Potential uses of *Artocarpus altilis* Heartwood Extract in Cosmeceuticals

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Abstract

Nowadays, there are a lot of cosmeceutical products which are contained the extracts as active ingredient because of consumer demand on natural ingredients. *Artocarpus altilis* (breadfruit) is one of the plant economy which is not only used as a nutrition but also widely used in folk medicine including skin diseases. *A. altilis* heartwood extract have been reported to have several potential uses in cosmeceuticals, such as antioxidation, antiinflammation, antityrosinase and antiaging. The objective of this review is to propose the comprehensive knowledge of phytochemistry and biological activities of *A. altilis* heartwood extract and also the mechanisms of action of the extract.

Keywords: *Artocarpus altilis* heartwood extract, phytochemistry, biological activities in cosmeceuticals

Introduction

Artocarpus is a group of trees belonging to Moraceae family. This plant genus is widely used in food, agriculture industry and as traditional folk medicine in Southeast Asia to treat several diseases including skin disorders, such as ulcers and dermatitis. *Artocarpus altilis* (Synonyms: *Artocarpus incisus*), English name: breadfruit; Thai name: Sa-ke, is one of species in this genus, and its biological activities including antioxidant (Itsarasook, Ingkaninan, & Viyoch, 2014; Lan, Tzeng, Lin, Yen, & Ko, 2013; Lee et al., 2013a; Lin, Liu, Tu, Ko, & Wei, 2009), antiinflammatory (Lee et al., 2013a; Wei et al., 2005), antiplatelet (Weng et al., 2006), anticancer (Arung et al., 2009; Fang et al., 2008), 5α-reductase inhibitory (Shimizu, Fukuda, Kondo, & Sakai, 2000) and melanogenesis inhibitory (Lan et al., 2013; Buranajaree, Donsing, Jeenapongsa, & Viyoch, 2011; Donsing, Limpeanchob, & Viyoch, 2008; Shimizu, Kondo, Sakai, Lee, & Sato, 1998), activities have been revealed. Additionally, the extract isolated from the heartwood of *A. altilis* could restore functional properties of aged-fibroblasts (Viyoch et al., 2010) and prevent skin damages in UVA and UVB-irradiated mice (Tiraravesit et al., 2015; Itsarasook et al., 2014; Lee et al., 2013a; Lee et al., 2013b). Therefore, these pharmacological activities of *A. incisus* extract are suitable for application in cosmetics. However, it has no effective use in cosmeceuticals, if the extract toxic to the skin. Cytotoxicity is one of the most important methods for biological evaluation. In vitro evaluation of cytotoxicity of the extract from *A. altilis* heartwood has been studied on many skin cells, including melanocytes, keratinocytes and fibroblasts. Previous in vitro cytotoxicity study showed that the number of viability and the morphology of melanocyte cells treated with the extract (40 μg/mL) did not alter. Likewise, the cytotoxicity studies using XTT assay showed that the concentration of 50 μg/mL of the extract did not significantly affect neither the viability nor the proliferation of primary human skin keratinocytes and fibroblasts (Tiraravesit et al., 2015; Itsarasook et al., 2014). Furthermore, there has been in vivo study on the protective effect of *A. altilis* extract by topical administration to the skin against UVB. The experimental study showed that *A. altilis* extract could

decrease or suppress structural alterations including the epidermal thickening in skin damaged by chronically UVB-exposed skin in mice (Tiraravesit et al., 2015; Lee et al., 2013a). In addition, an in vivo study of UVB-induced hyperpigmentation in C57BL/6 mice revealed that after topical application nanoemulsion containing heartwood extract of *A. incisus* for four weeks could reduce hyperpigmentation. Moreover, after stopping application, at dorsal skin sites treated with the extract were not found the permanent depigmentation, edema or scaling (Buranajaree et al., 2011).

Figure 1 Photograph of *Artocarpus altilis*

1. Phytochemistry

Phytochemical analyses of the Artocarpus genus including phenolic compounds (for example flavonoids and stilbenoids) have been widely studied (Sikarwar et al., 2014). From our previous studies (Tiraravesit et al., 2015; Itsarasook et al., 2014; Buranajaree et al., 2011; Viyoch et al., 2010; Donsing et al.; 2008), artocarpin, a prenylated polyphenol is a main compound found in the diethylether extract from heartwood of *A altilis*. The content of artocarpin showed the different number during 44.5 ± 0.1- 90.6 ± 5.1% w/w of extract, depending on the maceration and purification method. Table 1 shows structure of artocarpin and other flavonoid compounds that have been reported biological activities relating to cosmetic application.

Table 1 Structure and biological activities of flavonoids found in the heartwood extracts of *A. altilis*.

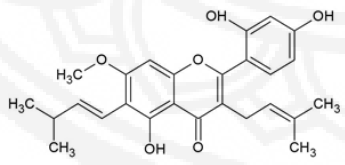
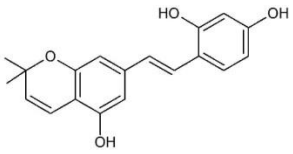
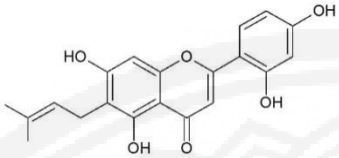
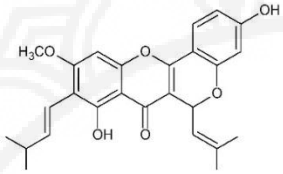
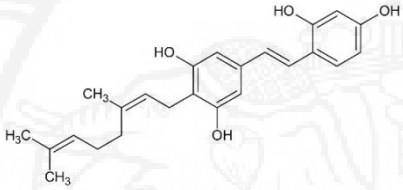
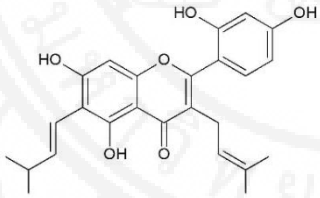
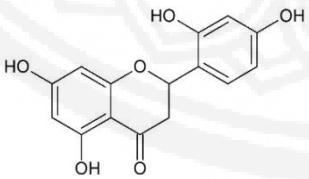
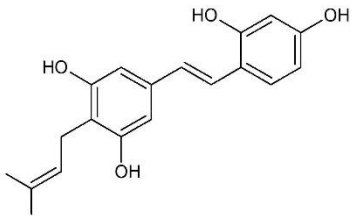
Name	Structure	Biological activity
Artocarpin		1. Antioxidation (Itsarasook et al., 2014; Lan et al., 2013; Lee et al., 2013a; Lee et al., 2013b; Lin et al., 2009; Donsing et al., 2008) 2. Antiinflammation (Tiraravesit et al., 2015; Lee et al., 2013a; Lee et al., 2013b; Han, Kang, Windono, Lee, & Seo, 2006; Wei et al., 2005) 3. Tyrosinase and melanogenesis inhibition (Lan et al., 2013; Buranajaree et al., 2011; Donsing et al., 2008; Shimizu, Kondo, Sakai, Takeda, & Nagahata, 2002; Shimizu et al., 1998) 4. Restoration of wrinkled-skin fibroblast (Itsarasook et al., 2014; Viyoch et al., 2010) 5. Prevention of UVA and UVB-induced skin damage (Tiraravesit et al., 2015; Itsarasook et al., 2014; Lan et al., 2013) 6. Antimicrobial activity (Septama & Panichayupakaranant, 2016)

Table 1 (Cont.)

Name	Structure	Biological activity
Artocarbene		Tyrosinase inhibition (Shimizu et al., 1998)
Artocarpesin		Tyrosinase inhibition (Arung, Shimizu, & Kondo, 2011; Shimizu et al., 1998)
Cycloartocarpin		Antitubercular activity (Jagtap & Bupat, 2010)
Chlorophorin		Tyrosinase inhibitor (Shimizu et al., 1998)
Dihydromorin		Tyrosinase inhibitor (Shimizu et al., 1998)
Norartocarpin		1. Melanogenesis inhibition (Arung et al., 2011) 2. Cytotoxic activity (Arung, Yoshikawa, Shimizu, & Kondo, 2010)
Norartocapanone		Tyrosinase inhibitor (Shimizu et al., 1998)
4-prenyloxy-resveratrol		Tyrosinase inhibitor (Shimizu et al., 1998)

2. Biological activities of *A. altilis* heartwood extract

2.1 Antioxidant and antiphotoaging activities

UV exposure is a major cause of photoaging as UV can generate free radicals which lead to crosslink or oxidize the functional groups of biological macromolecules, such as DNA and proteins. Generally, our skin has defensive mechanisms by upregulating the expressions of biomolecules for antioxidant activity and cellular repair (Phetdee, Rakchai, Rattanamanee, Teaktong, & Viyoch, 2014, Ho et al., 2005). However, decreasing functionality of defensive mechanisms has been found in excessive UV exposed-skin (Viyoch, Mahingsa, & Ingkaninan, 2012). Moreover, decreased type I procollagen and increased matrix metalloproteinase-1 (MMP-1) expression in photoaged skin have been reported (Viyoch et al., 2010; Varani, Perone, Fligiel, Fisher, & Voorhees, (2002); Varani et al., 2000). These together lead to histological changes, such as disorganization and fragmentation of type I collagen, which appear as physical changes, such as saggy skin and wrinkles. In this reason, regular application of antioxidants has been suggested to prevent and/or minimize harmful effects of UV exposure. Our previous studies found that diethylether extract containing 45.2 ± 0.5% (Donsing et al., 2008) and 90.6 ± 5.1% w/w (Itsarasook et al., 2014) of artocarpin had free radical scavenging activity with an EC50 of 169.5 ± 9.7 μg/ml and 116.0 ± 5.1 μg/ml, respectively. It seems that higher content of artocarpin (artocarpin-enriched extract) provide higher antioxidant activity. Another study in hairless mice indicated that topical application of artocarpin decreased level of ROS and lipid peroxidation in UVB-irradiated skin (Lee et al., 2013b). Additionally, the artocarpin-enriched extract showed ability to reverse activity of UVA-irradiated fibroblasts by restoration of type I collagen and suppression of MMP-1 overproduction (Itsarasook et al., 2014) and ability to prevent UVB-induced skin damage by suppression of MMP-1 overproduction in fibroblasts (Tiraravesit et al., 2015). Actually, histologic changes in skin associated with photoaging result from alteration of skin cells functions. These cells, such as keratinocytes, fibroblasts and mast cells interact with each other through various pathways, contributing overproduction of MMP-1. MMP-1 is collagenase that majorly degrades type I collagen, resulting a loss of dermal connective tissue. Therefore, the multifunctional activities, for instances, antioxidant and antiaging activities, of artocarpin-enriched extract may be useful for restoration and/or prevention of photoaged skin.

2.2 Antiinflammatory activity

The occurrence of damaged molecules in skin tissues results from the interaction between ROS and target macromolecules, consequently leading to skin disorders. DNA strand breaks can also be generated directly from UVB radiation. These damage molecules trigger the release of several cytokines associated with skin photoaging and carcinogenesis. Our study found that the heartwood extract enriched with artocarpin (88.2 ± 0.1% w/w) suppressed TNF-α and IL-6 overproductions in UVB-irradiated keratinocytes and protected skin epidermal hyperplasia, a marker of skin inflammation, from chronic UVB exposure in mice (Tiraravesit et al., 2015). In addition, the study in UVB-irradiated hairless mice found that topical application of artocarpin decrease levels of TNF-α and IL-1β (Lee et al., 2013b). As these cytokines can stimulate MMP-1 production by fibroblasts via MAPK (mitogen-activated protein kinase) pathway (Choi & Lee, 2010, Reunanen, Li, Ahonen, Foschi, Han, & Kähäri, 2002), we theorize that the extract may suppress overproduction of MMP-1 in UVB-irradiated fibroblasts via TNF-α, interleukin/MAPK signal. To clarify this hypothesis, we determined the expression of biomolecules including Erk, that are related to MAPK pathway. We observed the alteration in the expression level of

phosphorylated Erk in UVB-irradiated fibroblasts pretreated with the artocarpin-enriched extract, as compared to untreated UVB-irradiated cells (unpublished data). Figure 2 illustrates the possible mechanism of artocarpin to suppress MMP-1 expression in UV-irradiated fibroblast.

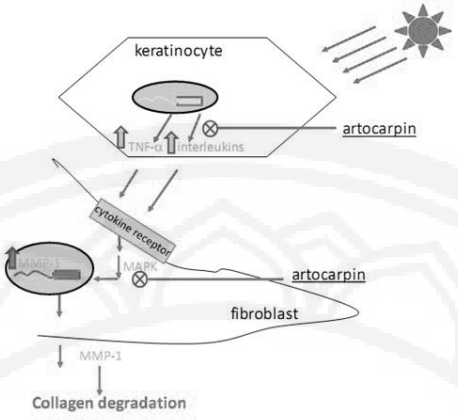


Figure 2 Possible mechanism(s) of *Artocarpus altilis* heartwood extract, artocarpin to suppress MMP-1 overproduction in UV-irradiated skin cells. Expose UV radiation stimulates MMP-1 overproduction through cytokines/MAPK pathway. Artocarpin could decrease cytokines, such as TNF-α and interleukin-6 expressions in keratinocytes and decrease MAPK-related protein expression in fibroblasts

2.3 Tyrosinase and melanogenesis inhibition

Melanogenesis is process of melanin production in melanocytes. It composes of several steps, and tyrosinase is a rate limiting enzyme for melanin synthesis in melanosome, a melanocyte organelle that is responsible for melanin synthesis and transportation. Therefore, alterations of tyrosinase production and/or activity is a main target for treatment of pigmentation defects, hypo- or hyperpigmentation. Tyrosinase inhibitory activity of artocarpin has been reported in the past. In vitro study in mouse melanoma cell line, B16 and in vivo study in guinea pig indicated inhibitory activity of artocarpin on melanin formation (Arung et al., 2011). Our previous studies also revealed tyrosinase and melanogenesis inhibitory activities of ether extract of *A. altilis* heartwood containing about 45% w/w of artocarpin (Buranajaree et al., 2011; Donsing et al., 2008). IC50 value of tyrosinase inhibitory activity was 10.3 ± 3.0 μg/ml, according to mushroom tyrosinase assay, and that of melanogenesis inhibitory activity was 30.2 ± 2.4 μg/ml, according to melanin synthesis inhibition in B16F1 melanoma cell. Moreover, we found that the melanogenesis inhibitory activity of the extract in B16F1 was strong as that of kojic acid, well known lightening compound that provided IC50 of 51.4 ± 5.1 μg/ml. The study in C57BL/6 mice induced hyperpigmentation by UVB found that the emulsion containing 0.02% ether extract could show depigmenting effect with temporary effect; the skin color of the applied area could return to the original color after stop application (Buranajaree et al., 2011). These findings imply that the extract at concentration used do not cytotoxic to skin cells, particular melanocyte cells. However, our study found that viability of B16F1 mouse melanoma decreased when cell had been treated with purified artocarpin (Donsing et al., 2008). It is possible that the artcarpin might cytotoxic to melanoma cell but not normal cell.

Conclusions and Suggestions

Plant extracts are playing important role in cosmetic market nowadays. Particularly, the extracts with

multifunctional activities; antioxidation, antiinflammation, antityrosinase and antiaging are interested to treat aged/photoaged skin. *Artocarpus altilis* has been used as traditional medicine for treating skin diseases. The diethyl ether extract of its heartwood contain artocarpin as a major compound. Artocarpin shows many biological activities which are useful for cosmeceutical application. Thus the activities of artocarpin extracted from *A. altilis* heartwood match the requirement. However, to assess the ultimate effects of the extracts, not only data from cell biomolecular study, but also from clinical study are needed. Additionally, clinical study using a large number of subjects and long duration of application should be performed to provide evidence of cosmeceutical efficacy of *A. altilis* heartwood extract. Moreover, physicochemical and stability properties of the extracts are important information for further development of the extracts into proper product form.

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