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Antidepressant-Like Activity and Physicochemical Analysis of Essential Oils from *Michelia alba* and *Plumeria alba* Flowers

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ABSTRAK

Depresi adalah gangguan mental dengan prevalensi yang meningkat. Selain antidepresan konvensional, minyak atsiri telah digunakan dalam aromaterapi sebagai pengobatan komplementer dan alternatif untuk mengurangi depresi. Dalam studi saat ini, aktivitas seperti antidepresan dari penghirupan minyak atsiri dari bunga Michelia alba (MAEO) dan Plumeria alba (PAEO) dianalisis menggunakan force swim test. Waktu imobilitas tikus dari kelompok yang diuji dievaluasi secara statistik dengan uji Kruskal Wallis non-parametrik, diikuti dengan uji post hoc Mann Whitney. Selain itu, karakterisasi kedua minyak atsiri ditentukan dengan indeks bias, kelarutan, dan analisis Gas Chromatography-Mass Spectrophotometry (GC-MS). PAEO menunjukkan aktivitas antidepresan yang lebih kuat dari MAEO (p<0,05) dan sama dengan kontrol positif (minyak esensial Lavandula angustifolia) (p lebih dari 0,05). Analisis GC-MS mengungkapkan beberapa agen penenang di MAEO dan PAEO seperti linalool, linalyl acetate, phenylethyl alcohol, dan methyl anthranilate.

ABSTRACT

Depression is a mental disorder with an increased prevalence. Other than conventional antidepressants, essential oils have been used in aromatherapy as a complementary and alternative medicine to reduce depression. In the current study, the antidepressant-like activity of the inhalation of essential oils from Michelia alba (MAEO) and Plumeria alba (PAEO) flowers was analyzed using the forced swim test. The immobility time of mice from tested groups was evaluated statistically by the non-parametric Kruskal Wallis test, followed by the Mann Whitney post hoc test. Also, the characterization of both essential oils was determined by refractive index, solubility, and Gas Chromatography-Mass Spectrophotometry (GC-MS) analysis. PAEO showed stronger antidepressant-like activity than MAEO ($p<0.05$) and it was equal to the positive control (essential oil of Lavandula angustifolia) ($p>0.05$). The GC-MS analysis revealed some calming agents in MAEO and PAEO such as linalool, linalyl acetate, phenylethyl alcohol, and methyl anthranilate.

1. INTRODUCTION

Depression is a common mental disorder that could decrease the quality of life and cause other diseases such as cardiovascular, metabolism, and neurological disorder (Yankelevitch-Yahav et al., 2015). It was predicted as the most prevalent mental disease by 2030 (Abbasi-Maleki et al., 2020). The rise of the global estimated prevalence of depression up to 25% due to COVID-19 outbreak (Bueno-Notivol et al., 2021). People suffering from depression consume antidepressant drugs with many disadvantages such as side effects and low efficacy (Bogdanova et al., 2013). On the other hand, aromatherapy has been used for centuries as complementary and alternative medicine to relieve stress and depression. Aromatherapy is described as using essential oils to accomplish physiological and psychological needs through inhalation, oral, or direct application to the skin (Sindle & Martin, 2020). Many experiments have been conducted to elucidate the antidepressant-like effect of essential oils and their volatile components such as terpenes and aromatic compounds (Sousa et al., 2017; Zhang et al., 2021).

Moreover, the plants as sources of essential oils are abundant in Indonesia, including *Michelia alba* (white champaca) and *Plumeria alba* (white frangipani). The leaves oil of *M. alba* showed a sedative effect in human studies (Koomhin et al., 2020) and antibacterial activity (Songsamoe et al., 2021). Meanwhile, its extract could prevent UVB-induced photodamage (Chiang et al., 2012). The essential oil of *P. alba* flower exhibited antibacterial activities. Additionally, essential oil also had antioxidant activity, and its stem bark

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extract and leaves extract showed antiparasitic and antiarthritis activity, respectively (Anggoro & Hariono, 2020).

The flower part of *M. alba* and *P. alba* are used in daily life in the religious activities of Balinese Hindus. However, their usage to reduce depression is poorly studied. This is the first report on the antidepressant-like activity on the inhalation of essential oil from *M. alba* and *P. alba* flowers using the forced swim test (FST). The FST can analyze antidepressant-like potential by studying mice behavior (Abbasi-Maleki et al., 2020). Also, the physicochemical characterization of the oils was analyzed. The current study was expected to increase the benefit of the plants and to provide evidence-based for aromatherapy to reduce depression.

2. METHODS

Essential oils of *M. alba* and *P. alba* flowers were purchased from Gallery Essential Oil & More (Denpasar, Bali). Essential oil of *L. angustifolia* was purchased from Rumah Atsiri (Karanganyar, Central Java). Other materials were 96% ethanol (Merck; Darmstadt, Germany) and aquadest. The refractive index of each essential oil was estimated based on a method described by Karakaya *et al.* (2012) with slight modification. Essential oil 200 µL was put into the Atago NAR-1T Solid refractometer. The measurement temperature was 20°C. The procedure to determine the solubility of essential oil in 96% ethanol was modified from previous research (Anwar et al., 2011). Essential oil 1 mL was put into a test tube, then 96% ethanol was added into the tube until a clear solution was obtained. The chemical composition of essential oil was analyzed using the instrument of 7890B GC, 5977B MSD (Agilent Technologies) equipped with HP-5MS UI column (30 m length, 0.25 mm film thickness, and 0.25 µm internal diameter). The temperature was increased from 70°C to 290°C with rate 10°C/minute.

The procedure was adopted from previous studies (Ito & Ito, 2011; Swati et al., 2013). Mice were adapted for 7 days and randomly divided into 4 groups (negative control, positive control, *M. alba* essential oil (MAEO), and *P. alba* (PLEO) groups (n=7). Afterward, essential oils were diluted with aquadest until 1% and put into a diffuser. The diffuser was turned on inside a test room for 15 minutes until the entire room was saturated with essential oil. For negative control, the test room was saturated with aquadest. Meanwhile, for positive control, the lavender essential oil (LAEO) was used because it is the most studied essential oil as antidepressant (Ito & Ito, 2011). Afterward, the antidepressant effect marked by immobility time was observed with the following steps. First, mice were placed inside the saturated test room for 5 minutes. Then, mice were transferred into an open cylindrical container (10 x 25 cm) containing 15 cm of water at 25°C for 8 minutes. Immobility time was observed for the last 6 minutes and determined as the time when mice stop moving in the water. The procedure in this study has been approved by Animal Ethics Committees, Faculty of Veterinary Science, Udayana University (Number: B/121/UN14.2.9/PT.01.04/2021). The antidepressant effects of essential oils were expressed as median immobility time (*s*), with minimum and maximum values in parentheses. Data were evaluated by the non-parametric Kruskal Wallis test, followed by the Mann Whitney post hoc test. P values less than 0.05 were considered to be statistically significant. The SPSS 24 for windows was used to perform the statistical analysis.

3. RESULTS AND DISCUSSION

Result

Each tested essential oil was characterized using physical color appearance, refractive index, solubility, and GC-MS analysis (Table 1 and Table 2). The refractive index of essential oils is usually ranging from 1.450 to 1.590. Moreover, the solubility of essential oils in ethanol notifies their quality. Solubility is often reduced in oils that have been aged or inadequately stored. Essential oils contain phytochemicals, such as terpenes (mono- and sesquiterpene), their oxygenated (hydroxyl and carbonyl) derivatives, aliphatic aldehydes, alcohols, and esters (Sell, 2016). These compounds vary due to some factors, such as methods of extraction, geographical origin, and botanical source. Benzyl alcohol was the major compound in MAEO and PLEO (Table 2). A different result was revealed that linalool (72.76%) was predominant in the flower oil of *M. alba* (Ueyama et al., 2011). Meanwhile, benzyl salicylate (33.98%) and limonene (9.1%) were the highest abundance component in the essential oil of *P. alba* flower from India and Nigeria, respectively (Lawal et al., 2014; Sahoo et al., 2021).

Table 1. Physical properties of essential oils tested

Sample	Characteristic		
	Physical color and appearance	Refractive index (20°C)	Solubility
MAEO	Liquid, yellow	1.475	Soluble in 3 mL of 96% ethanol
PLEO	Liquid, yellow	1.482	Soluble in 2 mL of 96% ethanol

MAEO = *Michelia alba* essential oil, PLEO = *Plumeria alba* essential oil

Table 2. The chemical composition in the essential oils tested by GC-MS

Peak	Rt*	Name	Area %
M. alba essential oil			
1	6.790	Benzyl alcohol	34.98
2	8.169	Linalool	4.17
3	8.462	Phenylethyl Alcohol	4.62
4	9.955	Benzene methanol, .alpha.-methyl-, acetate	1.72
5	10.537	Citronellol	1.18
6	10.957	Linalyl acetate	2.70
7	12.405	2,6-octadiene, 2,6-dimethyl-	0.70
8	12.886	2-propenoic acid	0.97
9	16.241	Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester	8.54
10	16.408	cis-3-Hexenyl salicylate	0.79
P. alba essential oil			
1	6.854	Benzyl alcohol	33.75
2	8.227	Linalool	4.27
3	9.472	Acetic acid, phenylmethyl ester	3.87
4	11.680	Indole	0.62
5	11.840	2-Propen-1-ol, 3-phenyl	2.29
6	12.356	Methyl anthranilate	0.71
7	13.793	1-(4-tert-Butylphenyl)propan-2-one	0.43
8	14.031	2(3H)-Furanone, -5-hexyldihydro-	0.82
9	16.273	Cyclopentaneacetic acid, 3-o6xo-2-pentyl-, methyl ester	7.57

*Rt = retention time (minute)

All samples revealed lower immobility time than negative control which suggested their potential effect as antidepressants (Table 3). MAEO was the weakest antidepressant, marked by its higher immobility time compare to PLEO and positive control (LAEO). On the other hand, statistical analysis showed that the immobility time of PLEO was not significantly different with the positive control (LAEO) which pointed out an equal antidepressant-like activity. Thus, next exploration should be focused on PLEO.

Table 3. Immobility time (*s*) and P values from the Mann Whitney post hoc test from tested groups

Group	Median (min-max)	P values			
		MAEO	PLEO	Negative control	Positive control (LAEO)
MAEO	41.5 (21-52)	-	0.260	0.004*	0.037*
PLEO	31.5 (25-44)	0.260	-	0.004*	0.054
Negative control	65 (61-99)	0.004*	0.004*	-	0.004*
Positive control (LAEO)	24.5 (16-33)	0.037*	0.054	0.004*	-

MAEO = Michelia alba essential oil, PLEO = Plumeria alba essential oil, LAEO = Lavandula angustifolia essential oil, *significant difference ($p<0.05$)

Essential oils have been used in alternative medicine as aromatherapy to maintain mental and body health (Sindle & Martin, 2020). Many plants produce essential oils with antidepressant activity (Sousa et al., 2017). In the current study, essential oil from *Lavandula angustifolia* (LAEO) was used as a positive control since it has been studied widely as an antidepressant agent (Ito & Ito, 2011). Furthermore, essential oil from *Michelia alba* flower (MAEO) and *Plumeria alba* flower (PAEO) were studied to reveal their physicochemical characteristic and antidepressant activity. The essential oils were selected since they are coming from plants that are commonly used in religious activities of Balinese Hindus. This exploration is expected to increase the health benefit of the plants. The antidepressant-like effect was carried with a forced swim test. In this method, the antidepressant effect was determined through immobility time, which was referred as the period when the mice tried to float on water without struggling and only tried to maintain their head above the water (Abbasi-Maleki et al., 2020). The immobility reveals a measure of behavioural despair, thus a shorter immobility time reflects less depression (Yankelevitch-Yahav et al., 2015). This method has been widely used in other studies (Abbasi-Maleki et al., 2020; Dougnon & Ito, 2020; Liang et al., 2018; Sohrabi et al., 2017; Tabari et al., 2018).

Antidepressant-like effect due to inhalation of essential oils caused by the existence of certain bioactive compounds, including monoterpenes, sesquiterpenes, and aromatic compounds (Zhang et al., 2021). Many studies have proved the effectiveness of the individual volatile compounds in essential oils to reduce depressive behavior. Based on literature, some of the calming agents contained in MAEO and PLEO were linalool, linalyl acetate, phenylethyl alcohol, and methyl anthranilate. Linalool is a monoterpene and its derivate, linalyl acetate, showed antidepressant-like activity through interaction with the monoaminergic system such as SERT and 5-HT1A receptors (Avram et al., 2021; Guzmán-Gutiérrez et al., 2015). Phenylethyl alcohol could reduce depressive behaviors in mice when analyzed with an open field test and tail suspension test (Ueno et al., 2019). Methyl anthranilate extended the diazepam-induced sleep in mice, indicating an interaction with the gamma-aminobutyric acid receptor complex when given intraperitoneally (50-200 mg/kg) (Radulovič et al., 2013). Moreover, other bioactive compounds in tested essential oils might also contribute to their antidepressant-like activity. The optimum concentration and dosage of essential oils used could also affect their pharmacological activities. Therefore, future experiments should be carried out related to these topics.

4. CONCLUSION

The essential oil of *M. alba* and *P. alba* flowers showed antidepressant-like activity by forced swim test. The P. alba flower essential oil had a similar activity with the positive control group (essential oil from *L. angustifolia*). Moreover, GC-MS analysis showed both essential oils contained monoterpenes and sesquiterpenes with antidepressant-like activity such as linalool, linalyl acetate, phenylethyl alcohol, and methyl anthranilate.

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