PHOTON
Journal of Natural Sciences and Technology
p-ISSN: 2087-393X | e-ISSN: 2579-5953
http://ejurnal.umri.ac.id/index.php/photon

Antidepressant-Like Activity of Ethyl Acetate Extract of Old Areca Nut in Swiss Albino Mice Independently Assessed by the Forced Swim Test

Riryn Novianty*, Yuharmen, Nery Sofyanti, Fitra Audhi Ya'la
Faculty of Mathematics and Natural Sciences, Universitas Riau, Kampus Bina Widya Km. 12,5 Simpang Baru, Pekanbaru, Indonesia

Received 1 May 2025 | Accepted 25 May 2025 | Published 31 May 2025
DOI: https://doi.org/10.37859/jp.v15i2.9294

Keywords:
Antidepressant;
Ethyl acetate extract;
Forced Swim Test;
Old areca nut

Abstract. Depression is a global mental health issue and herbal antidepressants are increasingly sought due to the side effects of synthetic drugs. The present study aimed to evaluate the potential of ethyl acetate extract of old areca nut in treating depression of mice subjected to acute and sub-chronic Forced Swim Test (FST). Ethyl acetate extract was injected intraperitoneally 1 h before the FST at a dose of 50 and 100 mg/kg. The 100 mg/kg dose showed the greatest reduction in immobility time (22.29%) during acute testing. Following seven days of treatment, it was discovered that the extract significantly alleviated the immobility time in sub-chronic FST. The results of the phytochemical analysis showed that phenolics present in the ethyl acetate extract are probably active constituents with antidepressant properties. After prolonged administration, the substance has no toxic effects on the bodies of test animals.

*Corresponding author.
E-mail address: rirynnovianty@lecturer.unri.ac.id

1. Introduction

Depression is a mental disorder projected to become the leading global disease burden by 2030 (Santomauro et al., 2021). In Indonesia, among 16,204 households surveyed, 31,447 individuals aged 15 years and above were assessed, and 21.8% were found to experience moderate to severe depression (Nurtanti & Handayani, 2021). Often underestimated by those affected, depression is a serious condition as it may lead to other health complications (Lubis, 2009). Prolonged depression can severely impact psychological well-being, triggering harmful behaviors such as criminal activity or even suicide (Hammen & Watkins, 2018). Numerous factors contribute to depression (Novianty et al., 2023; Novianty et al., 2024), including a chemical basis involving the decreased levels of monoamine neurotransmitters (such as serotonin, dopamine, and norepinephrine) due to the activity of the enzyme Monoamine Oxidase (MAO) (Jiang et al., 2022).

Antidepressant drugs are commonly used to treat depression by inhibiting MAO or the reuptake of serotonin and norepinephrine (Gerlach et al., 2014). Inhibition typically occurs through covalent bonding between the substrate and target protein (Novianty et al., 2014). However, synthetic antidepressants widely available on the market can cause side effects such as hypotension, dry mouth, seizures, vomiting, and nausea (Agius & Bonnici, 2017). Moreover, the therapeutic efficacy of existing antidepressants is limited, sparking interest in discovering more effective and safer alternatives.

The current trend toward "back to nature" treatments has grown in popularity. Indonesia's rich biodiversity has been explored for various bioactivities including antimicrobial (Octarya et al., 2021), antidiabetic (Sy et al., 2017; Sy et al., 2019), immunomodulatory effects (Novianty & Devy, 2023; Novianty, 2023b), and also as sources of multifunctional oils (Novianty et al., 2023; Novianty, 2023c). Certain native microbes can degrade environmentally harmful compounds like naphthalene (Fitrida et al., 2019; Fitrida et al., 2020; Novianty et al., 2022; Novianty et al., 2020) and petroleum hydrocarbons (Antika & Novianty, 2019; Novianty et al., 2020; Novianty et al., 2021; Novianty & Yuharmen, 2023; Sari et al., 2019; Saryono et al., 2022; Novianty et al., 2020). In addition to *in vitro* studies, digital advancements have enabled drug discovery through computer-based applications (Ningsih et al., 2019a; Ningsih et al., 2019b). Molecular computational approaches, particularly *in silico* modeling, are frequently employed to predict the efficacy of potential drug compounds. Secondary metabolites from Indonesian plants have shown potential as antidepressants (Ananta & Novianty, 2022; Sirait & Novianty, 2022; Maylinda & Novianty, 2022; Novianty, 2020) and COVID-19 therapeutics (Novianty et al., 2021) through pharmacokinetic and molecular docking analyses. These findings reflect the growing interest among researchers in discovering drug candidates derived from natural products.

Areca nut (*Areca catechu* L.), a major plantation commodity in Riau Province, is particularly interesting due to its potential pharmaceutical value (Tong et al., 2024). Molecular docking studies have shown that guvacoline and homoarecoline compounds found in areca nut may act as MAO inhibitors (Novianty, 2022; Ningsih & Novianty, 2021), possibly working synergistically with standard antidepressants (Novianty et al., 2023). Additional constituents such as L-phenylalanine and L-tyrosine were predicted using SwissADME to have good bioavailability and low toxicity (Novianty, 2023b).

Research into areca nut as an antidepressant has gone beyond *in silico* approaches and has been tested in animal models using the Forced Swim Test (FST) (Ya'la & Novianty, 2023; Neldi & Novianty, 2023; Andriyani & Novianty, 2023; Sumarni & Novianty, 2023). However, existing studies followed standard FST protocols involving only single-dose treatments (Porsolt et al., 1978). In reality, antidepressant therapy typically requires several days to manifest its therapeutic effects (Gerlach et al., 2014; Stahl, 2013). This delay can be modeled through sub-chronic FST, as demonstrated by Yu et al., (2002) where Curcuma longa extract significantly reduced mice immobility time and even surpassed fluoxetine's effects after 7 days of treatment.

Based on the above, this study aims to evaluate the antidepressant activity using both acute and sub-chronic FST from old areca nut using ethyl acetate as semipolar solvent, while also assessing its potential toxicity after repeated administration.

2. The Methods

This research began with the extraction of old areca nut using ethyl acetate as a solvent via maceration. The extract's chemical constituents were analyzed through phytochemical screening. Antidepressant activity was evaluated using a behavioral method validated in test animals, the Forced Swim Test (FST). FST was conducted based on treatment duration: acute and sub-chronic. Mice subjected to sub-chronic FST were dissected to visually inspect for any potential toxic effects of the extract. The overall experimental procedure is illustrated in Figure 1.

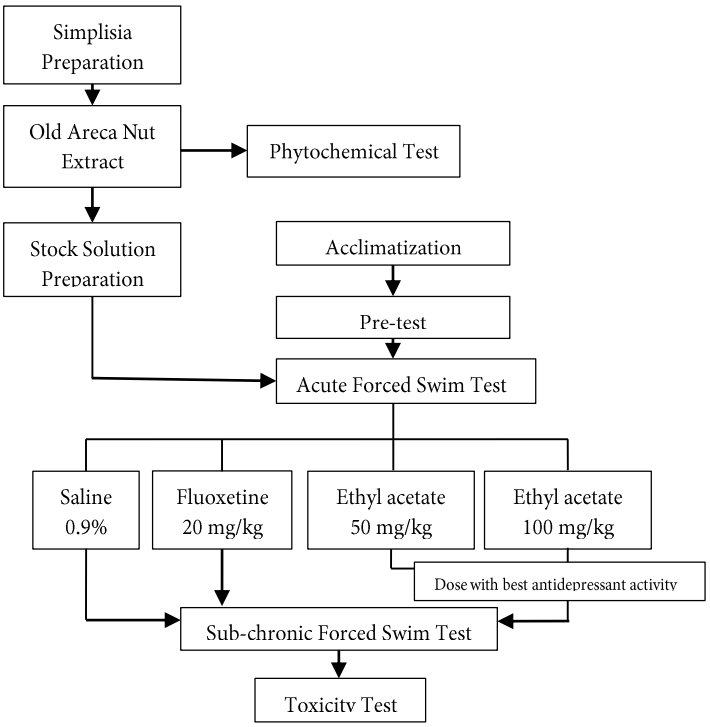

Figure 1. The research flowchart.

2.1 Preparation of Ethyl Acetate Extract from Old Areca Nut

A total of 500 g of peeled and dried old areca nuts was sourced from local farmers in Pekanbaru. The nuts were cleaned to remove impurities, then ground into a coarse powder and soaked in 1300 mL of ethyl acetate in a maceration bottle. After shaking, the mixture was left to stand for 24 hours. The extract was filtered to obtain the first macerate. The residue was then re-macerated up to four times until the extract became clear in color (Musdja et al., 2020). All macerates were combined and concentrated using a vacuum rotary evaporator.

Phytochemical screening were conducted to identify secondary metabolites in both the areca nut sample and the ethyl acetate extract. Tests were performed for alkaloids (Mayer and Dragendorff reagents), flavonoids (alkaline reagent NaOH), phenolics (ferric chloride $FeCl_3$), saponins (frothing test), and steroids and terpenoids (Liebermann-Burchard reagent), following standard protocols.

2.2 Test Animals

Male Swiss albino mice aged 8–10 weeks, weighing 20–25 g, were used as test animals. Mice were acclimatized for 7 days under controlled conditions: 23–26°C, 12-hour light/dark cycle, and given ad libitum access to food and water. Each cage housed 5–6 mice. Only healthy mice with stable body weight (maximum 20% deviation) and normal behavior were selected. Experimental procedures began after acclimatization and were conducted between 08:00–15:00 local time. Ethical approval for animal use was granted by the Health and Medical Research Ethics Committee, Faculty of Medicine, Universitas Riau (Approval No: B/004/UN19.5.1.1.8/UEPKK/2023).

2.3 Forced Swim Test (FST)

The FST is a validated behavioral test to assess the efficacy of antidepressant agents in rodents. Mice were subjected to both acute and sub-chronic FST based on treatment duration. A pre-test was conducted one day prior to the acute FST as a stressor, where mice were forced to swim for 15 minutes in a FST tank (acrylic glass cylinder with 11 cm in diameter and 20 cm in height) filled with 10 cm of water at 25 ± 1°C. On the test day, mice were placed in the tank for 10 minutes, and immobility behavior—defined as minimal movement to keep afloat—was recorded during the last 8 minutes (Ueno

et al., 2022). A reduction in immobility time was used as an indicator of antidepressant activity (Sánchez-Mateo et al., 2007). In this study, the most effective dose was determined by calculating the percentage reduction in immobility time using the following formula:

$$\text{Immobility Time Reduction (\%)} = \left[\frac{(A - B)}{A}\right] \times 100\% \quad (1)$$

Where A represents the immobility time of the control group, while B represents the immobility time of the treatment group.

2.3.1. Acute FST

Acute testing was conducted one day after the pre-test. Mice received intraperitoneal (IP) injections 1 hour before the test. The groups were assigned as follows:
Group 1: Negative control, depressed mice injected with 0.9% saline (0.1 mL/20 g)
Group 2: Positive control, mice injected with fluoxetine (20 mg/kg)
Group 3: Mice injected with ethyl acetate extract (50 mg/kg)
Group 4: Mice injected with ethyl acetate extract (100 mg/kg)
Doses and routes of administration were selected based on prior studies (Abbasi-maleki et al., 2020; Khulbe et al., 2013; Shahamat et al., 2016).

2.3.2. Sub-Chronic FST

For the sub-chronic model, mice were injected daily for 7 consecutive days with either fluoxetine (20 mg/kg), saline (0.1 mL/20 g), or ethyl acetate extract (100 mg/kg). The FST re-test was conducted on Day 7, following the acute FST schedule.

2.4 Sub-Chronic Toxicity Test

Toxic effects of repeated dosing were evaluated organoleptically following the toxicity test protocol described by Abbas *et al* (2012). After completing the sub-chronic FST, mice were euthanized via cervical dislocation. The peritoneal region, the site of drug administration, was inspected for swelling or tumor-like growths. The area was dissected to examine signs of inflammation in the intestines or liver.

2.5 Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM), with n = 3 per group. Statistical significance was assessed using One-Way ANOVA, followed by Tukey's post hoc test for both acute and sub-chronic FST results. A p-value < 0.05 was considered statistically significant between drug treatment and negative control group.

3. Result and Discussion

3.1 Extraction and Phytochemical Screening

The ethyl acetate extract obtained from old areca nut was dark red with a slight yellow tint and weighed 28.36 g. Phytochemical tests showed that both the powdered areca nut and its ethyl acetate extract gave a strong positive result for phenolic compounds, indicated by a dark green color. Steroid and terpenoid tests also yielded positive results, as evidenced by a greenish coloration. The presence of saponins was confirmed only in the areca nut powder through foam formation. These findings are consistent with previous reports (Sari et al., 2020; Yang et al., 2012; Abbas et al., 2012).

Maceration was chosen as the extraction method because it is ideal for heat-sensitive natural compounds. Soaking the plant material breaks down cell walls, allowing secondary metabolites to diffuse into the solvent (Nugroho & Hartini, 2021). Ethyl acetate, a semi-polar solvent, can extract both

polar phenolic compounds and nonpolar steroids effectively. Areca nuts are known to contain 3,4-dihydroxybenzaldehyde, a phenolic compound. According to in silico molecular docking studies by Novianty *et al* (2024), this compound exhibits similar binding interactions to harmine (a native ligand of MAO-A), forming hydrophobic interactions with the TYR407 residue at the enzyme's active site. This simulates the compound's ability to inhibit MAO-A activity, thereby preventing the breakdown of monoamine neurotransmitters, which suggest that phenolic constituents in the ethyl acetate extract are likely the key compounds responsible for its antidepressant activity.

3.2 Acute FST

The FST is widely used to identify compounds with potential antidepressant effects. In this model, mice are placed in water for an extended period, after which they display passive behavior characterized by immobility (Kraeuter & Guest, 2019). This floating posture reflects behavioral despair when facing an inescapable situation (Kelliher et al., 2003). Antidepressant-treated animals tend to show increased swimming activity, indicating a reduction in stress (Kraeuter & Guest, 2019). Acute drug administration is considered effective in reducing stress in test animals, without the need to account for clinical onset time, as mouse behavior reliably predicts antidepressant effects (Petit-Demouliere et al., 2005). Therefore, the acute FST involved a single dose to evaluate its effect on depression symptoms and determine the optimal dose.

IP injection was chosen as the route of administration, which is commonly used in rodent studies. The animal is positioned with its head lower than the abdomen, and the needle is inserted into the lower abdominal quadrant at a 10° angle to avoid liver damage (Cunliffe-Bearner & Les, 1987; Simmons & Brick, 1970). IP-administered drugs are absorbed via mesenteric vessels and delivered to the liver through the portal vein. The substances then metabolized by the liver before reaching systemic circulation (Shoyaib et al., 2019). Table 1 shows the effect of ethyl acetate extract and fluoxetine on immobility time in mice undergoing acute FST. Both doses of the extract significantly reduced immobility time compared to the control group. The 100 mg/kg dose showed the highest reduction (22.29%), which was statistically similar to fluoxetine (20.65%). This indicates that the extract has comparable antidepressant efficacy at this dose.

Table 1. The effect of ethyl acetate extract of old areca nut on mice subjected to acute FST

Treatment	Immobility Time (seconds)	Reduction in Immobility Time (%)
Control (Saline 0.1 mL/20 g)	408.33 ± 9.82[b]	-
Fluoxetine (20 mg/kg)	324.00 ± 6.35[a]	20.65
Ethyl acetate extract (50 mg/kg)	333.67 ± 10.73[a]	18.29
Ethyl acetate extract (100 mg/kg)	**317.33 ± 10.27[a]**	**22.29**

Notes: Different letter notations (a and b) in the same column indicate a statistically significant difference in mice immobility time ($p < 0.05$) based on Tukey's test

In Figure 2 illustrated the effect where the 100 mg/kg dose of ethyl acetate extract significantly reduced immobility time ($p<0.001$), similar to fluoxetine. The 50 mg/kg dose also had a significant effect ($p<0.05$) but was less potent.

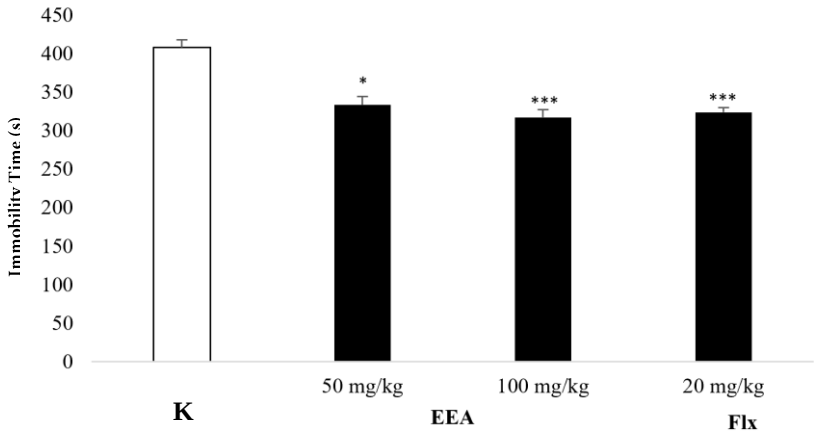

Figure 2. The effect of ethyl acetate extract of old areca nut (EEA) and fluoxetine (Flx) on mice immobility time in the acute FST. *p<0,05 indicates significant and ***p<0,001 indicates highly significant differences compared to the control group (K)

The superior effect of the 100 mg/kg dose supports its antidepressant potential. A similar pattern was observed in prior studies using methanol extract of old areca nut (Novianty et al., 2024). Mechanistically, the extract likely acts as a competitive MAO-A inhibitor, similar to harmine. In competitive inhibition, compounds compete with the natural substrate (e.g., serotonin) for the active site of MAO-A (Nelson & Cox, 2013). A higher concentration of active metabolites results in more effective enzyme inhibition, increasing serotonin levels in the synapse and alleviating depressive symptoms (Stahl, 2013).

The 100 mg/kg dose showed similar antidepressant-like effects to fluoxetine. This was evidenced by the immobility time of mice receiving a single dose of 100 mg/kg extract being statistically comparable to that of the fluoxetine-treated group (positive control), as shown in Table 1. These findings are consistent with the study by Abbasi-maleki & Mousavi (2017), in which *Carthamus tinctorius* extract and fluoxetine produced comparable immobility times in mice based on ANOVA analysis.

3.3 Sub-chronic FST

Sub-chronic studies involved daily dosing for 7 days, simulating real-world antidepressant therapy. FST re-testing was performed on Day 7 following acute FST, based on the protocol by Suman *et al* (2018), who observed significant changes in immobility time under these conditions. This approach differs from short-term protocols, such as the 2-day FST by Ueno *et al* (2022), which showed no significant difference.

Table 2. The effect of ethyl acetate extract of old areca nut on mice subjected to sub-chronic FST

Treatment	Immobility Time (seconds)	Reduction in Immobility Time (%)
Control (Saline 0,1 mL/20 g)	420,33 ± 17,15^{c}	-
Fluoxetine (20 mg/kg)	237,33 ± 4,63^{a}	43,54
Ethyl Acetate Extract (100 mg/kg)	347,67 ± 9,68^{b}	17,29

Notes: Different letter notations (a and b) in the same column indicate a statistically significant difference in mice immobility time (p < 0.05) based on Tukey's test

Table 2 presents the immobility times for sub-chronic FST. Fluoxetine resulted in the highest reduction (43.54%), while the ethyl acetate extract showed a smaller reduction (17.29%) compared to

the acute results. This indicates the extract was less effective over repeated administration, possibly due to tolerance or metabolic adaptation. Figure 3 confirms that the extract significantly reduced immobility ($p<0.05$), while fluoxetine showed a highly significant effect ($p<0.001$). Despite the reduced efficacy over time, the extract still exhibited a measurable antidepressant effect.

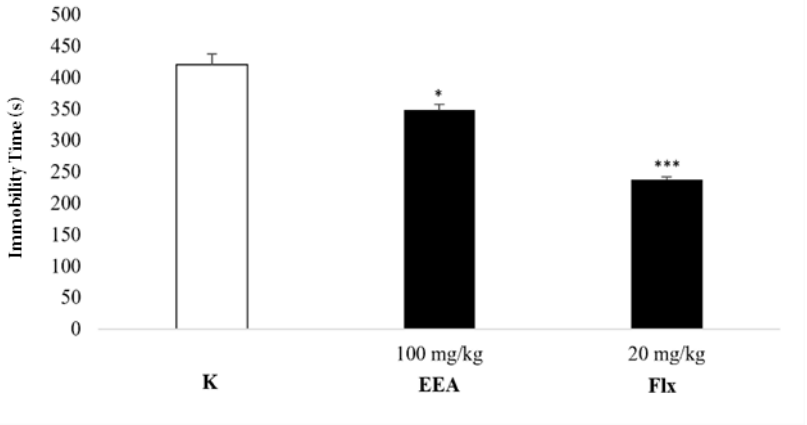

Figure 3. The effect of ethyl acetate extract of old areca nut (EEA) and fluoxetine (Flx) on mice immobility time in the sub-chronic FST. *p<0,05 indicates significant and ***p<0,001 indicates highly significant differences compared to the control group (K)

3.4 Toxicity Evaluation

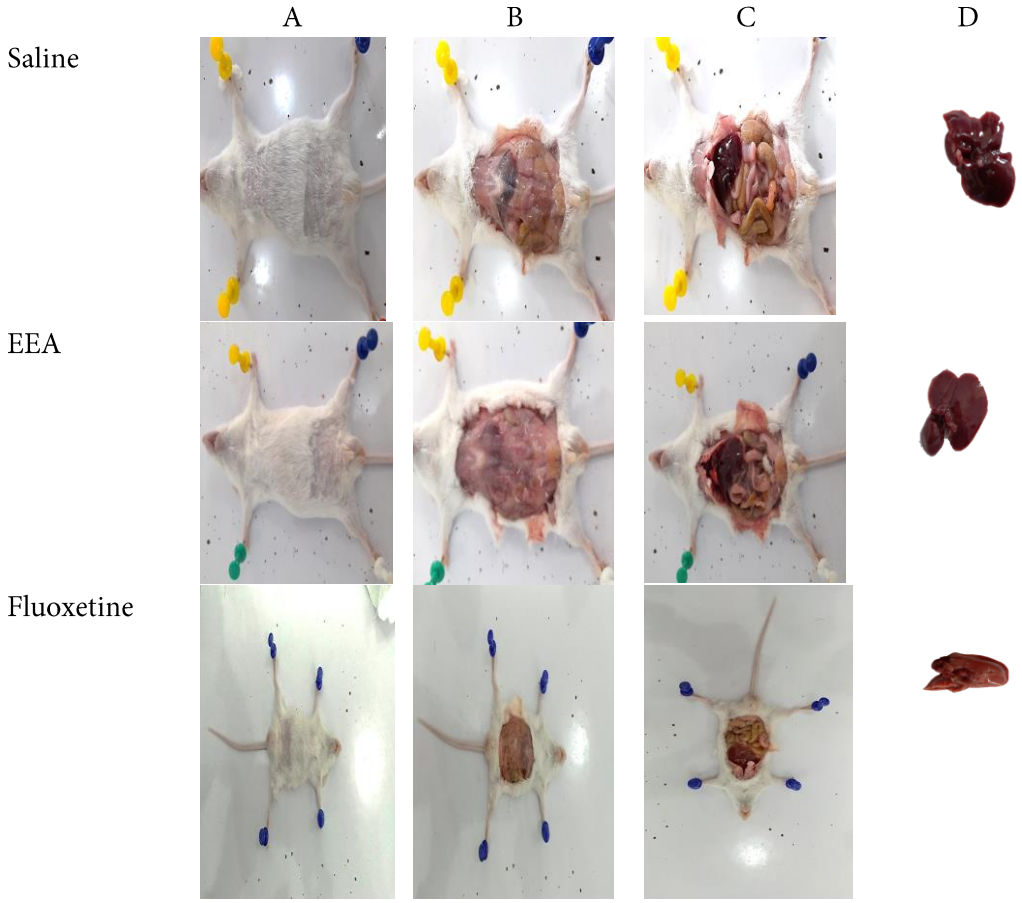

Figure 4. The effects of saline, ethyl acetate extract, and fluoxetine on the test animals' bodies in (A) The abdominal cross-section; (B) The abdominal cross-section after skin removal; (C) The intestinal organs; and (D) Liver.

Sub-chronic toxicity was assessed through visual inspection after animal dissection. Mice treated with 100 mg/kg ethyl acetate extract, saline, and 20 mg/kg fluoxetine showed no signs of swelling or tumor growth in the peritoneal region (Figure 4a). No inflammation was observed in the intestines, no yellow fluid accumulation (Figure 4b and 4c), and the liver appeared normal with no lesions (Figure 4d). This suggests that the phenolic and steroid compounds in the extract do not induce toxic effects under repeated administration. In contrast, the combination of saponins and tannins in ethanolic extracts of areca nut has been associated with tumor formation, intestinal inflammation, and yellow fluid accumulation in the peritoneal cavity (Abbas et al., 2012).

The study conducted organoleptic observations of the liver and intestines of test animals. This was based on the consideration that the liver is the first organ targeted by drugs absorbed through the intestines via the portal vein. Therefore, the liver is recognized as the primary site for drug metabolism and detoxification (Gamiswarna et al., 1995). Exposure to substances with toxic properties may lead to organ damage or abnormalities. According to Robbins & Kumar (1992), a normal liver has a smooth surface and reddish-brown coloration. In contrast, an abnormal liver may display surface irregularities such as fibrous tissue, cysts, or spots, along with color changes ranging from red to yellowish.

4. Conclusion

Based on the findings of this study, the ethyl acetate extract of old areca nut demonstrates potential as a candidate antidepressant agent. This is evidenced by its ability to significantly reduce immobility time in mice during both acute and sub-chronic FST. However, while the extract showed notable antidepressant-like activity in acute administration, its effect diminished over the 7-day sub-chronic treatment compared to fluoxetine, a standard antidepressant. The phenolic compounds identified in the extract are suspected to be the primary active constituents responsible for the observed antidepressant activity. Importantly, repeated administration of the extract at the effective dose (100 mg/kg) did not induce visible toxic effects in test animals.

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