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Comparative Antidepressant, Anxiolytic, and Acute Toxicity Evaluation of Lemon Peel and Peppermint Leaves Extracts in Mice

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Abstract

Depression and anxiety are prevalent psychiatric disorders, and current treatments are often limited by side effects, delayed onset, and resistance. Natural products are being explored as safer alternatives, and lemon peel (*Citrus limon*) and peppermint leaves (*Mentha piperita* L.) contain diverse bioactive compounds with neuroprotective potential. This study evaluated the antidepressant and anxiolytic effects of their ethanolic extracts, individually and in combination, in male Swiss Webster mice. Phytochemical screening confirmed the presence of alkaloids, flavonoids, phenols, tannins, saponins, and steroids in both extracts. Antidepressant activity, assessed by the Forced Swimming Test (FST) and Tail Suspension Test (TST), showed that both extracts and their low-dose combination significantly reduced immobility time, with effects comparable to fluoxetine. In contrast, the high-dose combination did not enhance efficacy. Anxiolytic activity, evaluated using the Elevated Plus Maze (EPM) and Light-Dark Box (LDB), revealed that peppermint extract exerted the strongest effect, followed by the low-dose combination and lemon peel. Acute oral toxicity testing at 2000 mg/kg showed no mortality or adverse effects. These findings suggest that lemon peel and peppermint extracts possess antidepressant and anxiolytic properties with favorable safety profiles, supporting their potential as natural alternatives or adjuncts for managing mood disorders.

Keywords: Antidepressant; anxiolytic; *Citrus limon*; *Mentha piperita* L.

INTRODUCTION

Depression and anxiety are among the most prevalent mental health disorders worldwide, affecting hundreds of millions of individuals. They contribute significantly to disability, morbidity, and socioeconomic burden (Zhdanava et al., 2021). According to the World Health Organization (WHO), depression is a leading cause of disability globally, while anxiety disorders are also recognized as major contributors to the global mental health crisis (World Health Organization, 2001). These disorders are often comorbid and share overlapping neurobiological mechanisms, including dysregulation of monoaminergic neurotransmission, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, oxidative stress, and neuroinflammation (Liu et al., 2024).

Depression is a mood disorder that characterized by persistent feeling of sadness, emptiness, hopelessness, and loss of interest. Anxiety disorders are cluster of mental disorder which indicated by excessive fear, chronic worry, or avoidance of perceived threats as response to external or internal environment (Craske & Stein, 2016). A study conducted by Simanjuntak reported that 23.14% of Indonesian aged 18 – 65 years old exhibited symptoms of depression, while the prevalence of anxiety was found to be 20.2% (Simanjuntak et al., 2023).

Although pharmacotherapy with antidepressants and anxiolytics has provided clinical benefits for many patients, current treatments face several limitations and challenges. These include delayed onset of action, treatment resistance, withdrawal symptoms, and adverse side effects, which often lead patients to discontinue therapy (Melaragno, 2021; Zhdanava et al., 2021). These shortcomings encourage the exploration of alternative treatments derived from natural sources. Medicinal plants, in particular, have emerged as promising candidates for novel therapeutic development due to their diverse bioactive compounds and generally lower risk of side effects compared to synthetic drugs.

Lemon (*Citrus limon*) is a plant from the Rutaceae family commonly consumed for various purposes, such as food ingredient, drinks, and immune booster. The fruit of the lemon possesses several pharmacological activities, such as antimicrobial, antifungal, and cytotoxic (Sania et al., 2020). Not only the fruit, but also the peel of the lemon contains numerous bioactive compounds. As a by-product of lemon processing, lemon peel has

attracted increasing scientific interest due to its rich phytochemical profile. Studies have identified various compounds in lemon peel, such as glycosides, coumarins, essential oils, β and γ sitosterol (Sania et al., 2020; Sultana et al., n.d.). Additionally, lemon peel contains apigenin, a flavonoid known for its neuropharmacological effects. Apigenin has been shown to alleviate depressive-like symptoms in mice subjected to chronic stress models (Yi et al., 2008).

Peppermint plants (*Mintha piperita* L) is an aromatic herb widely used in both culinary and medicinal contexts. Peppermint has traditionally been used to relieve stress, improve mood, and enhance cognitive function. Similar to lemon, peppermint leaves contain essential oils that make this plant also used as aromatherapy. These leaves are rich in various bioactive compounds, including flavonoids, phenolic acids, terpenoids, lignans, and essential oil (Mahendran & Rahman, 2020a; Sharif Mughal, 2022). The characteristic strong aroma of peppermint is primarily attributed to its essential oil content, the majority of which consists of monoterpenes (Beigi et al., 2018a). Among these, menthol is the most abundant, comprising approximately 35–60% of the total monoterpene content. Due to its diverse phytochemical profile, peppermint exhibits a wide range of pharmacological activities, including antibacterial, antifungal, antioxidant, antiviral, anti-inflammatory, analgesic, hepatoprotective, and neuroprotective effects (Mahendran & Rahman, 2020a).

Despite the individual potential of lemon peel and peppermint in supporting mental health, few studies have investigated their comparative or combined efficacy in standardized models of depression and anxiety. Considering the complexity of neuropsychiatric disorders, phytotherapeutic combinations may offer enhanced efficacy through synergistic interactions between different bioactive compounds. The combination of lemon peel and peppermint extract could potentially provide a broader spectrum of neuropharmacological activity.

This study aimed to evaluate the antidepressant and anxiolytic effects of ethanolic extracts of lemon peel and peppermint leaves, both individually and in combination, in mice. The animals were subjected to four standardized behavioral tests: the Forced Swimming Test (FST) and Tail Suspension Test (TST) to assess antidepressant-like activity, and the Light-Dark Box (LDB) test and Elevated Plus Maze (EPM) to evaluate anxiolytic behavior. By comparing behavioral outcomes across treatment groups, this research seeks to elucidate the therapeutic potential of lemon peel and peppermint extracts, and their combination, as natural alternatives or adjuncts in the management of mood disorders.

MATERIALS AND METHODS

Materials

Fresh lemon (*Citrus limon*) fruits were obtained from a local plantation in Jepara, Central Java, Indonesia. Dried peppermint (*Mentha piperita* L.) leaf powder was purchased from Indoplant. Fluoxetine suspension, used as the reference drug, was prepared from commercially available 20 mg fluoxetine capsules (Elizac® 20). Male mice were obtained from Java Rat Lab. The solvents and reagents used in this study included 96% ethanol, Dragendorff reagent, magnesium powder, hydrochloric acid (HCl), amyl alcohol, ammonia solution, Mayer's reagent, and ferric chloride ($FeCl_3$).

Procedure

Extraction

Lemon peel was thoroughly rinsed with distilled water and then dried. The dried material was ground to reduce particle size. Both lemon peel and peppermint leaf powders were extracted using 96% ethanol. An initial extraction was performed using a material-to-solvent ratio of 1:10, followed by two subsequent extractions with a 1:5 ratio to ensure optimal extraction of bioactive compounds. The combined liquid extracts were then concentrated using a rotary evaporator.

Phytochemical screening

Both lemon peel and peppermint extracts underwent qualitative phytochemical screening to detect the presence of alkaloids, flavonoids, phenols, saponins, tannins, steroids, and terpenoids using standard procedures. For testing flavonoid, the extract was mixed with 100 mL of hot distilled water and boiled for 5 minutes in a water bath. The solution was then filtered, and 5 mL of the filtrate was added with 50 mg of magnesium powder and 1 mL of concentrated hydrochloric acid (HCl), followed by vigorous shaking. The presence of flavonoids was indicated by the formation of a reddish or orange coloration.

For alkaloid detection, the extract was dissolved in 1 mL of 2N HCl and diluted with distilled water to a final volume of 10 mL. The solution was heated in a water bath for 2 minutes, allowed to cool, and filtered. The filtrate was divided equally into two test tubes: 3 drops of Dragendorff's reagent were added to the first tube, and 3 drops of Mayer's reagent to the second. The formation of an orange color (tube 1) or white precipitate (tube 2) indicated the presence of alkaloids.

For tannin detection, the extract was combined with 10 mL of hot distilled water and boiled for 15 minutes in a water bath. After filtration, 2–4 drops of ferric chloride ($FeCl_3$) were added to the filtrate. A dark green or blue-black coloration indicated the presence of tannins.

For saponin detection, a portion of the extract was placed in a test tube and mixed with 10 mL of hot distilled water. The tube was sealed and shaken vigorously in a vertical motion for 10 seconds, then left

to stand for another 10 seconds. The formation of a stable froth or foam indicated the presence of saponins. One drop of 2N HCl was then added to observe any change in the foam layer.

For steroid and triterpenoid detection, the extract was mixed with 2 mL of ethyl acetate and shaken thoroughly. The ethyl acetate layer was separated, then left to dry. Two drops of concentrated sulfuric acid were added. The appearance of a red, blue, or green coloration indicated the presence of steroids or triterpenoids.

Animal Treatment

Thirty-six male Swiss Webster mice, aged 8 weeks, with weight of 20 – 30 gram, were acclimatized for 7 days under controlled conditions at a constant room temperature of 25 °C, with a 12-hour light/12-hour dark cycle. During the acclimatization period, the animals had continuous access to food and water ad libitum. All studies were conducted in accordance with the Institutional Animal Care Committee at Faculty Medicine, Universitas Negeri Semarang.

The mice were randomly divided into six groups (n = 5 per group):

- Group I (Negative Control, NC): received 0.5% sodium carboxymethyl cellulose (CMC-Na) as the drug suspending agent.
- Group II (Positive Control, PC): received fluoxetine at a dose of 20 mg/kg body weight (BW).
- Group III (LP): received ethanolic extract of lemon peel at a dose of 200 mg/kg BW.
- Group IV (PL): received ethanolic extract of peppermint leaves at a dose of 200 mg/kg BW.
- Group V (LP+PL Low): received a combination of lemon peel extract (100 mg/kg BW) and peppermint leaf extract (100 mg/kg BW).
- Group VI (LP+PL High): received a combination of lemon peel extract (200 mg/kg BW) and peppermint leaf extract (200 mg/kg BW).

All treatments were administered orally once daily using an oral gavage for 14 consecutive days. At the end of the treatment period, the animals were subjected to behavioral tests to evaluate antidepressant and anxiolytic effects.

Forced Swimming Test (FST)

Each mouse was individually placed in a transparent 2L beaker glass filled with 1.5 L of water. The animals were allowed to swim for 6 minutes, and the duration of immobility was recorded during the final 4 minutes of the test. A mouse was considered immobile when it ceased active struggling and remained floating in an upright position, making only the minimal movements required to keep its head above the water.

Tail Suspension Test (TST)

In the Tail Suspension Test (TST), each mouse was suspended by the tail using adhesive tape affixed approximately 1 cm from the tip of the tail, at a height of 58 cm above the floor. After an initial 2-minute habituation period, the duration of immobility was recorded during the following 4 minutes. A mouse was considered immobile when it hung passively and remained completely motionless, indicating behavioral despair.

Figure 1. Tail Suspension Test Apparatus.

Elevated Plus Maze Test (EPM)

The Elevated Plus Maze (EPM) apparatus consists of two open arms (16 × 5 cm) and two closed arms (17 × 5 × 30 cm) with an open roof, arranged in a plus (+) configuration and elevated 75 cm above the floor surface. Each mouse was placed at the center of the maze, facing one of the open arms, to begin the test. During a 5-minute observation period, the following parameters were recorded: the number of entries into the open arms and the time spent in the open arms. Increased exploration of the open arms was interpreted as an indication of reduced anxiety-like behavior.

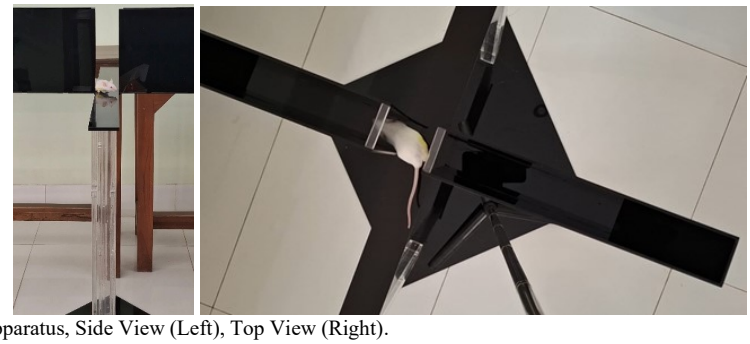

Figure 2. Elevated Plus Maze Apparatus, Side View (Left), Top View (Right).

Light Dark Box Test (LDB)

The Light-Dark Box (LDB) apparatus consists of two connected acrylic chambers: a light compartment and a dark compartment. The light compartment measures 27 × 27 × 27 cm and is illuminated by a 40-watt lamp, while the dark compartment measures 27 × 18 × 27 cm and remains unlit. A transition door measuring 7.5 × 7.5 cm connects the two compartments, allowing the mice to move freely between them.

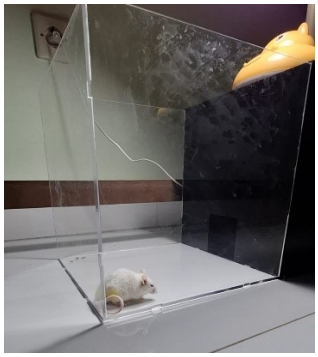

Figure 3. Light Dark Box Apparatus.

Acute Oral Toxicity Test

An acute oral toxicity test was conducted on the ethanolic extract of lemon peel (2000 mg/kg BW), peppermint leaves (2000 mg/kg BW), and their combination (2000 mg/kg BW each), in accordance with OECD Guideline 420 (Fixed Dose Procedure) using the limit test approach (OECD, 2001). Extracts were given in a single dose. The study used five healthy female mice, aged 8 weeks and weighing between 25-35 grams. The animals were administered the test substance orally and observed closely for clinical signs of toxicity. Mice were monitored closely for first 30 minutes post-dosing, periodically during the first 24 hours, and then once daily for a total period of 14 days. All animals were monitored for behavioral changes, clinical symptoms, morbidity, and mortality.

Data Analysis

Data were presented as mean ± standard error of the mean (SEM). Parametric data, such as immobility time and time spent in specific compartments, were analyzed using one-way analysis of variance (ANOVA), followed by the Least Significant Difference (LSD) post hoc test to identify significant differences between groups. Non-parametric data, such as the number of entries into the light compartment and open arms, were analyzed using the Kruskal-Wallis test. A p-value of < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Results

Phytochemical Contents

Both lemon peel extract and peppermint leaf extract contained all of the screened phytochemical metabolites, as shown in Table 1.

Table 1. Results of Phytochemical Screening.

Metabolites	Lemon Peel Extract	Peppermint Leaves Extract
Alkaloid	+	+
Flavonoid	+	+
Phenol	+	+
Steroid	+	+
Tannin	+	+
Saponin	+	+

Antidepressant Activity

Both extracts exhibited antidepressant activity, as shown in Figure 4.

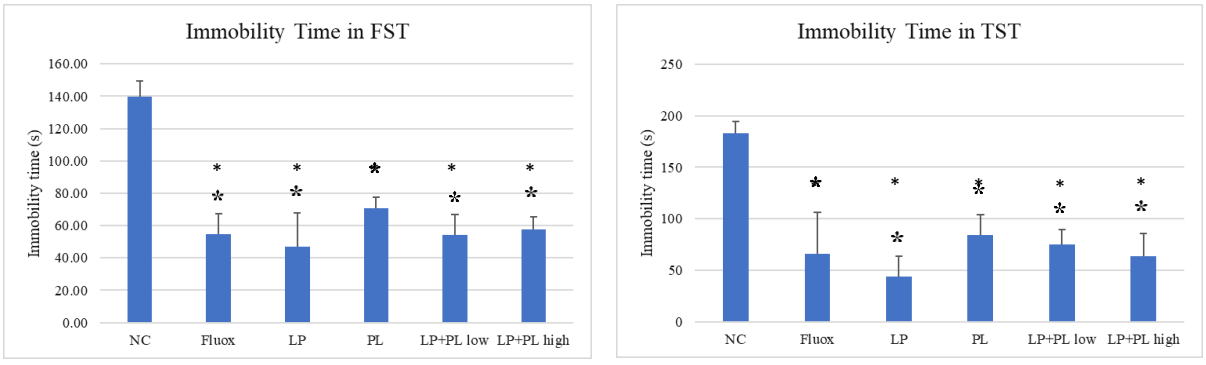

Figure 4. Immobility time in Forced Swimming Test (left) and Tail Suspension Test (right). NC: negative control, fluox: fluoxetine, LP: lemon peel extract, PL: peppermint leaves extract, LP+PL low: combination of lemon peel 100 mg/kgBW and peppermint leaves 100 mg/kgBW, LP+PL high: combination of lemon peel 200 mg/kgBW and peppermint leaves 200 mg/kgBW. *) significant compared to negative control ($p < 0.05$).

Anxiolytic Activity

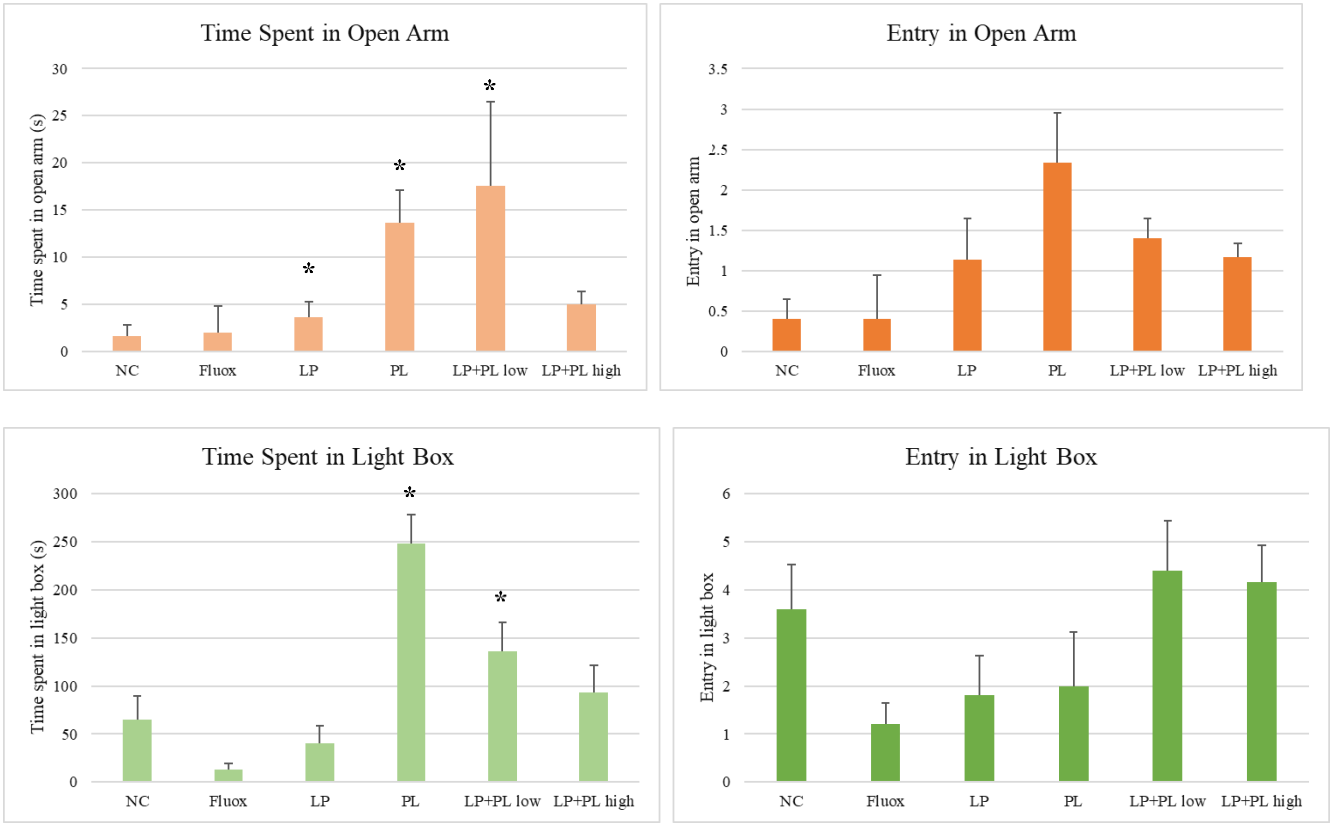

Figure 5. Result of Anxiolytic Activity in Elevated Plus Maze and Light Dark Box Test. NC: negative control, fluox: fluoxetine, LP: lemon peel extract, PL: peppermint leaves extract, LP+PL low: combination of lemon peel 100 mg/kgBW and peppermint leaves 100 mg/kgBW, LP+PL high: combination of lemon peel 200 mg/kgBW and peppermint leaves 200 mg/kgBW. *) significant compared to negative control ($p < 0.05$).

Acute Oral Toxicity Study

No mortality was observed at the oral dose of 2000 mg/kg for each extract and for the combination.

Discussion

The phytochemical screening of lemon peel and peppermint leaf extracts revealed the presence of diverse bioactive constituents, including alkaloids, flavonoids, phenols, steroids, tannins, and saponins. These findings are consistent with previous reports on the phytochemical richness of citrus peels and aromatic herbs such as peppermint (Hudz et al., 2023). The wide range of metabolites detected indicates that the extracts possess multiple pharmacological potentials relevant to neuropsychiatric disorders. Flavonoids and phenolic compounds are of particular importance due to their antioxidant and anti-inflammatory effects, as well as their ability to modulate monoaminergic neurotransmission (Nájera-Maldonado et al., 2024). The extract of lemon peel contains various constituents such as limonene, linalool, citronelal, apigenin, hesperidin, β-Bisabolene, trans-Caryophyllene, Nerylacetate, α-Terpineol, β-Pinene, γ-Terpinene (Huang et al., 2025; Taktak et al., 2021). Meanwhile, peppermint leaves are rich in flavonoids, including hesperidin, catechin, epicatechin, rutin, myricetin, luteolin, apigenin (Mahendran & Rahman, 2020b).

Luteolin contained in peppermint leaves extract exerts its antidepressant effects through multiple molecular and cellular pathways. It has been shown to enhance uptake of noradrenaline (NE), inhibit reuptake of 5-hydroxytryptamine (5-HT), and increase the expression of key synaptic and neuroprotective proteins such as synaptophysin, postsynaptic density protein 95, brain-derived neurotrophic factor (BDNF), B-cell lymphoma protein-2 (Bcl-2), superoxide dismutase (SOD), and glutathione S-transferase (GST) (Zhou et al., 2025). Apigenin, present in both extracts, may contribute to the observed antidepressant activity through modulation of serotonergic and catecholaminergic pathways. Its pharmacological effects have been associated with interactions involving α-adrenergic receptors as well as 5-HT_3, D_1, D_2, and D_3 receptors. Experimental studies have shown that apigenin, at doses of 25 and 50 mg/kg BW, was able to prolong mobility time in rats pretreated with serotonergic inhibitors and catecholaminergic antagonists, indicating its role in enhancing monoaminergic neurotransmission (Al-Yamani et al., 2022). Menthol, one of the main constituents of peppermint leaves, may alleviate depressive symptoms

by enhancing dopaminergic activity through D1 and D2 receptor modulation (Mohaghegh Daghigh, 2024).

The behavioral outcomes from the Forced Swimming Test (FST) and Tail Suspension Test (TST) showed that both lemon peel and peppermint leaf extracts significantly reduced immobility time compared with the negative control, reflecting antidepressant-like activity. The magnitude of these effects was comparable to fluoxetine, indicating that the extracts may act through similar neurochemical pathways. In rodent models, reduced immobility is interpreted as diminished behavioral despair, which is predictive of antidepressant efficacy. Interestingly, the combination of both extracts with low dose (half of each extract) produce similar antidepressant activity compared to the single extracts, indicating additive interaction. However, the high dose combination did not produce an increase in antidepressant activity. This finding may be explained by overlapping mechanisms of action, since both extracts are rich in flavonoids and phenolic compounds that target monoaminergic systems, antioxidant defenses, and neurotrophic signaling (Mahendran & Rahman, 2020b; Taktak et al., 2021). Another possibility is that certain phytochemicals from lemon peel and peppermint compete for the same receptor sites or metabolic pathways, resulting in a plateau effect rather than potentiation. Further studies on dose optimization and interaction profiles are needed to clarify the pharmacodynamic relationship between the two extracts.

In the anxiety tests, increased time spent and entries into the open arms of the Elevated Plus Maze (EPM) and the light compartment of the Light-Dark Box (LDB) were interpreted as indicators of reduced anxiety-like behavior. In this study, only certain groups demonstrated anxiolytic activity to some extent, namely the peppermint leaf extract group, the lemon peel extract group, and the low-dose combination group. Interestingly, the positive control group (fluoxetine) did not display anxiolytic activity and instead showed a tendency to increase anxiety, although this effect was not statistically significant. This finding is consistent with previous studies reporting that a single intraperitoneal injection of fluoxetine at doses of 5 or 10 mg/kg reduced the time spent in the open arms of the EPM, suggesting an anxiogenic effect. At higher doses (15 mg/kg), fluoxetine produced sedative effects, as indicated by a shorter total distance traveled within the maze. (Drapier et al., 2007).

Peppermint leaf extract consistently demonstrated strong anxiolytic activity across both models, while lemon peel extract exhibited anxiolytic effects in the Elevated Plus Maze (EPM) but not in the Light-Dark Box (LDB). These differences may reflect variation in the sensitivity of each test to specific neurochemical pathways. The anxiolytic activity of both extracts can be attributed in part to terpenoids such as menthol, limonene, and α-terpineol, which are abundant in peppermint and lemon peel essential oils (Alvarado-García et al., 2024; Beigi et al., 2018b; Huang et al., 2025). These compounds have been reported to modulate GABAergic neurotransmission, enhancing inhibitory signaling in key brain regions such as the amygdala and hippocampus, thereby reducing anxiety-like behavior (Mahendran & Rahman, 2020a). In addition, flavonoids and phenolic acids present in both extracts, such as apigenin, luteolin, and catechins, are known to exert anxiolytic effects through serotonergic regulation, antioxidant activity, and neuroprotective mechanisms (Al-Yamani et al., 2022; Zhou et al., 2025). The coexistence of these phytochemicals suggests that their combined action may contribute to the observed behavioral outcomes.

The low dose combination group also produced anxiolytic effects comparable to peppermint extract alone, suggesting possible synergistic interactions between the two extracts when administered at balanced concentrations. Such synergy may arise from complementary mechanisms, with terpenoids modulating GABAergic signaling while flavonoids regulate monoaminergic pathways and oxidative stress, together amplifying the anxiolytic response. In contrast, the high dose combination failed to show anxiolytic activity. This unexpected result may be explained by pharmacodynamic antagonism, receptor desensitization, or competition between overlapping active compounds at higher concentrations. Excessive stimulation of serotonergic or GABAergic receptors can paradoxically lead to anxiogenic or sedative effects, masking the anxiolytic potential of the extracts.

The absence of mortality at an oral dose of 2000 mg/kg for both lemon peel and peppermint leaf extracts, as well as their combination, suggests that these extracts can be considered practically non-toxic according to the OECD classification system (OECD, 2001). Substances with an LD_{50} value greater than 2000 mg/kg are generally regarded as safe and fall into the lowest toxicity category. In addition to the absence of mortality, no overt signs of toxicity, morbidity, or behavioral abnormalities were observed during the 14-day observation period. This further supports the tolerability of the extracts at relatively high doses.

Taken together, the results of this study provide strong evidence that lemon peel and peppermint extracts, both alone and in combination, possess antidepressant and anxiolytic activities, likely mediated through multi-target mechanisms involving monoaminergic, GABAergic, and antioxidant pathways. Their efficacy, combined with their favorable acute safety profile, highlights their potential as safe, natural alternatives or adjuncts to conventional antidepressant and anxiolytic therapies. Nonetheless, further studies, including sub-chronic toxicity evaluations, molecular docking, and clinical trials, are needed to establish their precise mechanisms and therapeutic relevance in humans.

CONCLUSIONS

This study demonstrates that lemon peel and peppermint leaf extracts, both individually and in combination, exhibit antidepressant and anxiolytic activities linked to their rich phytochemical profiles. Peppermint showed the strongest anxiolytic effect, while the low-dose combination suggested synergistic interactions between the two extracts. The absence of acute toxicity at 2000 mg/kg indicates a favorable safety profile for potential therapeutic use. These findings highlight the promise of lemon peel and peppermint as safe, natural alternatives or adjuncts to conventional treatments for mood disorders.

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Competing Interests: The authors declare that there are no competing interests.

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