur. J. Pharmacol. 1978, 47, 379–391, doi:10.1016/0014-2999(78)90118-8.

12. Yankelevitch-Yahav, R.; Franko, M.; Huly, A.; Doron, R. The Forced Swim Test as a Model of Depressive-like Behavior. J. Vis. Exp. 2015, doi:10.3791/52587.

13. Mezadri, T.J.; Batista, G.M.; Portes, A.C.; Marino-Neto, J.; Lino-de-Oliveira, C. Repeated Rat-Forced Swim Test: Reducing the Number of Animals to Evaluate Gradual Effects of Antidepressants. J. Neurosci. Methods 2011, 195, 200–205, doi:10.1016/j.jneumeth.2010.12.015.

14. Pellow, S.; Chopin, P.; File, S.E.; Briley, M. Validation of Open : Closed Arm Entries in an Elevated plus-Maze as a Measure of Anxiety in the Rat. J. Neurosci. Methods 1985, 14, 149–167, doi:10.1016/0165-0270(85)90031-7.

15. Walf, A.A.; Frye, C.A. The Use of the Elevated plus Maze as an Assay of Anxiety-Related Behavior in Rodents. Nat. Protoc. 2007, 2, 322–328, doi:10.1038/nprot.2007.44.

16. Hiramatsu, M.; Mizuno, N.; Kanematsu, K. Pharmacological Characterization of the Ameliorating Effect on Learning and Memory Impairment and Antinociceptive Effect of KT-95 in Mice. Behav. Brain Res. 2006, 167, 219–225, doi:10.1016/j.bbr.2005.09.009.

17. PORSOLT, R.D.; PICHON, M.L.; JALFRE, M. Depression: A New Animal Model Sensitive to Antidepressant Treatments. Nature 1977, 266, 730–732, doi:10.1038/266730a0.

18. Behr, G.A.; Moreira, J.C.F.; Frey, B.N. Preclinical and Clinical Evidence of Antioxidant Effects of Antidepressant Agents: Implications for the Pathophysiology of Major Depressive Disorder. Oxidative Med. Cell. Longev. 2012, 2012, 609421, doi:10.1155/2012/609421.

19. Tang, Z.-J.; Zou, W.; Yuan, J.; Zhang, P.; Tian, Y.; Xiao, Z.-F.; Li, M.-H.; Wei, H.-J.; Tang, X.-Q. Antidepressant-like and Anxiolytic-like Effects of Hydrogen Sulfide in Streptozotocin-Induced Diabetic Rats through In-

hibition of Hippocampal Oxidative Stress. Behav. Pharmacol. 2015, 26, 427–435, doi:10.1097/fbp.0000000000000143.

20. Réus, G.Z.; Santos, M.A.B. dos; Abelaira, H.M.; Titus, S.E.; Carlessi, A.S.; Matias, B.I.; Bruchchen, L.; Florentino, D.; Vieira, A.; Petronilho, F.; et al. Antioxidant Treatment Ameliorates Experimental Diabetes-induced Depressive-like Behaviour and Reduces Oxidative Stress in Brain and Pancreas. DiabetesMetab. Res. Rev. 2016, 32, 278–288, doi:10.1002/dmrr.2732.
21. Beppe, G.J.; Dongmo, A.B.; Foyet, H.S.; Dimo, T.; Mihasan, M.; Hritcu, L. The Aqueous Extract of Albizia Adianthifolia Leaves Attenuates 6-Hydroxydopamine-Induced Anxiety, Depression and Oxidative Stress in Rat Amygdala. BMC Complement. Altern. Med. 2015, 15, 374, doi:10.1186/s12906-015-0912-0.
22. Zhu, H.; Du, Z.; Lu, R.; Zhou, Q.; Shen, Y.; Jiang, Y. Investigating the Mechanism of Chufan Yishen Formula in Treating Depression through Network Pharmacology and Experimental Verification. ACS Omega 2024, 9, 12698–12710, doi:10.1021/acsomega.3c08350.
23. Yuan, N.; Gong, L.; Tang, K.; He, L.; Hao, W.; Li, X.; Ma, Q.; Chen, J. An Integrated Pharmacology-Based Analysis for Antidepressant Mechanism of Chinese Herbal Formula Xiao-Yao-San. Front. Pharmacol. 2020, 11, 284, doi:10.3389/fphar.2020.00284.
24. Amini-Khoei, H.; Boroujeni, S.N.; Maghsoudi, F.; Rahimi-Madiseh, M.; Bijad, E.; Moradi, M.; Lorigooini, Z. Possible Involvement of L-Arginine-Nitric Oxide Pathway in the Antidepressant Activity of Auraptene in Mice. Behav. Brain Funct. 2022, 18, 4, doi:10.1186/s12993-022-00189-1.
25. Jiménez-Fernández, S.; Gurpegui, M.; Garrote-Rojas, D.; Gutiérrez-Rojas, L.; Carretero, M.D.; Correll, C.U. Oxidative Stress Parameters and Antioxidants in Patients with Bipolar Disorder: Results from a Meta-analysis Comparing Patients, Including Stratification by Polarity and Euthymic Status, with Healthy Controls. Bipolar Disord. 2021, 23, 117–129, doi:10.1111/bdi.12980.
26. Ji, N.; Lei, M.; Chen, Y.; Tian, S.; Li, C.; Zhang, B. How Oxidative Stress Induces Depression? ASN Neuro 2023, 15, 17590914231181036, doi:10.1177/17590914231181037.
27. Keren, H.; O'Callaghan, G.; Vidal-Ribas, P.; Buzzell, G.A.; Brotman, M.A.; Leibenluft, E.; Pan, P.M.; Meffert, L.; Kaiser, A.; Wolke, S.; et al. Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across FMRI and EEG Studies. Am. J. Psychiatry 2018, 175, 1111–1120, doi:10.1176/appi.ajp.2018.17101124.
28. Lawson, K. A Brief Review of the Pharmacology of Amitriptyline and Clinical Outcomes in Treating Fibromyalgia. Biomedicines 2017, 5, 24, doi:10.3390/biomedicines5020024.
29. Schneider, J.; Patterson, M.; Jimenez, X.F. Beyond Depression: Other Uses for Tricyclic Antidepressants. Clevel. Clin. J. Med. 2019, 86, 807–814, doi:10.3949/ccjm.86a.19005.
30. Kobayashi, K.; Ikeda, Y.; Sakai, A.; Yamasaki, N.; Haneda, E.; Miyakawa, T.; Suzuki, H. Reversal of Hippocampal Neuronal Maturation by Serotonergic Antidepressants. Proc. Natl. Acad. Sci. 2010, 107, 8434–8439, doi:10.1073/pnas.0912690107.
31. Bugiardini, R.; Merz, C.N.B. Angina With "Normal" Coronary Arteries: A Changing Philosophy. JAMA 2005, 293, 477–484, doi:10.1001/jama.293.4.477.
32. Khodanovich, M.; Kisel, A.; Kudabaeva, M.; Chernysheva, G.; Smolyakova, V.; Krutenkova, E.; Wasserlauf, I.; Plotnikov, M.; Yarnykh, V. Effects of Fluoxetine on Hippocampal Neurogenesis and Neuroprotection in the Model of Global Cerebral Ischemia in Rats. Int. J. Mol. Sci. 2018, 19, 162, doi:10.3390/ijms19010162.
33. Glynn, L.M.; Davis, E.P.; Sandman, C.A.; Goldberg, W.A. Gestational Hormone Profiles Predict Human Maternal Behavior at 1-Year Postpartum. Horm. Behav. 2016, 85, 19–25, doi:10.1016/j.yhbeh.2016.07.002.
34. Mathew, S.J.; Shah, A.; Lapidus, K.; Clark, C.; Jarun, N.; Ostermeyer, B.; Murrough, J.W. Ketamine for Treatment-Resistant Unipolar Depression. CNS Drugs 2012, 26, 189–204, doi:10.2165/11599770-000000000-00000.
35. Bratsos, S.; Saleh, S.N. Clinical Efficacy of Ketamine for Treatment-Resistant Depression. Cureus 2019, 11, e5189, doi:10.7759/cureus.5189.
36. McClure, E.W.; Daniels, R.N. Classics in Chemical Neuroscience: Amitriptyline. ACS Chem. Neurosci. 2021, 12, 354–362, doi:10.1021/acschemneuro.0c00467.
37. Foudah, A.I.; Alqarni, M.H.; Alam, A.; Devi, S.; Salkini, M.A.; Alam, P. Rutin Improves Anxiety and Reserpine-Induced Depression in Rats. Molecules 2022, 27, 7313, doi:10.3390/molecules27217313.
38. Türkmen, C.; Sacu, S.; Furukawa, Y.; Cates, A.N. de; Schoevers, R.A.; Kamphuis, J.; Chevance, A.; Weisz, J.R.; Emslie, G.J.; Strawn, J.R.; et al. Side Effect Profile and Comparative Tolerability of Newer Generation Antidepressants in the Acute Treatment of Major Depressive Disorder in Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis. medRxiv 2025, 2025.04.02.25324485, doi:10.1101/2025.04.02.25324485.
39. Griffin, C.E.; Kaye, A.M.; Bueno, F.R.; Kaye, A.D. Benzodiazepine Pharmacology and Central Nervous System-Mediated Effects. Ochsner J. 2013, 13, 214–223.
40. Perez-Caballero, L.; Torres-Sanchez, S.; Bravo, L.; Mico, J.A.; Berrocoso, E. Fluoxetine: A Case History of Its Discovery and Preclinical Development. Expert Opin. Drug Discov. 2014, 9, 567–578, doi:10.1517/17460441.2014.907790.
41. Sun, Y.; Sun, X.; Qu, H.; Zhao, S.; Xiao, T.; Zhao, C. Neuroplasticity and Behavioral Effects of Fluoxetine after Experimental Stroke. Restor. Neurol. Neurosci. 2017, 35, 457–468, doi:10.3233/rnn-170725.
42. Levy, M.J.F.; Boulle, F.; Emerit, M.B.; Poilbout, C.; Steinbusch, H.W.M.; Hove, D.L.A.V. den; Kenis, G.; Lanfumey, L. 5-HTT Independent Effects of Fluoxetine on Neuroplasticity. Sci. Rep. 2019, 9, 6311, doi:10.1038/s41598-019-42775-w.
43. Matveychuk, D.; Thomas, R.K.; Swainson, J.; Khullar, A.; MacKay, M.-A.; Baker, G.B.; Dursun, S.M. Ketamine as an Antidepressant: Overview of Its Mechanisms of Action and Potential Predictive Biomarkers. Ther. Adv. Psychopharmacol. 2020, 10, 2045125320916657, doi:10.1177/2045125320916657.
44. Newport, D.J.; Carpenter, L.L.; McDonald, W.M.; Potash, J.B.; Tohen, M.; Nemeroff, C.B.; Treatments, A.C. of R.T.F. on N.B. and Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression. Am. J. Psychiatry 2015, 172, 950–966, doi:10.1176/appi.ajp.2015.15040465.
45. Averill, L.A.; Murrough, J.W.; Abdallah, C.G. Ketamine for Treatment-Resistant Depression, The First Decade of Progress. 2016, 99–121, doi:10.1007/978-3-319-42925-0_7.
46. Morris, L.S.; McCall, J.G.; Charney, D.S.; Murrough, J.W. The Role of the Locus Coeruleus in the Generation of Pathological Anxiety. Brain Neurosci. Adv. 2020, 4, 2398212820930321, doi:10.1177/2398212820930321.
47. Mejia-Carmona, G.E.; Gosselink, K.L.; Pérez-Ishiwara, G.; Martínez-Martínez, A. Oxidant/Antioxidant Effects of Chronic Exposure to Predator Odor in Prefrontal Cortex, Amygdala, and Hypothalamus. Mol. Cell. Biochem. 2015, 406, 121–129, doi:10.1007/s11010-015-2430-2.
48. Rabiei, Z.; Setorki, M. Effect of Ethanol Adiantum Capillus-Veneris Ext-

ract in Experimental Models of Anxiety and Depression. Braz. J. Pharm. Sci. 2019, 55, e18099, doi:10.1590/s2175-97902019000118099.

49. Kumar, A.; Garg, R.; Prakash, A.K. Effect of St. John's Wort (Hypericum Perforatum) Treatment on Restraint Stress-Induced Behavioral and Biochemical Alteration in Mice. BMC Complement. Altern. Med. 2010, 10, 18–18, doi:10.1186/1472-6882-10-18.
50. Adnan, Md.; Chy, Md.N.U.; Kamal, A.T.M.M.; Azad, M.O.K.; Chowdhury, K.A.A.; Kabir, M.S.H.; Gupta, S.D.; Chowdhury, Md.A.R.; Lim, Y.S.; Cho, D.H. Comparative Study of Piper Sylvaticum Roxb. Leaves and Stems for Anxiolytic and Antioxidant Properties Through In Vivo, In Vitro, and In Silico Approaches. Biomedicines 2020, 8, 68, doi:10.3390/biomedicines8040068.
51. Colares, J.R.; Schemitt, E.G.; Hartmann, R.M.; Licks, F.; Soares, M. do C.; Bosco, A.D.; Marroni, N.P. Antioxidant and Anti-Inflammatory Action of Melatonin in an Experimental Model of Secondary Biliary Cirrhosis Induced by Bile Duct Ligation. World J. Gastroenterol. 2016, 22, 8918–8928, doi:10.3748/wjg.v22.i40.8918.
52. Ding, L.; Zhang, C.; Masood, A.; Li, J.; Sun, J.; Nadeem, A.; Zhang, H.-T.; O'Donnell, J.M.; Xu, Y. Protective Effects of Phosphodiesterase 2 Inhibitor on Depression- and Anxiety-like Behaviors: Involvement of Antioxidant and Anti-Apoptotic Mechanisms. Behav. Brain Res. 2014, 268, 150–158, doi:10.1016/j.bbr.2014.03.042.
53. Naomi, R.; Rusli, R.N.M.; Teoh, S.H.; Bahari, H.; Zakaria, Z.A. Remodulation Effect of Elateriospermum Tapos Yoghurt on Metabolic Profile of Maternal Obesity Induced Cognitive Dysfunction and Anxiety-like Behavior in Female Offspring—An In Vivo Trial on Sprague Dawley Rats. Foods 2023, 12, 1613, doi:10.3390/foods12081613.