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Original Article

The fabric facial mask enhanced skin permeation of hydrophilic bioactive compounds in *Aquilaria crassna* leaf extract

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Abstract

The purpose of this study was to investigate the effects of a facial mask in enhancing skin absorption of iriflophenone 3,5-*C*-β-D-diglucoside (**1**), iriflophenone 3-*C*-β-D-glucoside (**2**) and mangiferin (**3**). Partition coefficients (log $P_{o/w}$) of **1**–**3** were determined. Facial essence containing *Aquilaria crassna* leaf extract was formulated and incorporated into a fabric facial mask. An *in-vitro* skin permeation of **1**–**3** from the formulation with and without the mask through human skin was evaluated using Franz diffusion cells. Log $P_{o/w}$ of **1**–**3** were -1.03 ± 0.14, -0.54 ± 0.01 and 0.26 ± 0.01, respectively. The permeations of **1**–**3** from the formulation without fabric mask were only 0.26%, 0.58% and 0.61% of applied dose, respectively while those with the fabric mask were 0.79%, 1.08% and 0.70% of applied dose, respectively. In conclusion, the fabric mask enhances the skin permeation of the hydrophilic compounds **1, 2** more than that of compound **3,** which is less hydrophilic.

Keywords: *A. crassna* leaf extract, cosmetics, partition coefficient, skin permeation, stability study

1. Introduction

Facial skin is one of the most exposed human parts to hostile environmental factors during the whole life. The facial skin appearance is important for the perceived age (Geng, Zhou, & Smith-Miles, 2007; Trojahn, Dobos, Lichterfeld, Blume-Peytavi, & Kottner, 2015) and affects an individuals' psychosocial well-being. Aging skin is defined as changing of the physiological process induced by both exogenous and endogenous factors resulting in the rough appearance with texture, wrinkles, laxity, less pliability, dryness or even atrophy (Landau, 2007; Zhang & Duan, 2018). Scientists and dermatologists are trying to develop novel techniques to maintain skin health and aesthetics. There are several current techniques that have been used for skin treatment and rejuvenation such as laser treatment (Papadavid & Katsambas, 2003), iontophoresis (Costello & Jeske, 1995; Rawat, Vengurlekar, Rakesh, Jain, & Srikarti, 2008) and

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mesotherapy (El-Domyati *et al.*, 2012). However, these techniques are expensive and invasive. Skin irritation by laser treatment has been noted (Haedersdal, 1999). To avoid these problems, natural therapy is an alternative treatment type. In addition, researching of new natural active ingredients is also necessary for further product development.

Aquilaria crassna Pierre ex Lecomte (Thymelaeaceae family) is commonly known as "agarwood". It is one of the five *Aquilaria* species that have been reported in Thailand (Smitinand, 2014) and its leaves have traditionally been used as an herbal tea for tonic and improvement of blood circulatory systems. Previous studies indicated that *A. crassna* leaf extract was promising for use as cosmetic ingredient as it had anti-oxidative (Kamonwannasit *et al.*, 2013; Manoka, Sungthong, Sato, Sugiyama, & Sato, 2016; Wongwad *et al.*, 2019), antiglycation, and anti-inflammatory (Wongwad *et al.*, 2019) properties. Moreover, the leaf extracts of *A. crassna* were found to be safe with no significant level of toxicity in laboratory mice testing (Ghan, Chin, Thoo, Yim, & Ho, 2016; Kamonwannasit *et al.*, 2013).

The main chemical constituents found in *Aquilaria* leaves include benzophenones such as iriflophenone 3,5-*C*-β-D-diglucoside (**1**), iriflophenone 3-*C*-β-D-glucoside (**2**), and xanthonoids such as mangiferin (**3**) (Ito *et al.*, 2012; Supasuteekul *et al.*, 2017; Wisutthathum *et al.*, 2019; Wongwad *et al.*, 2019) as potential active compounds for cosmetics. Among these, of particular of interest are compounds **1** and **2** which have shown antioxidant and anti-inflammatory activities via inhibition of interleukin-1α (IL-1α) and prostaglandin E_2 (PGE_2), secreted from human keratinocyte cells after irradiation with UVB; while **3** has antioxidant, antiglycation, anti-inflammatory (IL-1α and NO inhibitions) (Wongwad *et al.*, 2019) and vasorelaxant properties (Wisutthathum *et al.*, 2019).

To demonstrate the cosmetic application of *A. crassna* leaves and to maximize the economic benefit of *A. crassna* farming, further product development of *A. crassna* leaves needs to be illustrated. Facial mask products are one of the most prevalent cosmetics categories utilized for skin rejuvenation (Nilforoushzadeh *et al.*, 2018). Fabric facial masks are the most commonly available type of cosmetic facial mask in the marketplace. There are many advantages of a fabric facial mask over a conventional facial mask. Firstly, it is more convenient to use. Secondly, the active ingredients are expected to be deeper absorbed into the skin via the occlusive effect. Thirdly, it does not require washing off after use; some conventional face masks like mud and clay masks need to be washed off after use.

In this study, our purpose was to demonstrate that the fabric facial mask product could enhance skin permeation of cosmetic actives according to their physicochemical properties. The skin permeation and stability of compounds **1-3** in fabric mask product containing *A. crassna* leaf extracts was investigated and is reported.

2. Materials and Methods

2.1 Plant materials and extraction

A. crassna young leaves (1–3 from the top) were collected from Phitsanulok province, Thailand. The voucher specimen (collection number Wongwad001) was deposited at the Faculty of Science, Naresuan University, Phisanulok, Thailand.

To obtain the dried aqueous extract, powdered dried samples (500 g) of *A. crassna* leaves were infused in hot water (5 L) at 95ºC–100ºC for 30 min and the supernatants were filtered and lyophilized. The aqueous extract contained **1** (10.08±0.46% w/w), **2** (5.36±0.32% w/w) and **3** (7.88±1.00% w/w) as determined by HPLC.

2.2 Chemicals and standard compounds

Cosmetic grade xanthan gum, glycerine, propylene glycol, propylparaben, methylparaben, and Na_2EDTA were purchased from Sigma-Aldrich (St. Louis, USA). PEG-40 hydrogenated castor oil from BASF (Ludwigsafen, Germany) while Fragrance, (Lotus2562070) was obtained from TCFF (Ayudhaya, Thailand). Fabric masks made from 45 gsm spun lace non-woven fabric with 60% cotton / 40% polyester, are a product of Pathawin (Pathum Thani, Thailand). Analytical grade methanol, ethanol, acetic acid glacial and sodium acetate were obtained from Labscan (Bangkok, Thailand). HPLC grade methanol, ethanol, and acetonitrile were from Burdick & Jackon (Ulsan, South Korea). Sterile water was from A.N.B. Laboratories (Bangkok, Thailand).

The standard compounds **1** and **2** were isolated as previously reported (Supasuteekul *et al.*, 2017), and **3** was obtained from Assist. Prof. Dr. Uthai Wichai (Faculty of Science, Naresuan University, Thailand). The purities of these compounds were more than 95% as determined by NMR. The structures of the compounds **1**–**3** are shown in Figure 1.

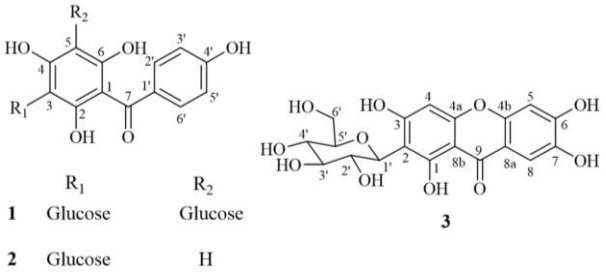

Figure 1. Chemical structures of compounds **1** (iriflophenone 3,5-*C*-β-D-diglucoside), **2** (iriflophenone 3-*C*-β-D-glucoside) and **3** (mangiferin)

2.3 Determination of partition coefficients of 1–3

The standard compounds **1**–**3** were used for determinations. Partition coefficient ($P_{o/w}$) of **1–3** was separately determined by the shake flask method as described in the OECD guideline of test No.107 (Organization for Economic Co-operation and Development [OECD], 1995). This method is suitable for the compounds of log $P_{o/w}$ between -2 and 4 (occasionally up to 5). Briefly, 1 mg each of **1–2** was separately weighed and dissolved in 20 mL water while 1 mg of **3** was dissolved in 20 mL *n*-octanol to produce 50 µg/mL stock solutions. The solutions were then kept at 25±1°C for 24 h before transferring to centrifuge tube (size 5 mL) containing *n*-octanol for each of **1**–**2** and containing water for **3,** in three different ratios 1:2, 1:1; and 2:1 (v/v). The tubes were vortexed for 5 min and centrifuged at 2500 rpm, 25±1°C for 5 min. Then, concentrations of **1–3** in the two separation phases

were quantitatively determined by HPLC. The $P_{o/w}$ of each compound was calculated using the equation below:

$$P_{o/w} = C_{n\text{-octanol}}/C_{water}$$

Where $C_{n\text{-}octanol}$ was the concentration of each **1–3** in the *n*-octanol phase and C_{water} was the concentration of each **1–3** in the water phase. The study was done in duplicates.

2.4 Solubility study for compound 3 of *A. crassna* leaf aqueous extract

The solubility of compound **3** of *A. crassna* leaf aqueous extract was determined in HEPES buffer (pH 7.4) using the shake flask method as described in the OECD guideline No. 105 (Organization for Economic Co-operation and Development [OECD], 1995). Briefly, the extract was slowly dropped into the centrifuge tube that contained 1 mL of HEPES buffer pH 7.4 (20 mM HEPES, 2.4 mM K_2HPO_4, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$ and 115 mM NaCl) (Srivilai, Waranuch, Tangsumranjit, Khorana, & Ingkaninan, 2018) until precipitation occurred while shaken in a water bath at 25±0.5°C for 24 h (n=3). Tubes were collected after 24 h, 48 h and 72 h and then were centrifuged at speed 2500 rpm; 25±0.5°C and filtered through a 0.45 µm membrane to obtain a clear solution. The solution was further diluted 2000 fold by acetate buffer (pH 3.7). Then 20 µL of the solution was injected to HPLC for quantification.

2.5 Stability study of the formulation

The facial essence formulation was similar to that in Table 1. Twenty grams of the formulation was added to the fabric mask sheet in an aluminum foil bag and sealed. The bags were kept at 4ºC, 25ºC, and 50 ºC for 30 days (Beringhs, Rosa, Stulzer, Budal, & Sonaglio, 2013; Deuschle, Deuschle, Bortoluzzi, & Athayde, 2015). At the end of the study, the products were tested for their physicochemical properties. The changing color was also determined using a spectrocolorimeter (ColorQuest XE, Virginia, US).

2.6 *In-vitro* skin permeation study

Facial essence containing standardized *A. crassna* leaf aqueous extract was formulated according to Table 1 but the percentage of *A. crassna* extract was adjusted to 10.00% w/w. This adjusting was based on the limited absorption of compounds **1**-**3** which might be quite difficult for quantitative analysis in skin permeation study using static Franz diffusion apparatus. Thus, to overcome the sensitivity of the detection limit of HPLC technique, the percentage of the extract was increased from 0.01% w/w to 10.00% w/w. All the test formulations were kept overnight in a refrigerator until being used. The permeation of **1–3** from the essence with and without fabric mark soaked with was tested with human foreskin skin mounted on Franz diffusion apparatus.

Human foreskins were obtained from 6 anonymous donors (age: 3 months–6 years). The investigational protocol had been approved by the Naresuan University Institutional Review Board (approval number 521/59). After removing the subcutaneous layer, the skin was then rinsed with isotonic HEPES buffer at pH 7.4 before use.

Table 1. Facial essence formulation for skin penetration study

Ingredient	Function	%w/w
water	co-solvent	up to 100
disodium EDTA	chelating agents	0.10
propylene glycol	humectant	2.00
glycerin	humectant	2.00
methylparaben	preservative	0.03
propylparaben	preservative	0.02
xanthan gum	thickener	0.30
PEG-40 hydrogenated castor oil	surfactant/ solubilizer	0.50
vitamin E	antioxidant	0.10
fragrance	fragrance	0.02
A. crassna leaf aqueous extract	active ingredient	0.01

The penetration study was performed according to OECD No. 428 (Organization for Economic Co-operation and Development [OECD], 2004). The Franz diffusion cells with 1.76 cm^2 donor and 7 mL receiver compartments were set at 37±0.5°C with circulated water through the outer jacket. The solution in the receiver chamber is HEPES buffer pH 7.4 and it was continuously stirred at 440 rpm with a magnetic bar. The skin piece was mounted with the epidermal side up onto the donor chamber and left for 1 h before applying 100 µL of facial essence either with or without fabric mask. The receiver solution (500 µL) was sampled at the pre-determined times 0, 0.5,1 to 8 h and replaced by an equal volume of fresh HEPES buffer. Each sample was analysed for **1–3** using HPLC. After 8 h, the skin piece was removed and pried off of the flat wax surface. It was then swabbed by a cotton ball and gently rinsed three times with the HEPES buffer. The stratum corneum layer was then removed by tape stripping until a shiny appearance. The tape-strips and the viable skin were then extracted with 50% methanol by sonication for 15 min. The amounts of **1–3** in the extract and the receiver solution were then determined by HPLC. The experiment was done in triplicates.

2.7 Quantitative analysis of compounds 1–3

An HPLC method based on our previous report (Wongwad *et al.*, 2019) was used to quantitate compounds **1–3**. A Shimadzu LC-20A (Shimadzu Corporation, Kyoto, Japan) HPLC system comprising Shimadzu SPD-20A UV/vis detector and Shimadzu column oven (CTO-10AS VP) was used. A Phenomenex Luna C18 column (150 mm×4.6 mm, 5 µm particle size) together with a guard column (5 µm Phenomenex C18, 4 mm×3 mm) (Phenomenex, Torrance, USA), were used for the separation. A mobile phase of acetate buffer solution (pH 3.7) (A) and acetonitrile (B) with the gradient condition using a flow rate of 1.0 mL/min was performed as follows: 0 to 5 min, 15% B; 5 to 10 min, 40% B and hold with 15% B for 5 min. The injection volume of 20 µL, the UV detector at 310 nm, and the column temperature setting at 30 ºC were used.

2.8 Statistical analysis

All experiments were performed in triplicate unless otherwise mentioned and the results obtained are expressed as

the mean ± standard deviation (SD). Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS, Chicago, USA).

3. Results and Discussion

3.1 The partition coefficients $P_{(o/w)}$ of 1–3

The partition coefficient or distribution coefficient ($P_{o/w}$) is defined as the ratio of the equilibrium concentration of a dissolved compound in two immiscible phases, here between *n*-octanol and water. This value could be used to predict a compound's skin permeation (Zhu, Jung, Hui, & Maibach, 2016). In this study, we determined the log $P_{o/w}$ of compounds **1–3** using the shake flask method and the results are shown in Table 2. This is the first time that log $P_{o/w}$ of compounds **1** and **2** is reported while the log $P_{o/w}$ of compound **3** has been previously noted with a wide range of values ranging from -0.59 (Khurana *et al.*, 2017) to 2.73 (Núñez-Sellés, 2005; Ochocka, Hering, Stefanowicz–Hajduk, Cal, & Barańska, 2017). These results indicate that compounds **1** and **2** are hydrophilic which makes it quite difficult to get them into the stratum corneum. In contrast, compound **3** was more hydrophobic than the others. Therefore, the fabric sheet mask was used to investigate if it could enhance skin permeation of these compounds, especially of compounds **1** and **2**.

Table 2. Partition coefficients of standard compounds 1–3 obtained by the shake flask method

Standard compound	Partition coefficient ($P_{o/w}$)†	Log $P_{(o/w)}$†
1	0.10±0.033	-1.03±0.14
2	0.29±0.006	-0.54±0.01
3	1.80±0.004	0.26±0.01

†Each value represents the mean ± SD of results (n=6).

3.2 Solubility study for compound 3 of *A. crassna* leaf aqueous extract

The solubility of compound **3**, the lowest solubility among this group according to partition coefficient, was evaluated using the shake flask method at 25±0.5ºC. The result was used to assure that the solubility was not the rate limiting step for skin permeation study. The result showed that the solubility of compound **3** was 80.00±4.83 µg/mL in HEPES buffer. Therefore, in this study, the compound **3** was classified as being a practically insoluble compound (Stegemann, Leveiller, Franchi, de Jong, & Lindén, 2007). According to this solubility, the thermodynamic activity of compound of interest in the receptor fluid did not exceeded 10% of its thermodynamic activity in the donor medium so that it can maintain a favorable driving force for permeation and assure reasonable and efficient collection of permeants.

3.3 Stability study

The facial masks containing *A. crassna* leaf extract were stored at 4ºC, 25ºC, and 50ºC for 30 days. The physicochemical properties (odor, color, weight loss, and pH) of the formulations were evaluated at the end of the storage time. Moreover, the remaining active compounds **1–3** were also determined. The results obtained from the study are listed in Table 3. No significant changes in odor, color, weight or pH were observed. There were also no black spots of mold. However, we observed the decrease in compound **2** when the formulation was kept at 25ºC or at 50ºC for 30 days. The intensive decrease was also noticed with compound **3** at 50ºC. The instability of compounds **2** and **3** in the formulation might be due to the hydrolysis and oxidation processes in aqueous environment. The thermal degradation of compounds **2** and **3** in the aqueous solution of *Cyclopia genistoides* were noted (Beelders, de Beer, & Joubert, 2015). In that report, the degradation of compound **3** was higher than of compound **2** which was different from our study. This might be because of the other compounds present in AE. However, that report also indicated that the addition of an *O*-linked glucopyranosyl moiety at *C*-4 in the benzene ring could increase thermal stability as in the case of iriflophenone-3-*C*-glucoside-4-*O*-glucoside in comparison to compound **2**. This information also supports our results and explanation of the presence of a glucose moiety at *C*-5 of the benzene ring in compound **1** conferring higher thermal stability than for compound **2**. Therefore, to maintain the bioactive compounds in the fabric facial mask containing *A. crassna* leaf extract, it was kept at 4ºC until use for further skin permeation study.

Table 3. Physiochemical characteristics of facial fabric mask after storing at 4ºC, 25ºC and 50ºC for 30 days

Temperature	Day	pH	Odor	Mold spot	Color†			Weight loss (%)	Remaining compound (%)		
					L*	a*	b*		**1**	**2**	**3**
4ºC	0	5.1±0.02	+++	-	91.5±0.02	-11.6±0.01	6.9±0.01	0.00	100.0	100.0	100.0
	30	5.4±0.11	+++	-	89.9±1.48	-11.6±0.02	6.9±0.01	0.15±0.01	96.8±0.66	98.3±2.06	101.6±7.05
25ºC	0	5.1±0.01	+++	-	89.9±0.32	-11.6±0.03	6.6±0.06	0.00	100.0	100.0	100.0
	30	5.2±0.05	+++	-	90.4±0.48	-11.6±0.01	6.7±0.17	0.11±0.01	93.8±1.48	54.3±0.25	94.8±2.47
50ºC	0	5.1±0.01	+++	-	90.5±0.01	-11.5±0.02	6.6±0.01	0.00	100.0	100.0	100.0
	30	5.3±0.10	++	-	90.4±0.14	-11.4±0.09	6.5±0.08	0.10±0.01	73.2±0.13	0.00	31.8±0.09

Each value represents the mean ± SD of results (n=3).
+++ = very good; ++ = good; + = fair
- means that no spot of mold was observed.
†CIE color coordinates; L*,lightness; a*, green/red coordinate; b*, blue/yellow coordinate

3.4 The skin penetration of 1–3 from facial essence containing *A. crassna* leaf extract with and without fabric mask

The essence containing *A. crassna* leaf extract was evaluated with and without fabric mask for the skin permeation of compounds **1**–**3**. The results showed that **1–3** in the facial essence without the fabric mask could permeate into the viable skin plus receiver compartment for only 0.26%, 0.58% and 0.61% of applied dose, respectively, while those with the fabric mask could provide superior skin permeation to the amounts of 0.79%, 1.08% and 0.70% of applied dose, respectively (Figure 2 and Table 4). The superior permeation of **1–2** from the formulation with fabric mask indicated that occlusive effect from covering the skin with fabric mask tends to enhance the skin absorption of **1–2** via skin hydration. This effect was less significant for the less hydrophilic compound **3.** The effects of occlusion on skin permeation have been intensively reviewed and reported (Hafeez & Maibach, 2013; Zhai & Maibach, 2002). However, our findings disagree with the previous report that mentioned the occlusion tended to increase skin penetration of lipophilic compounds more than that of hydrophilic compounds (Hafeez & Maibach, 2013). Moreover, it is wise to mention that the permeation of compounds with low partition coefficients could be also enhanced by some chemical enhancers in the formulation such as propylene glycol, glycerine and PEG-40 hydrogenated castor oil (Williams & Barry, 2004). From the literature review, the permeation of **3** through human thorax full skin has been studied (Ochocka *et al.*, 2017). The results suggest that compound **3** was deeper permeated into the skin when it was enhanced with ethanol solvent. However, no prior reports on skin penetration of **1** and **2** have been found in the literature. This is the first time that human skin permeation of **1** and **2** of *A. crassna* leaf extract has been determined and reported.

4. Conclusions

Fabric facial mask can enhance skin permeation of hydrophilic compounds **1** and **2** present in a cosmetic formulation containing *A. crassna* leaf aqueous extract, via skin hydration due to occlusive effect. The effect was less pronounced with the less hydrophilic compound **3**. Therefore, our finding confirmed the benefit of facial mask in cosmetic application for hydrophilic actives.

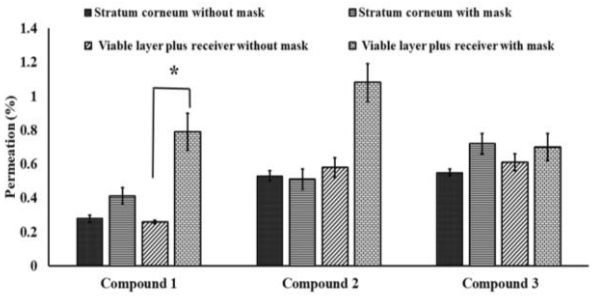

Figure 2. *In-vitro* skin permeation of **1–3** (expressed as percentage of applied dose±SEM) from facial essence with and without fabric mask containing *A. crassna* leaf extract after topical application onto excised human skin for 8 h. (n=3). *significantly different ($p < 0.05$, Student's *t-test*)

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Table 4. *In-vitro* skin permeation of compounds **1–3** (expressed as percentage of applied dose ± SEM) from facial essence with and without fabric mask containing *A. crassna* leaf extract after topical application onto excised human skin for 8 h. (n =3)

Formulation	Compound	Donor (%)	Stratum corneum (%)	Viable skin plus receiver (%)	Recovery (%)
(A) without fabric mask	**1**	94.39±3.58	0.28±0.02	0.26±0.01	94.93±3.61
	2	88.33±0.81	0.53±0.03	0.58±0.05	89.44±0.77
	3	100.05±8.59	0.55±0.02	0.61±0.05	101.19±8.52
(B) with fabric mask	**1**	90.47±2.72	0.41±0.05	0.79±0.11*	91.67±2.82
	2	87.94±1.18	0.51±0.06	1.08±0.11	89.53±1.20
	3	105.77±2.46	0.72±0.06	0.70±0.08	107.19±2.59

*significantly different versus the same compound without fabric mask ($p < 0.05$, Student's *t-test*)

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