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Antidepressant-like Effects of Young Areca Nut n-Hexane Extract Using Forced Swim Test in Mice Tested Individually

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Abstract− Depression is a common neuropsychiatric disorder that occurs in humans regardless of gender and age. *Areca catechu*, as a local plant, can be utilized as an antidepressant to treat depression. The current investigation aimed to determine the antidepressant action from an n-hexane extract of young areca nut using the Forced Swim Test (FST) as a standard method in screening antidepressants validated by the behavior of animals. Short-term medication or acute FST was performed by injecting mice with extract at doses 10 and 50 mg/kg, while the mice were treated with the best dose in long-term medication or sub-chronic FST. A day after the re-test on sub-chronic FST, toxicity test was performed. The extract at the dose of 50 mg/kg possessed antidepressant action during acute and sub-chronic FST. The results of the phytochemical analysis stated that the saponins and steroids present in the young areca nut n-hexane extract may be the active constituents that act as antidepressants. No toxic effects were detected from the young areca nut n-hexane extract in mice that had been injected for 7 consecutive days. n-Hexane extract from young areca nut presents antidepressant potential.

Keywords: Antidepressant, Depression, Forced swim test, n-Hexane extract, Young areca nut

1. INTRODUCTION

Depression (mental disorder) is signed by difficulty concentrating, unstable emotions, physical issues (such as difficulty sleeping or eating), a loss of interest in enjoyable activities, and feeling that the future is not promising or quickly despairing [1]. In 2020, depressive disorders ranked in second place globally in terms of the burden of disease, according to the World Health Organization [2]. Since the COVID-19 Pandemic, the prevalence of depression in Indonesia increased. The Indonesian government has tried to find a way to stop the spread of COVID-19 by issuing a Work From Home (WFH) regulation so that people's movements are restricted. However, it can affect psychological conditions and one of which is mental disorder, specifically depression [3], [4]. It is supported by data from the Indonesian Psychiatric Association (PDSKJI) that as many as 1.552 respondents experienced depressive disorders due to the COVID-19 pandemic [5].

Five factors cause depression, including genetic factors, neurophysiological factors, cognitive factors, psychodynamic factors, and psychosocial factors. Based on neurophysiological characteristics, depression begins with continuous stress conditions that can cause sub-sensitivity of receptors on the postsynaptic cell membrane so that the concentration of neurotransmitters (serotonin, epinephrine, norepinephrine, and dopamine) can decrease. It was reported that depressed patients have low concentrations of biogenic amines [6]–[9]. The lack of neurotransmitters due to the activity of the enzyme Monoamine Oxidase (MAO) which oxidized them. To inhibit its activity, Monoamine Oxidase Inhibitors or MAOIs (one of the antidepressant groups) which work to trigger the production of monoamines in the synaptic vesicles of the brain are used [10]. The process of inhibition occurs when the substrate is able to react or not with the targeted enzyme covalently [11]. Despite MAOIs, other often used antidepressant medications include Tricyclic antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) [12]. However, prolonged use of these medications might have serious side effects. There is a growing trend of using herbal antidepressants to treat severe depression, and many of them have been confirmed to function just as well as prescription drugs with fewer adverse effects [13].

Nature has offered humans abundant biodiversity, including microorganisms and plants, to treat various illnesses. Our previous studies have confirmed the ability of fungi metabolites as antimicrobial [14]; antidiabetic agents [15], [16], immunomodulators [17], [18], and alternative oils [19], [20] by utilizing plants' metabolites. Besides, for medication, indigenous microbes can decompose the potentially dangerous chemicals which can contaminate the environment, including petroleum hydrocarbons [21]–[27] and the naphthalene [28]–[31]. In the digital age, computer programs may be used to conduct experiments [32], [33], and evaluate a medicinal molecule's effectiveness using a molecular computational method commonly known as *in silico*. Like the earlier investigations, secondary metabolites from local plants, including *Myristica fragrans* and *Piper longum* BI, were reported to have antidepressant action as MAO inhibitor [34]–[37] and drug for COVID-19 [38]. In more than half of cases, full remission of depression is achieved with traditional antidepressant treatment. As a result, studies on the possible antidepressant effects of plants are becoming more widespread [39].

The Areca nut, also known as the betel nut, is a seed of the *Areca catechu*, which belongs to the palm tree in Asia, Africa, and the tropical Pacific Islands. It is extensively used all around the world [40]. Due to its several

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psychoactive compounds, people chew it to relieve tension, increase mood, and heighten consciousness [41]. It has been suggested that the areca nut could act as a stimulant for the nervous system, increase noradrenaline concentrations [42], and might have anxiolytic properties [43]. Several studies have confirmed the antidepressant activity of areca nut by using in silico [44]–[48]. In vivo experimental, the Forced Swim Test (FST) is an animal model used in preclinical studies to study the effects of acute stress and depression [49]. Previous studies have used acute FST to confirm the antidepressant properties of areca nut extract [50]–[54]. Antidepressants are more potent after long-term medication [55]. The antidepressant efficacy of n-hexane extract from young areca nut during sub-chronic medication has not been investigated. Therefore, acute and sub-chronic FST tests were carried out to determine the potency of the n-hexane extract of old areca nut as an antidepressant when used in short-term and long-term treatment, as well as the toxicity caused by long-term administration of the extract.

2. RESEARCH METHODOLOGY

2.1 Extraction process

Young *Areca catechu* nuts (5,5 kg) were obtained from a local farmer (Pekanbaru and Kampar, Riau Province, Indonesia). Areca nuts were powdered. Then, powdered material was extracted with 1.45 L of n-hexane for 24 hours at room temperature. It was filtered through filter paper to obtain the macerate. The residues were used in the subsequent extraction. Those steps were performed until four times repetition. A vacuum rotary evaporator evaporated the mixed macerate until it was thick.

Phytochemical tests of the nut and n-hexane extract for the appearance of alkaloids, flavonoids, phenolics, steroids, terpenoids, and saponins were accomplished respectively by utilizing Dragendorff and Mayer Reagent, alkaline reagent, ferric chloride reagent, Liebermann-Burchard reagent, and the capability of forming froth.

2.2 Animals and ethical clearance

The experiment used Swiss albino male mice weighing 20-25 grams at 8-10 weeks from the Abdurrab University. They were acclimatized for about 7 days and kept under a controlled environment (23-26°C) and 40-60% humidity. The animals were maintained with a 12-hour cycle of light and darkness. Five to six mice were kept in a standard cage with unlimited food and water. Mice were handled for several minutes on the morning of the fourth day by picking up their tail. The procedure was started on the eighth day from 08.00 a.m. – 3.00 p.m. It was aimed to reduce the circadian effect. The mice that will be used were healthy and did not show significant changes in body weight (maximum deviation of 20%). The medical school at Riau University's committee for animal experimentation granted ethical clearance (approval no: B/004/UN19.5.1.1.8/UEPKK/2023).

2.3 Forced Swim Test

Acute FST (AFST) and then sub-chronic FST (SFST) versions of this test were carried out based on the treatment length and stress level. The pre-test was carried out 15 minutes 24 hours before the observation in a similar tank (acrylic glass of 20 cm (height) x 11 cm (diameter)). The tanks were filled with water (23-25°C) about 7.5 cm. The pre-test is a stressor thought to cause a hopeless behavior or passive stress strategy for mice.

Each animal received drug treatment intraperitoneally 1 hour before the test. The immobility period was measured during the final 8 minutes in 10 minutes test duration based on Ueno et al. [56]. The immobility time for the test subject was indicated by the decreased movement to keep the animals' heads above the water surface.

a. Acute FST
   Vehicle control saline (0,1 ml/20 g), fluoxetine (20 mg/kg), and n-hexane extract from young areca nut (10 and 50 mg/kg) were injected to the test subjects. This procedure was carried out on the day after the pre-test session. Based on various literary works, the medication doses were selected [57]–[60]
b. Sub-chronic FST
   Fluoxetine (20 mg/kg) and the optimal dosage of n-hexane extract were administered to the test subjects for 7 consecutive days. On the 7th day following the initial test, a re-test was conducted 1 hour after the drug given. The test subject was injected daily for 24 hours after the first administration.

2.4 Sub-chronic toxicity test

A day after the re-test on sub-chronic FST, all animals were euthanized by cervical dislocation. Then, the drug administration site was observed to identify if there was a bulge. Mice were skinned on that site and dissected to observe the internal organs [61].

2.5 Statistical anlysis

Values were expressed using the mean ± standard error of the mean (SEM). One-way ANOVA was used, followed by Tukey's Test, to evaluate whether the groups had statistically significant differences. Each group was significantly different if $p<0.05$. All the statistical analyses were performed by using IBM SPSS (IBM SPSS Statistic 25.0, IBM Corporation, New York, US).

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3. RESULTS AND DISCUSSION

3.1 Extraction and phytochemical result

The crude extract was produced in the extraction stage after several procedures and had a yellow-brownish color. The extract measured 15.713 g. According to the phytochemical screening, areca nut demonstrated positive in saponins, phenolics, and steroids. The only constituents in the hexane extract were saponins and steroids.

3.2 Acute and forced swim test

The antidepressant property of n-hexane extract from young areca nut and fluoxetine in declining the period of immobility is presented in Table 1. The extract at 50 mg/kg dose exhibited antidepressant action. The immobility time of mice did not significantly differ with fluoxetine as positive control. In order to get a more profound understanding of the antidepressant action of extract and fluoxetine, we determined the percentage decrease in immobility time utilizing the following formula: [(A-B)/A] × 100% where the immobility time for the control group (A) and the antidepressant-injected mice (B) is shown by the respective values. The dose gave the most significant decline in the immobility period, exhibited by the extract at 50 mg/kg dose, with a percentage of 24.57%.

Table 1. Acute forced swim test results affect by n-hexane extract from young areca nut

	Dose	Immobility time (Sec)	Reduction immobility time (%)
Control (Saline 0.1 mL/20 g)		408.33 ± 9.82^{b}	-
Fluoxetine	20 mg/kg	324 ± 6.35^{a}	20.65
n-Hexane extract	10 mg/kg	399.67 ± 7.88^{b}	2.12
n-Hexane extract	**50 mg/kg**	**308 ± 4.16^{a}**	**24.57**

Note: Based on Tukey's test, the different notation (a and b) in the same column tells the immobility time significantly differ with $p<0.05$

The comparison between immobility time in the extract and fluoxetine groups with control is further explained in Figure 1. The maximal antidepressant effect of the hexane extract appeared at 50 mg/kg dose ($p = 2.4 \times 10^{-5}$). In contrast, the extract at the dose 10 mg/kg could not reduce the immobility time significantly ($p = 0.924$). Thus, the extract at 50 mg/kg was continuously given to mice in sub-chronic medication.

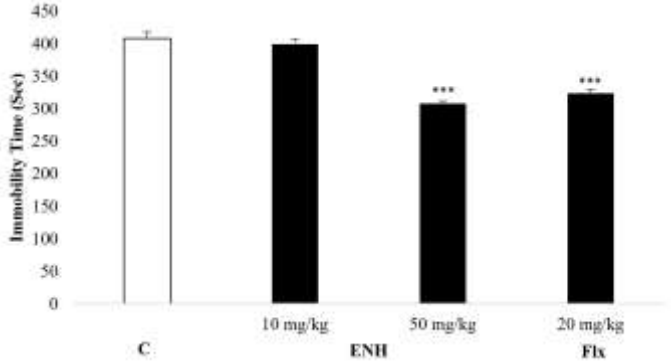

Figure 1. The effects of n-hexane extract (ENH) from young areca nut and fluoxetine (Flx) on immobility time in mice during acute FST. ***p<0.001-highly significant compared with control (C) group (n = 3 per dose)

In pre-clinical research, the FST was employed to assess the effectiveness of antidepressant medications and the impact of different neurobiological properties [62], [63]. The standard technique for FST involves placing the rodents at a height where they float on the water surface in a transparent glass filled with water. Immobility time, which indicates that the rat is depressed, is measured when the rodents are observed to be motionless and only move slightly to maintain their head above the water surface [62], and can be decreased by treating with an antidepressant [64].

Since the male mice were not impacted by hormones or pregnancy, as were the female mice, the sample used was manageable homogenous, and the anticipated results were more precise [65]. Adult male mice were used in the current study because they showed more immobility and less activity than juvenile mice, so depressive behavior was more accessible to learn [66].

The drug's pharmacokinetic properties and convenience factors are considered while choosing the drug's administration route [67]. In this current study, the intraperitoneal route was chosen because it is preferred over the oral route. Oral administration of drugs allows degradation or biopharmaceutical modification because the substance must be absorbed through the gastrointestinal system before being transported to the tissue target. Research by Nemes et al. [68] proved that the bioavailability of drugs administered intraperitoneally can be up to six times higher than oral.

During acute FST, the administration of antidepressants in test animals carried out was only a single dose to learn more about the acute effect of areca nut n-hexane extract as an antidepressant and to get the information on the

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dose with the best action in managing stress. Based on the AFST results, medication with n-hexane young areca nut extract on depressed mice appeared to reduce immobility dose-dependently, as shown in Fig. 1, which is similar to other findings [69]–[71]. The theory on the effect of substrate concentration on enzyme activity could be responsible for our results. The dose of 50 mg/kg is considered ideal because the protein's capacity to bind its substrate (a neurotransmitter) will be reduced since all of its allosteric sites will bind to metabolites in the extract. Consequently, depression will be dealt with, and the level of neurotransmitters will increase. In contrast, the 10 mg/kg dose was ineffective in reducing immobility time. Additionally, earlier reports confirmed the antidepressant properties of areca nut extract, extracted using polar solvents, including ethanol and methanol. Abbas et al. [61] discovered the areca nut ethanol extract's antidepressant-like effect in Sprague Dawley rats. The animals were given 10 to 100 mg/kg intraperitoneally and obtained a decreasing immobility time. The methanolic extract was given perorally at a dose of 250 mg/kg to adult Swiss albino mice, which significantly reduced the immobility time [72].

3.3 Sub-chronic forced swim test

The results of sub-chronic medication with n-hexane extract of young areca nut and fluoxetine can be seen in Table 2. The effect of giving fluoxetine and extract for seven days in a row was greater than the acute treatment; the reduction in immobility time increased to 43.54% and 26.01%, respectively.

Table 2. Sub-chronic forced swim test results affect by n-hexane extract from young areca nut

	Dose	Immobility time (Sec)	Reduction 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
n-Hexane extract	50 mg/kg	311 ± 3.46^{b}	26.01

Note: Based on Tukey's test, the different notation (a and b) in the same column tells the immobility time significantly differ with $p<0.05$

Effects of intraperitoneal administration of the hexane extract from young areca nut and fluoxetine as an antidepressant compared with control is presented in Fig. 3. ANOVA showed that the treatment of n-hexane extract of young areca nut significantly declined the immobility time ($p = 0.001$). In contrast, fluoxetine caused a decline in immobility time highly significant ($p = 4.2 \times 10^{-5}$).

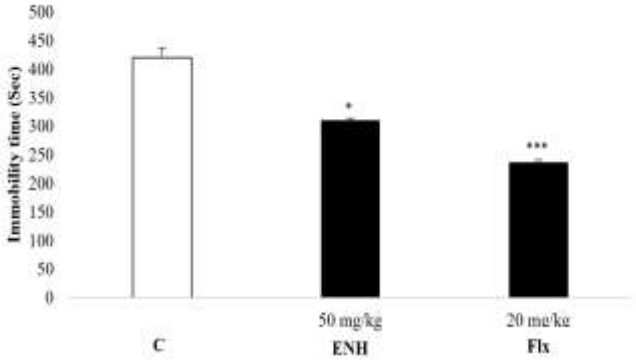

Figure 2. The effects of n-hexane extract (ENH) from young areca nut and fluoxetine (Flx) on immobility time in mice during sub-chronic FST. *p<0.05- significant, ***p<0.001-highly significant compared with control (C) group (n = 3 per dose)

Sub-chronic treatment is required to increase the effectiveness of the studied chemicals as antidepressants [63]. According to Abbas et al. [61], treating mice with an areca nut ethanolic extract for 7 consecutive days had an antidepressant effect by raising the level of the monoamine in the rats' hippocampi. The effect of n-hexane extract from young areca nut in minimizing stress levels increased after long-term medication. Although fluoxetine had better action than the extract after being administered in repeated dosages, the extract's efficacy in treating depression symptoms might be as low as 50%, as described in Table 2.

Antidepressant action in the n-hexane extract of areca nut was thought to be caused by secondary metabolites of saponins and steroids, which worked synergistically. It is appropriate an earlier report conducted by Abbas *et al.* [61] and Zhao et al. [73], that saponins and steroids have antidepressant activity, increasing noradrenaline and serotonin levels in the rats' hippocampus. The monoaminergic action of saponin was similar to Selective Serotonin Reuptake Inhibitor (SSRI), which could activate the serotonergic [74]. Herbal antidepressants have the advantage of being multitarget and have a synergistic effect. Herbal antidepressants are effectively used for long-term therapy because they can attract two receptors at once and are likely to contain not only antidepressant compounds but also anti-inflammatory, antioxidant, and other compounds. However, this herbal antidepressant drug has a relatively slow pharmacological effect compared to synthetic antidepressants, which is relatively fast.

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3.4 Implications of effect young areca nut n-hexane extract on mice toxicology

The test subjects were treated with hexane extract (ENH 50 mg/kg) sub-chronically, which obtained no toxic effects (Fig. 3). It can be seen that there was no tumor-like growth in the peritoneum (the area where medication was administered). All the internal organs, such as the intestine and liver, emerge healthy and look like control groups. A similar result appeared for the fluoxetine group. It had been thought that n-hexane extract from young areca nut had the potential to be a non-toxic antidepressant.

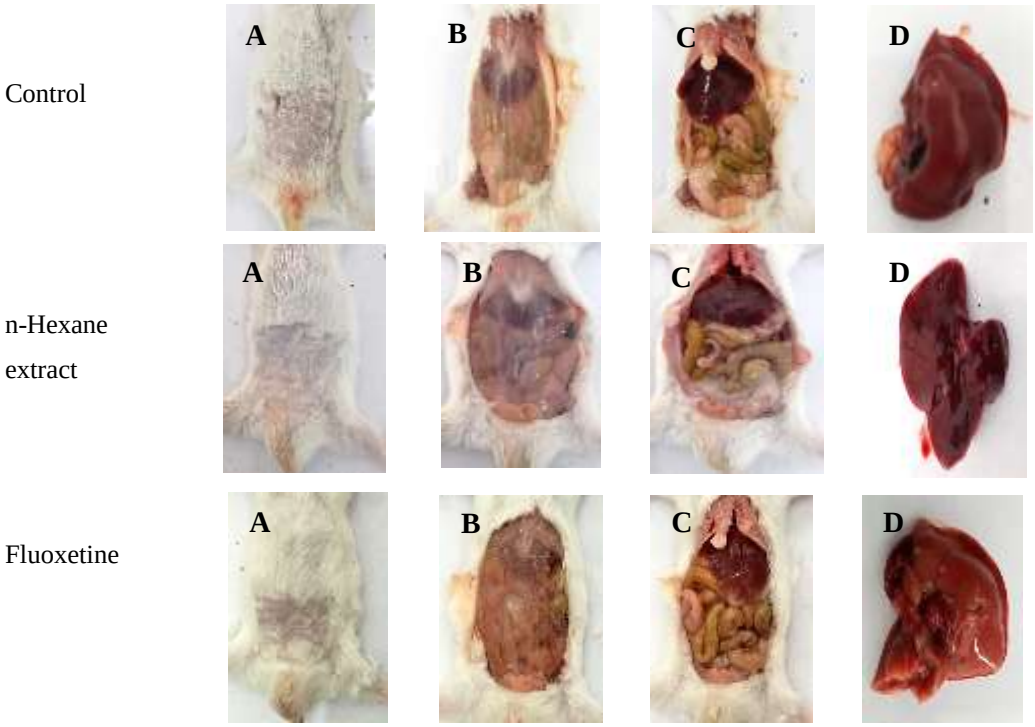

Figure 3. Effect of saline, n-hexane extract, and fluoxetine on toxicity in mice. (A) Peritoneum cross section (B) Peritoneum after skin removal (C) Intestine section (D) Liver

A prediction model is used in the toxicity test for drug exposure in mice to look into the effects in humans [75]. Some medications have severe side effects when used for an extended period. It has been confirmed that the ethanolic extract of areca nut contained tannin and saponin compounds, which lead to tumor-like growth in Sprague Dawley rats [61]. However, our research revealed that after 7 days of treatment, the steroid and saponin in the hexane extract worked synergistically and did not demonstrate any toxicity in mice. The test subject's liver was generally red tanned, indicating a healthy liver. The liver centers drug metabolism and detoxification [76]. A liver color that changes to yellowish red indicates liver damage due to exposure to toxic substances [77].

4. CONCLUSION

According to these findings, traditional medicine could alleviate depression. The young areca nut n-hexane extract induced antidepressant-like activity at the dose 50 mg/kg, which had a similar impact to fluoxetine after being administered acutely. However, it was presented as half as fluoxetine efficacy after being given sub-chronically. The saponins and steroids of the extract were the primary constituents that collaborated to shorten the immobility period in acute and sub-chronic FST. The metabolites did not cause adverse side effects in mice after being medicated for 7 days.

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