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Antidepressant Activity Evaluation of Keruing (*Dipterocarpus grandiflorus*) Oleoresin Aromatherapy Candle in Male Balb/C Mice (*Mus musculus*)

Evaluasi Lilin Aromaterapi Oleoresin Keruing (Dipterocarpus grandiflorus) Pada Mencit Balb/C Jantan (Mus musculus) Sebagai Antidepresan

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ABSTRACT

Depression represents a manifestation of prolonged stress, which, if left untreated, may lead to severe mental disorders. For depression treatment therapy, it can be carried out based on evidence-based treatment for depression and anxiety. Aromatherapy candles can be used as a non-pharmacological medium for depression therapy, where keruing has active compounds are phthalic acid di(3-methoxybenzyl) ester and phthalic acid, 5-ethyl-1,3-dioxan-5-yl octyl ester, causing keruing oleoresin to have a distinctive fragrance. This study aims to evaluate the pharmacological potential of keruing as an antidepressant for non-pharmacological therapy. Aromatherapy candles were formulated with keruing oleoresin at concentrations of 0%, 2.5%, 5%, 7.5%, and 10%, followed by testing their antidepressant activity using the Conditioned Place Preference (CPP) method. The results of the Paired T-test for groups F0, F2, and F4 or formulas containing 0%, 5%, and 10% of keruing oleoresin have a significant effect (sig. values <0.05) between pre and post-test being given aromatherapy and induction. In the One-way ANOVA test, between their groups, it can be seen there was no significant difference in test activity, namely for the pre-treatment test (sig. 0.445 > 0.05) and for the post-treatment test (sig. 0.065 > 0.05). Results indicated that while the candles met physical quality standards outlined by the Indonesian National Standard (SNI), no significant antidepressant effects were observed in mice. Further refinement in methodology, including the concentration of active compounds and delivery methods, is recommended to enhance the pharmacological potential of keruing oleoresin.

Keywords: antidepressants, aromatherapy, candles, keruing, oleoresin

ABSTRAK

Depresi merupakan manifestasi dari kondisi stress berkepanjangan yang apabila tidak tertangani dengan baik maka akan mengakibatkan gangguan mental. Pada terapi depresi seperti pengobatan dapat dilakukan berdasarkan pengobatan berbasis bukti (evidence-based treatment) untuk depresi dan kecemasan (anxiety) juga dapat dilakukan terapi psikologi seperti terapi perilaku yang lebih efektif untuk gangguan kecemasan yang termasuk pada non farmakologi. Lilin aromaterapi dapat digunakan sebagai media non farmakologi untuk terapi depresi, dimana metode ini merupakan suatu metode pengobatan alternatif yang memanfaatkan minyak atsiri dan komponen senyawa volatil, seperti terpen dan senyawa aromatik. Senyawa aktif dari oleoresin keruing berupa asam ftalat, yaitu asam ftalat di(3-metoksibenzil) ester dan asam ftalat, 5-etil-1,3-dioksan-5-il oktil ester menyebabkan oleoresin keruing memiliki wangi yang khas. Tujuan dari dilakukannya penelitian ini adalah untuk mengetahui aktivitas farmakologi dari lilin aromaterapi oleoresin keruing sebagai antidepresi berdasarkan kandungan senyawa metabolit sekunder oleoresin yang telah diketahui tersebut. Metode penelitian ini terdiri dari pembuatan sediaan lilin aromaterapi dengan konsentrasi 0%; 2,5%; 5%; 7,5%; dan 10%, yang kemudian dilanjutkan uji aktivitas antidepresi menggunakan Conditioned Place Preference test untuk diperoleh data perilaku (behavioral). Berdasarkan penelitian yang dilakukan bahwa oleoresin Keruing yang telah dibuat menjadi lilin aromaterapi selanjutnya dilakukan evaluasi uji mutu fisik dan telah memenuhi persyaratan dari SNI, yakni titik leleh tertinggi adalah 54.6^{o}C dan waktu bakar lebih lama dari 144 menit. Sedangkan untuk efek farmakologi lilin aromaterapi oleoresin keruing berdasarkan uji perilaku pada konsentrasi 0%; 2.5%; 5%; 7.5% dan 10% tidak memiliki aktivitas sebagai antidepresi.

***Kata Kunci** : antidepresan, aromaterapi, lilin, keruing, oleoresin*

INTRODUCTION

Based on Basic Health Research (Riskesdas) on 2018 data, it shows that more than 19 million people aged over 15 years old experience mental-emotional disorders, and more than 12 million people aged over 15 years old experience depression. Apart from that, based on the sample registration system carried out by the Research and Development Agency in 2016, annual suicide data was obtained from 1.800 people or every day five people commit suicide, and 47.7% of suicide victims are aged 10-39 years, which is the age of children, teenagers, and productive age. Mental health problems in Indonesia are related to the high prevalence of people with mental disorders. Currently, Indonesia has a prevalence of people with mental disorders of around 1 in 5 of the population, meaning that around 10% of the population in Indonesia has the potential for mental disorders (Balitbangkes RI., 2022).

It is known that depression often responds poorly to standard pharmaceutical treatments and psychotherapy techniques. This technique has resulted in increased awareness of the frequency and impact of depression, which is challenging to treat (Wang & Dwivedi, 2021; Fitzgerald, 2012). Depression is a manifestation of prolonged stress due to isolation from the outside world, as well as limited communication and lack of physical interaction with other people. Depression is a result of protracted stress characterized by symptoms of sleep disturbances, loss of interest or activities, changes in personality or mood, physical pain, difficulty with memory/remembering, and even thoughts of suicide (Agus & Khotib, 2023; Beheshti *et al*., 2016). When a person does not receive enough treatment for depression, based on evidence-based treatment for depression and anxiety, it is necessary to carry out psychological therapy such as behavioural therapy and antidepressant medication, which is more effective for anxiety disorders and is non-pharmacological therapy (Romlah *et al*., 2023; Hollingworth *et al*., 2010).

Aromatherapy candles are a diversified form of candle product with many functions such as lighting, therapeutic media, and room

freshener. Aromatherapy candles are an alternative application of aromatherapy by inhalation, where the aroma produced is obtained from a few drops of essential oil in a container filled with warm water (Butar-Butar M.E.T. *et al.*, 2024). When burned, this aromatherapy candle also produces a calming and relaxing aroma (Ahmad et al., 2022). Aromatherapy stimulates the nerves in the sense of smell and the central nervous system when the aromatherapy fragrance is inhaled (Lee KW. *et al*., 2023). The inhaled aroma will enter the nasal cavity and stimulate the nervous system in the brain, which plays the role of emotional regulation (Vora *et al.,* 2024). Physiologically, the therapeutic effect contains aromatic compounds that will correct emotional imbalances in the body system (Xu Y. *et al.,* 2023). The small response will produce a calming sensation, stimulating the brain's memory area and reducing depression (Ebrahimi *et al*., 2022; Molenaar *et al*., 2019).

Keruing, which contains essential oils, is a plant native to Kalimantan. Keruing is a plant that produces exudates in its essential oil with active compounds in terpenoids and ester groups. One of the active compounds of Keruing oleoresin is the phthalic acid di(3-methoxybenzyl) ester (14.74%), and phthalic acid, 5-ethyl-1,3-dioxan-5-yl octyl ester (15.92%). The ester group of phthalate compounds found in Keruing oleoresin has an aroma and can be used in the perfume industry as an essential ingredient for cosmetic products (Agus ASR *et al.,* 2024; Fernandes & Maharani, 2019).

Phthalic acid from kruing, a group of terpenoids and esters, has a working mechanism in influencing olfactory by crossing the blood-brain barrier and potential interaction with specific ares of the brain. Direct gas exchange to the respiratory system is done by diffusion. Lipophilic molecules can be delivered directly across the BBB. They can activate special areas in the central nerves system, which will positively induce physiological systems and reduce symptoms of mood disorders (Vora *et al.*, 2024).

METHODS

Tools and Materials

The tools used in this research are analytical balance, hotplate, porcelain cup, beaker glass, dropper pipette, capillary tube, stirring rod, candle mould, animal balance, animal cage, electrical inducer, Conditioned Place Preference (CPP) box, foot shock box, and stopwatch. The materials utilized in this study included stearic acid, beeswax, keruing oleoresin, candle wicks, and male Balb/C mice (*Mus musculus*).

Candles aromatherapy preparation

Preparation for making keruing aromatherapy candles begins by selecting formulations with various oleoresin concentrations. The formulation of these candles can be seen in Table 1.

Table 1. Formulation of candles

Materials	Function	Formula (%)				
		F_0	F_1	F_2	F_3	F_4
Oleoresin	Aromatherapy compounds	0	2,5	5	7,5	10
Beewax	Base	20	20	20	20	20
Stearic acid	Base	ad 100	ad 100	ad 100	ad 100	ad 100

This formulation uses stearic acid and beewax, heated separately in a water bath at 70^{o}C. Next, stearic acid and beewax are mixed until homogeneous, and then keruing oleoresin is added with various predetermined concentrations and stirred until homogenous. Once evenly distributed, pour it into a candle mould that has previously been given paraffin oil and place it on a flat place, leaving it until the wax hardness and is ready to be used for testing.

The manufacture of aromatherapy candles research was done with the concentration of 2.5-10%; it was found that the 10% oleoresin concentration had a more dominant aroma and colour than other concentrations (Butar-Butar *et al.,* 2024), so it was necessary to conduct as an antidepressant test of the activity of phthalate compounds, especially phthalic acid di(3-methoxybenzyl) ester (14.74%) and phthalate acid, 5-ethyl-1,3-dioxan-5-yl octyl ester (15.92%).

Preparation of test animals

The male Balb/c mice (*Mus musculus*) (weight between 20-25g) used in the study, aged two months, were adjusted to the Federer formula in determining the number of samples consisting of 5 test groups that adjust the concentration of oleoresin aromatherapy candles obtained a calculation of 5 test animals for each group. Each group consists of 5 male mice according to the calculation of the number of samples.

The number of 5 test groups that adjusted the concentration of the oleoresin aromatherapy

wax. Each group consisted of 5 males according to the sample size calculation.

The animals were kept at about (26±1°C) with a 12-h light: dark cycle and relative humidity of about 74%. They were fed with commercial rodent pellets and water ad libitum. The animals underwent a one-week acclimatization period prior to the initiation of the experiments (Umukoro, et al., 2018; Andersen*, et al*.,2014).

Antidepressant testing

This study employed an experimental design with a pre-and post-test control group, utilizing male Balb/C mice (*Mus musculus*). Aromatherapy classification was divided into several administration routes, oral or topical, with various techniques such as massage, psych-aromatherapy, cosmetic, medical, and olfactory stimulation. Olfactory stimulation can be used for compounds that function to treat stress by increasing serotonin and dopamine in the central nervous system through transcellular, paracellular, or intracellular pathways (Vora *et al.,* 2024) so that it would affect behaviour.

Wax containing oleoresin in various concentrations (0%, 2,5%, 5%, 7,5%, and 10% dispersed in the candles) is provided as a test material in aromatherapy. In the inhalation of essential oil test, the apparatus consisted of a square transparent cage (20cm x 20cm x 30cm) with a hole in the upside. Candles were poured into a Petri dish at the bottom of the cage to ensure efficient aromatherapy vaporization. Animals were exposed to the transparent cage for 15 minutes before induction and behavioural tests (Seol *et al.,* 2010).

The Conditioned Place Preference (CPP) method evaluates animal behaviour by seeing whether animals prefer one compartment over another (Huston *et al*., 2013). Before the test animals were treated, their behaviour was tested using CPP on day 0 to observe their behaviour under normal conditions.

Induction of Test Animals

All groups of test animals whose behaviour has been measured under normal conditions are expressed as pre-treatment data. Then, the test material was given as aromatherapy candles in a special box 30 minutes before the stress induction. The induction was provided using a foot shock for 10 minutes at 30-second intervals. The induction was done to all groups for 14 consecutive days by administering aromatherapy test materials, and 30 minutes later, stress induction was carried out. On the 14th day, animal stress was observed using the CPP test as post-treatment data.

Statistical analysis

The data obtained were expressed as mean±SEM (standard of mean) and analyzed using a statistical instrument. The data was collected using a T-test between groups, with normality distributed test and P-values less than 0.05 ($p<0.05$) considered statistically significant. Then, to see the relationship between activity groups as antidepressants, a One-way ANOVA analysis was used.

The Research Ethics

All experimental procedures were conducted by guidelines relevant to the care of experimental animals, as approved by the Research Ethics Committee of STIKES Dirgahayu Samarinda (Approval No:000434/KEP STIKES Dirgahayu Samarinda/2023).

RESULTS AND DISCUSSION

Physical test of aromatherapy candles

Physical tests were carried out for the first time for aromatherapy candles, which aimed to see the stability of candles with different keruing oleoresin contents. Every test carried out refers to SNI for the physical quality produced. Table 2 shows the melting point results of keruing oleoresin aromatherapy candles.

Table 2. Physical test of aromatherapy candles

Replication	Melting point (°C)				
	F0	**F1**	**F2**	**F3**	**F4**
1	56	54	55	53	53
2	55	55	54	54	53
3	56	55	54	53	51
Average	55,6	54,6	54,3	53,3	52,3

Description: F0: Oleoresin 0%; F1: Oleoresin 2,5%; F2: Oleoresin 5%; F3: Oleoresin 7.5%; F4: Oleoresin 10%.

Organoleptic testing revealed that formulations F3 and F4 exhibited a more pronounced yellow hue than F1 and F2, attributable to their higher keruing oleoresin concentrations, enhancing the aromatic profile. Testing the physical quality of aromatherapy candles made from keruing oleoresin needs to be carried out to find out whether the candles produced meet the requirements set by the Indonesian National Standards (SNI) or not; if they meet, then the candles can be used further in activity study. The physical test results of

aromatherapy candles made from keruing oleoresin are effortless to freeze after melting the raw material, and they can also be easily ignited based on the formula made, as seen in Figures 1 and 2. Based on the melting point test results, it is known that all formulas meet the standard, namely 52.3-55.6°C based on SNI 0386-1989-A/SII0348-1989, which states that the melting point of the candle is in the range of 50-58°C. From these results, all candles can be used as further antidepressant test materials.

Figure 1. Aromatherapy candles made from keruing oleoresin (F0: Oleoresin 0%; F1: Oleoresin 2,5%; F2: Oleoresin 5%; F3: Oleoresin 7.5%; F4: Oleoresin 10%).

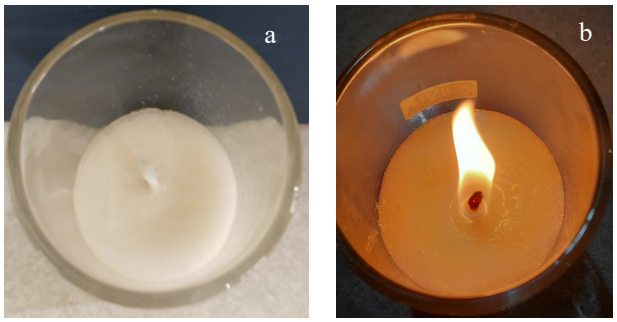

Figure 2. (a) Before and (b) after lighting keruing oleoresin aromatherapy candles

Antidepressant test of aromatherapy candles

In antidepressant activity tests, the measurement parameter is the behaviour of the experimental animals. The behaviour of the experimental animals will be measured first before being induced by placing them in a transparent chamber filled with steam from aromatherapy wax that has been saturated and leaving it for 15 minutes. Then, the test animals will be placed in the CPP apparatus, and their behaviour will be calculated before being induced, as seen in Figure 3(a). Next, the animal will be induced according to the induction procedure, which can be seen in Figure 3(b), and behavioural test measurements will be carried out again on the CPP device and the resulting data will become behavioural data after induction, which can be seen in Figure 3(c).

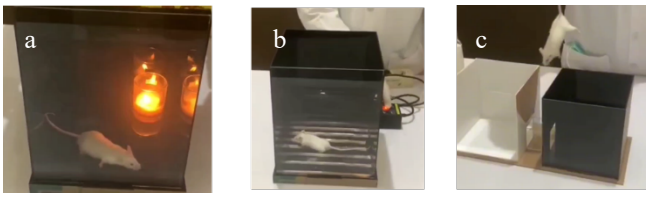

Figure 3. The process of antidepressant study from keruing oleoresin aromatherapy candles, (a) giving aromatherapy to animals test in the chamber, (b) the process of inducing depression with electric current using a foot shock device, (c) measuring behaviour using the CPP instrument.

To review the activity of aromatherapy candles that have been produced on the pharmacological effects of antidepressants. Carrying behavioural measurements on Mus musculus test animals using the Conditioned Place Preference (CPP) test. Measurement of behaviour during depression will be expressed in the form of pre-and post-treatment behavioural data. The behavioural test results for each group of aromatherapy candles can be seen in Table 3.

Table 3. Pre & post-treatment CPP Test Scores

Group Names	Pre-treatment (CPP test) (sec.)	Post-treatment (CPP test) (sec.)
Group F0	46	89
	71	140
	68	92
	78	100
	64	95
	66	116
Group F1	34	132
	23	157
	75	105
	85	95
	80	100
	86	110
Group F2	71	122
	88	112
	92	95
	78	100
	64	127
	66	180
Group F3	116	115
	79	112
	95	143
	97	119
	104	94
	91	91
Group F4	66	180
	68	180
	80	180
	109	131
	107	131
	38	93

Pre- and post-treatment behavioural scores were recorded and analyzed using paired T-tests to evaluate significant differences between treatments before and after aromatherapy or induction exposure. The results of the Paired T-test can be seen in Table 4.

Table 4. Paired T-test results

Groups	Mean	Sig. (2 tailed)	Results
Group F0	-39.83	0.003	Sig. < 0.05
Group F1	-52.67	0.052	Sig. > 0.05
Group F2	-46.17	0.036	Sig. < 0.05
Group F3	-15.33	0.158	Sig. > 0.05
Group F4	-71.17	0.010	Sig. < 0.05

For correlations in the CPP scores data, It can be concluded that in terms of the data above, only the group of F1 gave a correlation value pre and post-treatment (sig. values 0.004 < 0.05), which means there is a correlation between the resulting data. The Paired T-test results, referring to Table 4, were carried out to see whether there was a significant influence on the difference in treatment before and after induction and aromatherapy intervention. From the test results, It can be concluded that groups F0, F2, and F4 or formulas containing 0%, 5%, and 10% keruing oleoresin have a significant effect (sig. value <0.05) between before and after being given aromatherapy and induction, that the higher of the concentration, the better the influence on behavioural.

Table 3 presents the CPP scores, indicating the duration test animals remained on one side of the chamber, reflecting their behavioural state. Animal behaviour is said to be stressed if the animal remains on the bright side of the CPP box for a long time. However, with antidepressants, animals should stay on the dark side longer. So, the pre-treatment to see differences in the duration of the test animals during pre- and post-treatment comparison of pre-and post-treatment data can be seen in Figure 4. The test results show that the post-treatment values are higher than the pre-treatment value, which means there is no antidepressant activity.

From the Paired T-test, a follow-up test was carried out using One-way ANOVA to see the relationship between the groups, which produced different data before and after being given an induction or aromatherapy intervention. These results can be seen in Table 5.

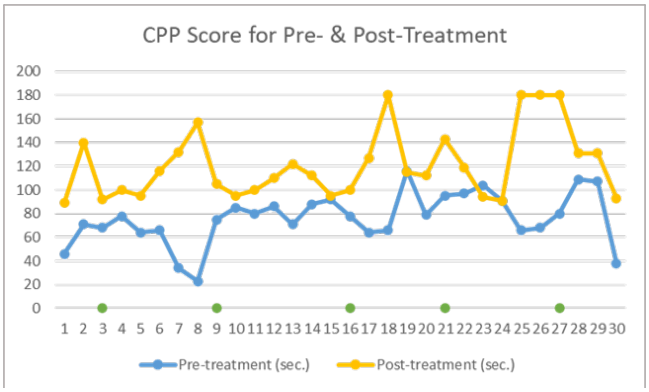

Figure 4. Pre- & post-treatment CPP Scores

Based on the data from the One-way ANOVA test, it can be concluded that between groups F0, F2, and F4 or groups with oleoresin content of 0%, 5%, and 10%, seen from the relationship test between pre and post-treatment values, it is stated that there is no significant difference in test activity, namely in the pre-treatment test (sig. 0.445 >0.05) and in the post-treatment test (sig. 0.065 >0.05) or it can be concluded that the test group with this concentration could not show activity as an antidepressant.

Tabel. 5 One-way Anova Test Results

Groups	Pre-treatment				
	Homogeneity			Anova Test	
	Levene Statistic	Sig.	Result	F	Sig.
F0, F2, F4	3.18	0.071	>0.05	0.86	0.445
	Post-treatment				
Groups	Homogeneity			Anova Test	
	Levene Statistic	Sig.	Result	F	Sig.
F0, F2, F4	1.571	0.24	> 0.05	3.307	0.065

It can be seen in the data in Figure 1 that the unstable behaviour was based on the duration value in each compartment at each concentration. Various variables affect the results, such as the concentration of phthalic acid in the oleoresin, the duration of exposure to wax, and the duration of induction given to the animals test.

CONCLUSION

Keruing Oleoresin to be made into aromatherapy product can be said to be successful, as seen from the physical quality test evaluation, which meets the requirements of SNI, namely having a higher melting point of 54.6°C

and a longer burning time of 144 minutes. Meanwhile, the pharmacological effects can be stated that aromatherapy candles from Keruing oleoresin for a concentration of 0%, 2.5%, 5%, 7.5%, and 10% have no activity as antidepressants based on statistical tests that have been carried out. This study concluded that while the physical properties of keruing oleoresin candles met the standards set by the Indonesian National Standard (SNI), no significant antidepressant effects were observed in behavioural tests. These findings suggest that the lack of efficacy may be due to suboptimal oleoresin concentrations, unsuitable carrier materials, or inefficiencies in aromatherapy delivery. Future studies should address these limitations by refining the formulation and testing protocols. Therefore, it is necessary to develop retesting with an evaluation of materials, methods, and other procedures to create a new drug based on endemic plants from Kalimantan.

Based on these results, further research is needed to increase the concentration of active ingredients, phthalic acid synthesis, behavioural testing with other methods, and measuring neurotransmitters using antibody reactions.

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