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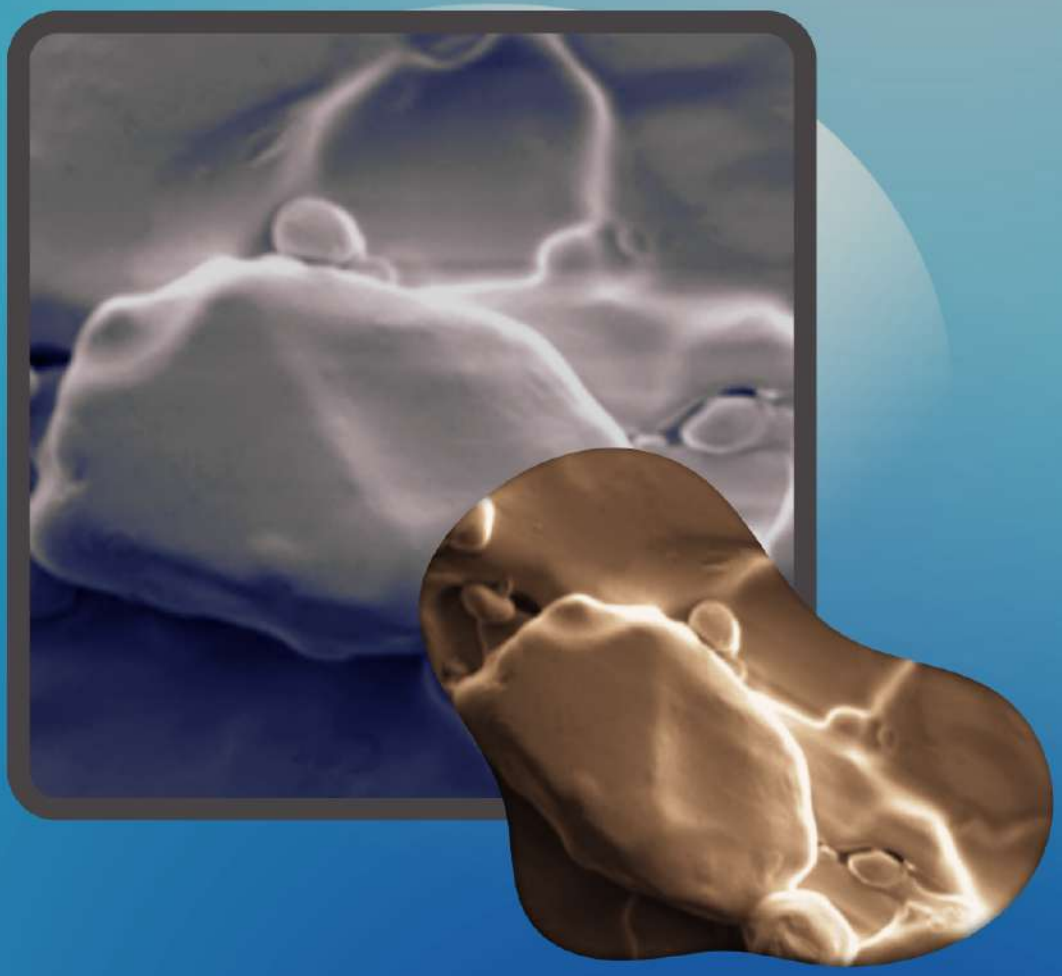

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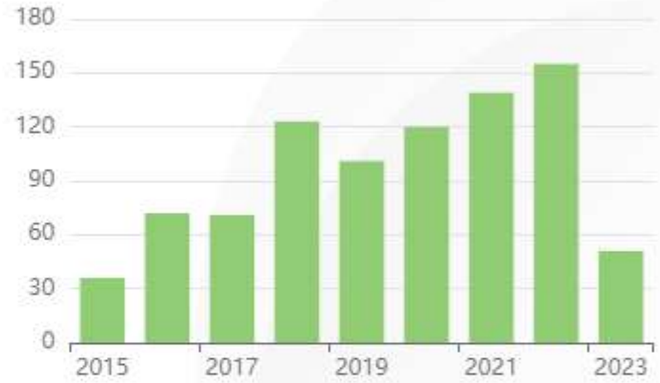

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ARTICLES

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Review Article

The Effect of Natural Essential Oil Depigmenting Agent for Alternative Treatment of Melasma

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Abstract: Melasma, known as a hyperpigmentation disorder, is more common in women of childbearing age with Fitzpatrick IV-VI skin types. The best treatment for melasma is with 2 – 4% hydroquinone, but because of the side effects, alternative treatments are mostly used for melasma. One of them is essential oils. The purpose of this review is to discuss the various effects of essential oils that can be used as depigmentation agents in the alternative treatment of melasma. 22 articles were used on 8 types of essential oils which are known to have a depigmenting potential for melasma. The databases used include PUBMED, Science Direct, and Google Scholar. *S. macrostachya* (hedgenettle/woundwort oils) has the strongest tyrosinase activity, with an IC_{50} of 22.86 ± 0.82 µg/mL (same as 0.02286 ± 0.00082 mg/mL), followed by *S. officinalis* (sage oils) with an IC_{50} of 0.73 ± 0.01 mg/mL. In this review, all essential oils have been shown to be useful in treating melasma, especially *S. macrostachya* and *S. officinalis* oils.

Keywords: melasma; essential oil; depigmenting agent; anti-tyrosinase

1. INTRODUCTION

Melasma is a hyperpigmentation disorder due to dysfunction of melanogenesis that is chronic, localized and acquired, and usually occurs in women [1], [2]. Epidemiologically, the prevalence of melasma in the global population is 1% and in high-risk populations ranges from 9-50%. This wide range is due to the many factors that influence the incidence rate, such as skin type, ethnicity, as well as differences in the level of UV exposure in various geographical conditions [3]. Hydroquinone with a concentration of 2-4% is the best treatment for melasma, but side effects such as dry, peeling, or erythematous skin can occur [4]. Therefore, alternative medicine is needed that helps in treating melasma and minimizes the side effects of pharmacological treatment.

Essential oils have long been known as an alternative treatment for skin diseases. This is due to its various biological activities, including as an analgesic, antiseptic, antimicrobial, diuretic, and as a depigmentation agent. Its function as a depigmentation agent can help in healing melasma, because of its anti-melanogenic effect, namely inhibition of enzymes involved in melanogenesis [5], [6]. Various types of essential oils have been studied for their benefits and can play a role in alternative treatment for melasma [7].

2. METHODS

This review aims to determine the effect of natural essential oil depigmenting agent for alternative treatment of melasma. In this review, 22 articles were used on 8 types of essential oils which are known to have a depigmenting potential for melasma, namely sage oils (*Salvia*), hedgenettle / woundwort oils (*Stachys*), lavender oils (*Lavandula*), tea tree oils (*Melaleuca alternifolia*), cinnamon oils (*Cinnamomum*), mountain tea oils (*Sideritis*), pomelo oils (*Citrus grandis* (L) Osbeck), and kaffir lime oils (*Citrus hystrix* DC). The databases used include PUBMED, Science Direct, and Google Scholar. The terms used for unpatterned searches are "Melasma", "Essential Oil", "Depigmenting Agent", and "Anti-Tyrosinase".

3. RESULTS AND DISCUSSION

3.1. Melasma

Melasma is a skin disorder characterized by irregular hyperpigmented macules on areas of the face that are exposed to sunlight, especially the cheeks, forehead, upper lip, chin, and nose [8]. The name melasma comes from the Greek word "melas" which means black. Melasma is also often called "chloasma", another Greek term meaning green or the mask of pregnancy, due to the high prevalence of melasma in pregnant women [9]. This disease is localized, chronic, acquired, and can be recurrent, and usually affects women of childbearing age with Fitzpatrick skin types IV-VI, but can also affect men [1], [4]. Genetic predisposing factors, exposure to ultraviolet (UV) light, hormones (female sex hormones and thyroid disease), pregnancy and drugs such as phenytoin are known risk factors for developing melasma [4]. Regarding genetic factors, the occurrence of melasma in first-degree family history is about 45% of cases [10]. In addition, ethnic differences also affect, namely Hispanics, Asians (Chinese, Korean, Japanese, Indian, and Pakistani), Mediterranean Africans, and Middle Easterners are more affected than whites. Its prevalence in Southeast Asia reaches 40% in adult women and 20% in adult men [11]. In a study conducted by Ikino [8], of 51 melasma patients, it was found that 49.02% of patients had a family history of melasma and 82.35% had Fitzpatrick type III and IV skin characteristics.

Like genetics, sun exposure is an important trigger factor for melasma. Ultraviolet (UV) radiation induces increased melanogenic activity, especially UVA (320 – 400 nm) and UVB (290 – 320 nm). This UV radiation causes lipid peroxidation in cell membranes, resulting in the formation of free radicals, which encourage melanocytes to produce excess melanin [1], [9]. This is because genes that regulate lipid metabolism, including peroxisome proliferator-activated receptor alpha (PPAR), arachidonate 15-lipoxygenase, PPAR gamma coactivator 1 alpha, ALOX 15B, and diacylglycerol o-acyltransferase are downregulated due to UV exposure. In addition, the histology of the skin biopsy shows thinning of the rete ridge and epidermis [4].

Melasma is also influenced by sex hormones. Levels of the hormones estradiol, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were found to be higher in the serum of women with melasma than in women without melasma, while progesterone levels were similar in both groups. In the serum of men with melasma, LH hormone levels were higher than in men without melasma, while FSH levels were similar and testosterone levels were lower [12]. In another study conducted in Pakistan with 138 women, serum estradiol, progesterone, and prolactin measurements were taken. Results showed a significant increase in estradiol levels in both the follicular and luteal phases in patients with melasma, when compared to controls [1]. In addition to sex hormones, in a meta-analysis study conducted by Kheradmand [13], using 7 studies, found that serum levels of

thyroid stimulating hormone (TSH), thyroid peroxidase (TPO) antibodies, and antithyroglobulin antibodies were higher in patients with melasma when compared to control patients. With regard to hormones, pregnancy was also known to be associated with the occurrence of melasma. This is because the process of melanogenesis can be stimulated by hormonal changes in pregnancy, with increased levels of melanocortin (MSH), estrogen, and progesterone, however, pregnancy-induced melasma is not associated with hyperpigmentation of other areas of the body [11].

The last factor that can cause melasma is medication. There are several case reports showing the effect of drugs on melasma. In a review by Vachiramon [14], discussed the case of a male patient with prostate cancer who received diethylstilboestrol therapy, experiencing melasma as a side effect. This is suspected because tyrosinase-related-protein 2, an enzyme involved in melanogenesis, increased 20-fold after exposure to diethylstilboestrol and estradiol. This is in line with the case report made by Roji [15], where there is a 25-year-old man who has complained of hyperpigmented macular patches on his cheeks and jaw in the last 11 months and then spread to his lower lip. On examination, hyperpigmented plaques were found with mild scaling above the lower lip with melasma over the maxillary area. From his medical history, it was known that this man had a history of seizures and had taken phenytoin in the last 4 years (200 mg daily for the first 2 years and 300 mg daily for 2 years). From the history and examination, this man was diagnosed with phenytoin-induced melasma with lichenoid eruption involving the lips. This certainly shows the relationship between phenytoin consumption and the incidence of melasma.

3.2. The Role of Essential Oils in Melasma Treatment

Essential oils are mostly known for their function as aromatherapy, but it turns out that this oil can also be used in various diseases, especially in hyperpigmentation diseases such as melasma. Most essential oils come from vegetable components such as flowers, leaves, wood, roots, fruit, and seeds. Essential oils are rich in polyphenolic compounds and terpenes that have potential as antimicrobial, antioxidant, and anti-inflammatory properties [16]. With regard to melasma, essential oils have been extensively studied as depigmenting agents due to their anti-tyrosinase potential [5].

Tyrosinase (monophenol, dihydroxyphenylalanine: oxygen oxidoreductase, EC 1.14.18.1) is a multifunctional, copper-containing enzyme that catalyzes the formation of melanin in the process of melanogenesis, so the inhibitory effect of tyrosinase is needed in hyperpigmentation disorders [17], [18]. Several skin hyperpigmentation disorders such as freckles, age spots, melasma, post-inflammatory melanoderma and other hyperpigmentation syndromes are the result of abnormal melanin accumulation. In the melanin production pathway, tyrosinase is the rate-limiting enzyme; this enzyme participates in the hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA). L-DOPA is further oxidized to its corresponding o-quinone, which induces the production of melanin pigments, making it a common target in the treatment of hyperpigmentation disorders such as melasma [19], [20]. Tyrosinase inhibitors, such as kojic acid (a byproduct of malted rice fermentation and produced naturally by some fungal species such as Aspergillus oryzae), azelaic acid (isolated from wheat, rye, barley, and naturally produced by Malassezia furfur), arbutin (extracted from the bearberry plant), magnesium-L-ascorbyl-2-phosphate, electron-rich phenols, hydroxyanisole, corticosteroids, N-acetyl-4-S-cysteaminylphenol, resinoids, salicylhydroxamic acid, dioic acid, and hydroquinone has been used in the pharmaceutical and cosmetic industries due to its ability to thwart excessive melanin production. Kojic acid is also often used in research as a positive

control because of its anti-tyrosinase potential [21]. Although these various inhibitors are recommended for treatment, they have mutagenic potential and risky side effects including skin irritation, contact dermatitis, low oxygen stability, high toxicity and inadequate skin and water penetration ability, and exogenous ochronosis [22]. To minimize these side effects, it is recommended to use natural tyrosinase inhibitors such as flavonols (eg kaempferol and quercetin), chalcones (eg: glabridin), coumarins (eg: aloesin), stilbenes (eg: oxyresveratrol), and aldehydes (eg: cinnamaldehyde, cuminaldehida, and anisaldehyde) are mostly of plant origin [17].

The catalysis of the tyrosinase enzyme is regulated by α-melanocyte-stimulating hormone (α-MSH), known as melanotropic hormone, a small peptide hormone derived from propiomelanocortin (POMC) [18], [23]. α-MSH acted as a cAMP inducer to stimulate melanin synthesis. α-MSH binds to melanocortin 1 receptors (MC1R) expressed on the surface of melanocytes, thereby inducing melanogenesis via several signaling pathways resulting from cAMP, protein kinase A (PKA), cAMP response element-binding protein (CREB), and microphthalmia-associated transcription factor (MITF) activity. MITF is a key transcription factor regulating the transcription of melanogenic enzymes such as tyrosinase, tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2) [23], [24].

3.3. Effects of Different Types of Essential Oils on Melasma

3.3.1. Sage Oils

Sage plants or known by the Latin name *Salvia*, is a genus of plants from the family *Lamiaceae* which is found widely in mountainous areas in Eastern Spain, Southern France, and North Africa [25]. The name *Salvia* comes from the Latin word "*salvare*" which means "to heal or to be safe and not hurt" in accordance with its biological effects, namely as an analgesic, antioxidant, sedative, antiseptic, and many more. These effects cannot be separated from the chemical compounds contained in the essential oil of this plant, namely volatile monoterpenoid compounds with the main components consisting of 1,8-cineole (11-25%) and camphor (11-36%) [25], [26]. In a study conducted by Gad [27] against three species of *Salvia*, namely *S. officinalis*, *S. virgata*, and *S. sclarea*, the results of the inhibition of tyrosinase enzyme activity ranged from 66.1 ± 0.61 to 128.4 ± 4.35 mg kojic acid equivalent (KAE)/g oil. Besides that, *S. officinalis* (IC_{50} 0.73 ± 0.01 mg/mL), exhibited stronger tyrosinase ability than standard inhibitor, kojic acid (IC_{50} 0.75 ± 0.01 mg/mL).

3.3.2. Hedgenettle / Woundwort Oils

Hedgenettle / Woundwort plant or known by the Latin name *Stachys* has been widely consumed in various European and American countries as herbal teas for traditional disease treatment. The essential oil of this plant has been proven in various studies to have a role as anti-spasmodic, disinfectant, antitussive, wound healing, anti-asthma, anti-cancer, anti-bacterial, anti-fungal, anti-anxiolytic, as well as being an inhibitor of several enzymes [28]. Monoterpenoid and sesquiterpenoid compounds are found in the essential oil. The dominant components consist of linalool, germacrene D, caryophyllene, α-pinene, and β-pinene compounds [29]. Based on the research conducted by Bahadori [29], the essential oil of the *S. lavandulifolia* species turned out to have a strong tyrosinase enzyme inhibitory potential of 35.07 mg KAE/g oil, while other species such as *S. byzantina* and *S. inflata* had inhibitory values of 25.26 and 24.44 mg KAE/g oil. This was confirmed by the research of Karaoglan [30], which showed the tyrosinase inhibitory activity of *S. macrostachya* with IC_{50} 22.86 ± 0.82 μg/mL, meanwhile, the positive control, kojic acid, had an IC_{50} 3.86 ± 0.94 μg/mL, so it can be concluded, this oil is proven to be used in alternative melasma treatment.

3.3.3. Lavender Oils

Lavender plant or known by the Latin name *Lavandula* is one of the most popular medicinal plants. Lavender essential oil has been on the market since 1976. Recently, there were studies on the inhibitory effect of *Lavandula angustifolia* essential oil on the fungal tyrosinase enzyme. In mushrooms, these enzymes play different biological roles than the human body. In plants and fungi, tyrosinase can oxidize various phenolic compounds, causing undesirable blackening effects of fruits and vegetables, leading to a decrease in the nutritional quality and commercial value of the commodity. So that this essential oil is widely studied for this purpose, one of which is. This tyrosinase inhibitory effect is due to the compounds contained in it, namely oxygenated monoterpenes (60,419%), followed by monoterpene hydrocarbonates (29,704%), and oxygenated sesquiterpenes (6,587%). The main compounds identified were linalool (26.783%), terpinen-4-ol (22.143%), and 3-carene (21.668%) [31]. This is proven in the research of Aumeeruddy-Elalfi [21] who discussed the anti-tyrosinase effect of lavender essential oil. From this study, the IC_{50} result was 19.36 ± 0.196 g/mL when compared to kojic acid which was 2.28 ± 0.054 g/mL.

3.3.4. Tea Tree Oils

Tea tree essential oil is an essential oil obtained from the steam distillation process of the leaves and tree branches of *Melaleuca alternifolia*. This plant of the *Myrtaceae* family, is native to the states of New South Wales and Queensland in Australia. This tea tree essential oil contains nearly 100 chemical compounds, most of which are monoterpenes and related to alcohol. These compounds were dominated by at least 30% by terpinene-4-ol compounds and a maximum of 15% from 1,8-cineole compounds [32]. Terpinene-4-ol is the main active compound among the complex mixture of compounds in tea tree essential oil. This compound is the main one because of its antifungal, anti-inflammatory, antimicrobial, and antiviral effects [33]. In a study conducted by Alfred Ngenge [34], regarding tea tree essential oil, it was found that the composition of the main compounds in the oil consisted of terpinene-4-ol (45.6%), γ-terpinene (19.4%), α-terpinene (9.3%), 1,8-cineole (5.2%), terpinolene (3.2%), p-cymene (7.6%), dan α-terpineol (3.5%). In addition, the anti-tyrosinase activity of this oil was also measured and the IC_{50} was 82.3 ± 0.5 g/mL, smaller than the positive control, kojic acid, which was 23.5 ± 0.3 g/mL.

3.3.5. Cinnamon Oils

Cinnamon or *Cinnamomum* is a member of the *Lauraceae* family and is one of the most important spices and traditional herbal medicines in the world. This plant is widely distributed in China, Madagascar, India, Sri Lanka, Seychelles, Vietnam, and Malaysia. Essential oil is considered as a vital component in *C. cassia* species which is usually extracted from plant parts such as leaves, flower petals, twigs, seeds, and bark [35]. Essential oil from *C. cassia* has various benefits such as antimicrobial, antitumorigenic, antioxidant, antidiabetic, anti-inflammatory and of course many more [36], [37]. In a study conducted by Chou et al. (2013), 16 compounds were identified in *C. cassia* essential oil. The main compounds found were cis-2-methoxycinnamic acid (43.06%) and cinnamaldehyde (42.37%). Then, the anti-tyrosinase effect of *C. cassia* essential oil and trans-cinnamaldehyde compounds was investigated, each having IC_{50} values of 6.16 ± 0.04 mg/mL and 4.04 ± 0.08 mg/mL. In addition to the anti-tyrosinase effect, α-MSH activity was also investigated using α-MSH-stimulated B16 melanoma cell samples. The amount of melanin increased threefold after 72 hours of α-MSH exposure. Then given treatment with 5.0 g/mL *C. cassia* essential oil and 2.5 g/mL trans-cinnamaldehyde, which decreased melanin significantly by 42% and 31%, respectively [18]. Meanwhile, in the research conducted by Aumeeruddy-Elalfi [21] on the *Cinnamomum zeylanicum* species, the IC_{50} was 2.05 ± 0.074 g/mL, significant when compared to the positive control, namely kojic acid which was 2.28 ± 0.054 g/mL. This shows that essential oil can be an alternative treatment for melasma.

3.3.6. Mountain Tea Oils

The mountain tea plant or *Sideritis* is one of the most important members of the *Lamiaceae* family, which is widely distributed over 150 species in the Mediterranean area. This plant is known to have various biological effects such as antioxidant, anti-inflammatory, antimicrobial, antiviral, antinociceptive, anti-ulcer, and many more. *Sideritis stricta*, a species endemic to Turkey, is used as a herbal tea and is popularly known as 'Dağ ayı' and 'Tosbağa ayı' in Southern Anatolia. This species is considered herbal medicine because of its carminative and appetizing effects [38]. These biological activities are of course due to the compounds contained in this plant. In the study of Deveci [39], it was found that the types of compounds in the essential oil of *S. stricta* were sesquiterpene hydrocarbons (55.9%) and oxygenated sesquiterpenes (37.9%), which were then identified into 27 compounds, representing 99.4% of the total compounds in the oil, consisting of δ-cadinene (18.3%), cubenol (17.6 %), β-caryophyllene (14.4%), and caryophyllene oxide (10.5 %) as the main compound. Regarding melasma, in a study conducted by Axiotis [40], the tyrosinase enzyme inhibitory activity of the essential oil of *S. sipylea* species was 24.64%, smaller than the positive control, namely kojic acid of 47.68% at the same concentration (150 g/mL). However, the activity increases with increasing concentration.

3.3.7. Pomelo Oils

Pomelo fruit or also known by the Latin name *Citrus grandis* (L) Osbeck comes from the family *Rutaceae*. In China, pomelo is a seasonal fruit and is an important fruit consumed at festivals because of its unique taste. While in Taiwan, this fruit is produced 70,000 tons every year. This is because in Asia many people consume this fruit whole, juiced or in the form of preserved snacks [41]. The compounds contained in it also vary depending on genetic and geographical factors of a country. Pomelo leaf essential oil in China contains the main compounds E-ocimene and β-pinene, while pomelo leaf essential oil in Iran contains the main compounds limonene, linalool, and citronellal. In a study using an essential oil sample of one of the pomelo variants in Taiwan, namely "Mato Peiyu", the main compounds contained in it, namely citronellal and citronellol, were 50.71% (with steam distillation (SD)) and 59.82% (with solvent-free microwave extraction (SFME)). Regarding melasma, in this study, the IC_{50} of essential oils with SD and SFME techniques was 0.771% and 0.882% (v/v). This is probably due to the effects of the citronellal and citronellol compounds [42]. Meanwhile, from the research of Aumeeruddy-Elalfi [21], pomelo leaves from Mauritius became an effective inhibitor of the tyrosinase enzyme, with an IC_{50} value of 2.07 ± 0.152 g/mL, comparable to the positive control, kojic acid.

3.3.8. Kaffir Lime Oils

Kaffir lime or *Citrus hystrix* DC comes from the family *Rutaceae* and is distributed in India and Southeast Asia [43]. This plant has aromatic fruits and leaves, and has various properties such as anti-tumor, antimicrobial, anti-inflammatory, and antioxidant activities [44]. The bark and leaves are generally used for medicinal purposes. The essential oil of kaffir lime peel is commonly used in the form of creams, ointments, and tonics for cleansing and nutritional purposes. However, there is still little research on the benefits of this plant skin. In a study conducted by Kulig [45] on kaffir lime peel essential oil, it was found that the anti-tyrosinase effect in this oil was high. At the lowest concentration tested (10 g/mL), this essential oil significantly inhibited the tyrosinase enzyme up to 25%. Meanwhile, at concentrations of more than 80 g/mL, the inhibition increased to more than 50%. The positive control, kojic acid, showed almost 100% inhibition at a concentration of 40 g/mL. The other report that referred to the tyrosinase enzyme inhibitory activity by *C. hystrix* using fruit juice samples. In this study, kaffir lime juice samples as an anti-tyrosinase agent, it showed that the percentage of inhibition of the tyrosinase enzyme was 80.79%, lower than the positive control, namely kojic acid, which was 90.87% [44]. In addition, in the study of Aumeeruddy-Elalfi [21] who used kaffir lime leaf samples as an anti-tyrosinase agent, the IC_{50} results were 2.08 ± 0.253 g/mL, significant when compared to the positive control, kojic acid, which was 2.28 ± 0.054 g/ml. The main content of the leaf

is known to consist of terpinen-4-ol (13.0%), β-pinene (10.9%), α-terpineol (7.6%), 1,8-cineole (6.4%), citronellol (6.0%), and limonene (4.7%).

4. CONCLUSION

Melasma is a hyperpigmentation disorder that is influenced by various factors and usually affects women. One alternative treatment that can be used for melasma is essential oils. Various types of essential oils can be used in alternative treatment of melasma, but their use is still minimal due to lack of research. In this review, it was proven that the essential oils of sage (*Salvia*), hedgenettle/woundwort (*Stachys*), lavender (*Lavandula*), tea tree (*Melaleuca alternifolia*), cinnamon (*Cinnamomum*), mountain tea (*Sideritis*), grapefruit (*Citrus grandis* (L) Osbeck), and kaffir lime (*Citrus hystrix* DC) effective against melasma. But from these essential oils, *S. macrostachya* (hedgenettle/woundwort oils) has the strongest tyrosinase activity, with an IC_{50} of 22.86 ± 0.82 μg/mL (same as 0.02286 ± 0.00082 mg/mL), followed by *S. officinalis* (sage oils) with an IC_{50} of 0.73 ± 0.01 mg/mL. However, the parameters used were mostly only with anti-tyrosinase activity, due to the limitations of the research conducted. So it is hoped that the results of existing research can be developed again so that essential oils can be an effective alternative treatment against melasma in the future.

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