Anti-Melanogenic Activity of Calocedrus formosana Wood Essential Oil

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Calocedrus formosana (Cupressaceae) is one of the five precious woods of Taiwan. C. formosana wood essential oil (CFEO) could be a potential melanogenesis inhibitor. Among the composition of C. formosana wood essential oil (CFEO), thymol exhibited the strongest the inhibitory melanin production activity the anti-melanogenesis principal of CFEO might be thymol.

Keywords: Calocedrus formosana ; Cupressaceae ; essential oil ; anti-melanogenesis

1. Introduction

Melanin is a group of natural pigments found in most living organisms. Cellular melanin is biosynthesized through a complicated process, called melanogenesis, which takes place in the melanosome, an intracellular organelle found within the melanocytes. The melanin-containing melanosomes are transported to the neighboring keratinocytes in the epidermis. Based on melanin concentration in the epidermis, skin color and shade were determined [1]. Cutaneous melanin plays a functional role in epidermal homeostasis, is important for responding to and protecting the skin from environmental stress, including ultraviolet radiation from the sunlight. However, abnormal melanin production leads to various dermatological disorders, such as freckles, solar lentigo, melasma, vitiligo, melanoma, and other hyper pigmentary skin diseases [2]. Therefore, regulating melanogenesis is one of the desirable strategies to control hyperpigmentary skin diseases and beauty-enhancing cosmetic purposes. Indeed, the development of anti-melanogenic agents is not only important for curing hyperpigmentation for cosmetic, pharmaceutical, and medicinal purposes; this is also effective in melanoma therapy, in which melanogenesis and the concentration of melanin level can affect chemo-/radiotherapies and the survival period of patients with melanoma [3].

The types and amounts of melanin production in melanocytes were determined by various endogenous factors (hormonal changes, stem cell factors, inflammation, and aging) and exogenous factors (repetitive UV exposure, pathogenic infection, environmental pollution, chemical stimuli, and physical damage) [4]. Upon stimulation by either extrinsic or intrinsic factors, melanocytes produce melanin. There are three key enzymatic components playing a central role in melanin biosynthesis: tyrosinase (TYR), tyrosinase-related protein-1 (TRP-1), and dopachrome tautomerase/tyrosinase-related protein-2 (DCT/TRP-2). Microphthalmia-associated transcription factor (MITF) is a basic helix leucine zipper transcription factor regulating tyrosinase and tyrosinase-related family genes in melanin-producing cells. Tyrosinase, a copper-containing enzyme, catalyzes two rate-limiting reactions during melanin biosynthesis, including hydroxylation of $_L$-tyrosinse into $_L$-3,4-dihydroxyphenylalanine ($_L$-DOPA) and further oxidation of $_L$-DOPA into DOPA quinone, whereas TRP-1 and TRP-2 play a crucial role in catalyzing eumelanin-producing reactions. TRP-2 catalyzes DOPA chrome into 5,6-dihydroxyindole (DHI) or 5,6-dihydroxyindole-2-carboxylic acid (DHICA). In the final step, DHI and DHICA are oxidized by TRP-1 and leading to melanin production [5].

Since tyrosinase is a key player in melanogenesis, tyrosinase inhibition is a common strategy for the development of anti-melanogenic agents. Now, there are two major strategies are following to identify potential anti-melanogenic agents: They are the therapeutic agent that directly inhibits tyrosinase enzyme activity or modulate cellular signaling cascades involved in melanin biosynthesis [6]. Numerous tyrosinase inhibitors from synthetic or natural sources, including polyphenols, terpenoids, benzoate derivatives, long-chain fatty acids, and sterols have been identified [7]. However, few tyrosinase inhibitors have been withdrawn from medical and cosmetic usage due to their toxicity or severe side effects [7]. Owing to safety concerns, it is necessary to identify an alternative and natural tyrosinase inhibitor or melanin biosynthesis pathway modulator without producing adverse side effects.

Essential oils, also known as plant volatiles, are widely incorporated into modern cosmetic products due to their complexity of active ingredients, strong fragrance, and attractive marketing image [8]. In recent years, essential oils and

their components are gaining public interest because of widespread consumer acceptance and broad-spectrum of functional use. Accumulating scientific evidence proved that essential oils can be used to treat various skin disorders, including acne, pre-mature aging, hyperpigmentation, as well as protecting skin from UV radiation. It has been reported that Origanum (*O. syriacum* and *O. ehrenbergii*) essential oils [9], leaf essential oils of *Alpinia zerumbet* [10], *Melaleuca quinquenervia* [11], leaf and rhizome essential oils of *Alpinia nantoensis* [12], flower essential oils of *Eucalyptus camaldulensis* [13], stem bark essential oils of *Cinnamomum cassia* [14] exhibited strong anti-melanogenic activity in vitro.

Taiwan incense cedar, *Calocedrus formosana* (syn. *C. macrolepis* var. *formosana*) belonging to the Cupressaceae family, has been used to make incense since ancient times in Taiwan. More than 100 compounds have been isolated from the plant, including monoterpenoids, diterpenoids, lignans, and steroids [15][16]. The compounds of *C. formosana* possessed diverse activities, such as anti-oxidative [17][18], anti-termites and anti-fungal [19], anti-inflammatory [20], and anti-cancer [21] properties.

2. Anti-Melanogenic Activity of *Calocedrus formosana* Wood Essential Oil

To pursue beauty is human nature. However, people have a different opinion of beauty; many people from East Asian countries want white and flawless skin [22]. The World Health Organization (WHO) survey found that up to 40% of women in China, Malaysia, the Philippines, and South Korea have experience in using whitening products [23]. According to research by Global Industry Analyst, a US market research firm, the global skin whitening market sales in 2017 was USD 4.8 billion, and it is estimated to double in 2027 [24]. The whitening products in the market mostly contain acid ingredients, which have high cytotoxicity, insufficient penetrating power, and low activity and also often cause skin sensitivity and contact dermatitis for long-term application. Therefore, the development of safe, bio-compatible, and naturally derived skin whitening agents become the mainstream of whitening product development [25]. Essential oils provide a broad spectrum of health benefits and preservatives, which is predominantly used in the preparation of pharmaceutical and cosmetic products since ancient times [26]. Moreover, the pleasant aroma of essential oils also permits it to apply in various cosmetic products. Specifically, essential oils are well studied for their direct tyrosinase inhibitory activity, which is a key strategy for the development of skin-lightening agents [27]. *C. formosana* has been used to make incense due to its pleasant aroma. Several studies have demonstrated that the extracts and derivate compounds of *C. formosana* have diverse activities.

Inhibitory activity against mushroom tyrosinase is a primary method to determine the skin whitening efficacy of candidature agents since tyrosinase enzyme plays a central role in melanin biosynthesis. *Cinnamomum zeylanicum*, *Citrus grandis*, and *Citrus hystrix* exhibited strong tyrosinase inhibitory effects with an IC50 value of 2.05 µg/mL, 2.07 µg/mL, and 2.08 µg/mL, respectively, which were similar to that of kojic acid (IC_{50}; 2.28 µg/mL). CFEO significantly as well as dose-dependently inhibited mushroom tyrosinase activity with an IC_{50} value of 2.72 µg/mL. According to the mushroom tyrosinase inhibitory assay, CFEO presented better inhibitory activity than several plant essential oils, indicating that CFEO has the potential to inhibit melanin production.

Melanin biosynthesis is orchestrated with several sequential steps, including receptor activation, production of intracellular cAMP, transcriptional activation of MITF, and transcription of tyrosinase family genes. Forskolin and α-MSH were identified as potent cAMP activators which trigger melanogenesis in vitro [28]. CFEO treatment significantly blocked melanin production in B16 cells, which is well correlated with other observations that essential oils from *Cinnamomum cassia, Melaleuca quinquenervia, Alpinia zerumbet*, *Alpinia nantoensis, Eucalyptus camaldulensis, Origanum syriacum,* and *Origanum ehrenbergii* showed strong melanin inhibition in a similar condition to in vitro experiments [9][10][11][12][13]. In addition, essential oils have the capability to inhibit melanogenesis through dual inhibitory mechanisms, including direct inhibition of tyrosinase enzyme activity and downregulating the melanin biosynthesis pathway through modulating cellular signaling cascades [14][29]. Tyrosinase family proteins, including TYR, TRP-1, and TRP-2 were the key players of melanin biosynthesis. CFEO failed to modulate TYR expression, whereas TRP-1 and TRP-2 expression levels were significantly downregulated; the positive drug control KA does not affect the TRP-1 expression, which is well correlated with other observations [13]. Transcriptional and post-transcriptional regulation of MITF is a hallmark event of melanogenesis. MITF can upregulate tyrosinase and its related proteins by binding to an M-box motif in their promoter site because MITF contains a basic helix-loop-helix-leucine zipper domain in its structure [30]. CFEO treatment significantly reduced MITF expression and activity even better than kojic acid. That is, CFEO inhibited TRP-1 and TRP-2 expression then reduced the production of melanin through reduced MITF activity.

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