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Efficacy and Safety of a Facial Mask Containing *Aquilaria crassna* Leaf Extract: a Double-Blind Randomized Controlled Trial

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ABSTRACT

Aquilaria crassna Pierre ex Lecomte (Agarwood) is a common plant in Southeast Asia. Both *A. crassna* leaf extract and its component, mangiferin, have been reported as having antioxidant, anti-inflammatory and antiglycation activities. The objectives of this study were, first, to test the standardized aqueous extract of *A. crassna* leaves (eAC) and formulations containing eAC, for skin irritation, and second, to test the cosmetic efficacy of facial masks containing eAC via a double-blind, randomized, placebo-controlled trial. For the skin irritation tests, patches containing either 1% or 5% eAC in water, or 0.1% and 0.2% eAC formulation were applied to the skin and the extent of skin irritation was measured by the Mean Cumulative Irritation Index. To test the cosmetic efficacy, facial masks containing a formulation of 0.2% eAC, or a placebo formulation, were randomly applied to either the left or the right half of the face of the 33 participants for 8 weeks. The result showed that the formulae containing 0.1% and 0.2% eAC caused no skin irritation. However, higher eAC doses of 1% and 5% in water

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caused mild irritation. The efficacy study showed that the formulation of 0.2% eAC significantly increased skin hydration from 30.9±1.3 (baseline) to 39.6±1.4 at week 4 and 45.9±1.3 at week 8 (p=0.001), while the effect of the placebo facial mask was negligible. Skin elasticity was not affected by either treatment. In conclusion, eAC at appropriate concentrations improves skin hydration while having no adverse or toxic reactions, thus showing promise as a bioactive ingredient in cosmetic products.

Keywords: *Aquilaria crassna* leaves; Mangiferin; Phytocosmetics; Skin irritation; Skin hydration

1. Introduction

Plant extracts have long been used in skincare products for their antioxidant and anti-aging properties. One such plant is *Aquilaria crassna* Pierre ex Lecomte [1], commonly known as agarwood or eaglewood, one of five Aquilaria species found in Thailand. This plant contains essential oils (agarwood oil) that have been used in products such as frankincense, spa oils, and perfumes [2]. Extracts of young leaves of *A. crassna* have been shown in *in vitro* tests to reduce the cellular and tissue function damage caused by advanced glycation, expressed by an IC_{50} of 9.0 ± 1.4 μg/mL for water extracts (eAC) and of 5.2 ± 0.5 μg/mL for ethanolic extracts. The eAC inhibited UVB-induced secretion of interleukin 1α (IL-1α) and interleukin 8 (IL-8) by cultured keratinocytes and slightly reduced prostaglandin E2 (PGE2) [3].

Prominent constituents of eAC are iriflophenone 3, 5-C-*β*D- diglucoside, iriflophenone 3-C-*β*-D-glucoside, genkwanin 5-O-*β*-primevoside, and mangiferin which present as major components. These compounds showed anti-inflammatory effects via inhibition of IL-1α and PGE2 secreted by human keratinocyte cells after being irradiated with UVB [3]. In addition, mangiferin showed *in vitro* antioxidant, antiglycation, and inflammatory properties [4]. Previous reports stated that mangiferin potently inhibits glycation (IC_{50} 2.05±0.08 μg/mL), but is less potent as an antioxidant (IC_{50} 7.7±0.20 μg/mL) [3]. These compounds showed satisfactory stability, solubility, and partition coefficient in eAC [5], favouring their inclusion in skin treatment formulations. Recently, our group reported that the fabric facial mask could enhance skin permeation of the hydrophilic bioactive compounds found in eAC [5].

This study was conducted to demonstrate the efficacy and safety of eAC as a bioactive ingredient in cosmetic products. The expectation of skincare and cosmetic products by their users is an improvement to the physical properties of the skin, through the application of safe, non-toxic formulations. To this end, the objectives of this current study, with human participants, were to: (i) incorporate eAC standardized to be at least 5% w/w mangiferin into facial masks and to test for skin irritation, (ii) to measure the cutaneous hydration and skin elasticity achieved with such masks. Skin hydration was measured by corneometry and skin elasticity was measured by cutometry.

2. Materials and Methods

2.1 eAC preparation

The leading 3 leaves of new growth were collected from *A. crassna* in Phitsanulok Province, Thailand, during the rainy season, May and June. The leaves were dried in an oven at 60°C for 3 days, then pulverized and infused with deionized water (500g in 5L) at 95°C-100ºC for 30 min. The supernatants were filtered, and the filtrate was lyophilized. The resultant eAC was standardized by mangiferin using HPLC method [5] and a content >5% w/w was deemed acceptable.

2.2 Approval

The study was approved (P10169/63) by the Institutional Research Board of Naresuan University (COA No. 522/2020) and by the Thai Clinical Trials Registry Committee (TCTR20210701009, 07/01/2021) before the study started (18/02/2021). All participants provided written informed consent prior to inclusion in the study.

2.3 Participant selection criteria

Inclusion criteria: Male or female aged 30- 60 y that agreed to undertake procedures and requirements, including pre- arranged attendances for assessments. Participants had sagging of the facial skin was clearly measured from the Rao Goldman 5-point scale [6].

Exclusion criteria: (1) pregnancy or lactating (2) showing active dermatoses or skin marks in the experimental area that could interfere with study results; (3) having a history of allergic reactions to topical products, cosmetics, or drugs; immunodeficiency; (4) current topical or systemic use of topical immuno-suppressants, (5) taking antihistamines, nonsteroidal anti-inflammatory drugs, or corticosteroids currently or up to 2 weeks before screening; (6) concurrent participation in another clinical study; (7) having a history of allergy, particularly for materials used in the study, and (8) did not meet the study eligibility criteria or decided not to participate in the study.

During the study, the participants were asked (i) not to apply any product on the experimental region that could interfere with study assessments, or to change other cosmetic habits, including hygiene products, (ii) not to use nonsteroidal anti-inflammatory drugs, corticoids, antihistamines, immunosuppressants, vitamin A and its derivatives, or any esthetic, cosmetic, or dermatological treatment at the test sites.

Withdrawal criteria: participants who had erythema skin irritation rated at 3+ (strong uniform redness) as evaluated by a dermatologist, who use product for less than 80% of the test instructions and more than 10% volunteers have serious adverse events (SAE) including burning, itching, swelling, redness, or inflammation requiring admission to hospital the project was terminated.

2.4 Skin irritation study

2.4.1 Study design and test products

This study included 33 participants. Participants received written information about their participation. The duration of the project was three days. The data were collected at the Cosmetics and Natural Products Research Center (COSNAT). Four preparations were assessed for skin irritation by the patch test. They contained either 1% or 5% eAC in sterile water and 0.1% or 0.2% eAC w/w in a formulation (Table 1).

Table 1. Ingredients of the placebo and the test formulations containing 0.1 and 0.2% eAC (w/w).

Ingredients List (INCI Name)	Placebo	0.1% eAC	0.2% eAC
Water	93.58	93.48	93.38
Disodium EDTA	3.00	3.00	3.00
Propylene glycol	2.00	2.00	2.00
Glycerin	0.10	0.10	0.10
Methyl paraben	0.10	0.10	0.10
Propyl paraben	0.30	0.30	0.30
Xanthan gum	0.50	0.50	0.50
PEG-40 hydrogenated castor oil	0.10	0.10	0.10
Tocopheryl acetate	0.10	0.10	0.10
Butylated hydroxytoluene (BHT)	0.10	0.10	0.10
Butylated hydroxyanisole (BHA)	0.02	0.02	0.02
Fragrance (Lotus Fragrance, 2562070)	0.10	0.10	0.01
eAC	None	0.10	0.20

2.4.2 Patch tests for adverse events

The position of each test patch was randomized using a method created by an independent actor who was not involved in the data collection or analysis. Participants were asked to avoid showering, submerging their forearms in water, scratching the patched areas, or undertaking heavy exercise

that might cause heavy sweating. The participants returned to the treatment room 24 hr after patch application, at which point the patches were removed. After a further 0.5 hr, 1 hr, and 24 hr, the patched sites were visually inspected by a dermatologist (PW), grading for irritation using the Frosch and Kligman (1979) criteria and grading irritating potential as determined by the mean cumulative irritation index (MCII) [7] using the following equation:

$$MCII = \left[\frac{\left(\frac{\sum Scores(D1 \ldots D33)}{Number\ of\ reading} \right) Sub1 + \cdots + \left(\frac{\sum Scores(D1 \ldots D33(n-1)x^2)}{Number\ of\ reading} \right) SubN}{Number\ of\ Subjects\ (N)} \right].$$

2.4.3 Evaluation of efficacy

1) Study design

Fully-blinded, placebo-controlled trial where every participant received both eAC and placebo treatments randomized to one or the other cheek. Randomization tables were used to allocate 0.2% eAC to the treatment side. Per-protocol analysis was used in this study.

This study required 33 participants (33 intervention sides and 33 placebo sides) as determined by the G*Power program version 3.1.9.2. Each participant was identified by a random code.

2) Preparation of facial mask fabric

Fabric masks were made from 45 gsm spun lace non-woven fabric comprising 60% cotton / 40% polyester, (Pathawin Co., Pathum Thani, Thailand).

Masks without eAC were used as the placebo and the treatment masks had the 0.2% eAC formulation (Table 1) as determined by the Scientific Committee on Consumer Safety (SCCS) [8]. The amount of formulation applied on a facial mask was 10 ml. The specifications for the fabric facial mask containing 0.2% eAC are provided in Table 2.

Table 2. Specifications for the fabric facial mask containing 0.2% eAC.

Characteristic	Fabric facial mask containing eAC
Color	Light brown
Odor	Distinctive
pH	4.5 – 6.0
Mangiferin	Not less than 0.01 %w/w
Microbial contamination	
- Bacteria	Less than 1.0 x 10^3 CFU / g. or mL
- Yeast and mold	Less than 1.0 x 10^3 CFU / g. or mL
- *Pseudomonas aeruginosa*	not be found in 1 g or 1 ml
- *Staphylococcus aureus*	not be found in 1 g or 1 ml
- Clostridium spp.	not be found in 1 g or 1 ml

3) Intervention

Before applying the masks, the participants washed and dried their faces thoroughly. They then applied the mask for 15-20 minutes, 3 times a week for 8 weeks. The positioning of the experimental facial masks was randomized. The participants were given a diary as a reminder for patch application and were asked to record the date and time and how they felt regarding the skin softness, hydration, firmness, and wrinkles after each application and whether they experienced any adverse reactions.

The participants presented their diaries at their 4-week visit and again at their 8-week final visit.

4) Measurement of end-points

To evaluate the efficacy after applying the mask on the cheek lateral to the nasolabial fold (9), as shown in Fig. 1, for 0, 4, and 8 weeks, the participants returned to the testing laboratories and acclimatized at 25 ± 1°C and 45 ± 5% relative humidity for 30 min.

Skin hydration:

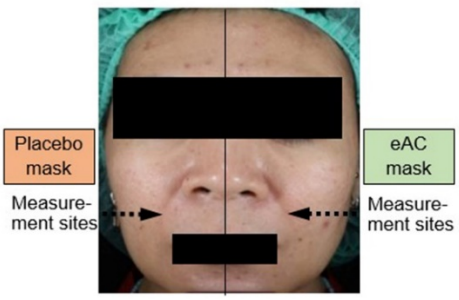

Fig. 1. The positions used to test corneometry and cutometry.

Skin hydration: Hydration was measured using a CM 825 skin probe corneometer attached to an MPA5 80 controller unit (Courage & Khazaka Electronics GmbH, Cologne, Germany). This device measures skin electrical capacitance which enables the corneal layer thickness to be estimated, normally falling between 10-20 um for facial skin. An increased thickness implies corneal hydration.

Skin elasticity: Cutaneous mechanical properties were measured with a cutometer (MPA 580, Courage Khazaka, Germany) in mode 1, coupled to an open-ended probe of internal diameter 2 mm, that was placed on the skin. The probe shines a parallel beam across the aperture. Pressure within the probe is reduced by 400 mbar for 2-5 s (the 'on-time'), then restored to atmospheric pressure for 3 s (relaxation or 'off-time') [9]. During the on-time, the skin is drawn into the probe and the dispersed light is continually measured and displayed as a rising phase. On releasing the suction, the falling phase indicates skin elasticity. From these waveforms, skin overall suppleness (R2), net elasticity (R5), skin firmness (R6), and visco-elasticity (R7) could be derived and the closer the respective values are to one, the higher the parameter.

5) Self-assessment questionnaire

To monitor side effects and satisfaction, the participants were given diaries that they used to enter specific comments about their observations of the treatments to each cheek, and any adverse effects at that current date. The diaries also contained the scheduled appointments and trial information. After the last treatment, at week 8, the participants were asked to complete a satisfaction questionnaire.

6) Statistical analysis

Continuous variables are expressed as mean ± SEM using the Student's paired t-test between repeated measures comparing the placebo and eAC-treated facial masks. At week 0, a test to establish a baseline was conducted, and further skin tests at 4 and 8 weeks were conducted. Questionnaire satisfaction scores for test/placebo were compared by the Wilcoxon signed-rank test. The data are expressed as mean ± SD.

3. Results and Discussion

3.1 Results

3.1.1 Patch tests for skin irritation

For the patch tests, 53 applicants were screened, of whom 33 met the selection criteria and were enrolled into the study. All 33 completed the study and all underwent dermatological assessments at every time-point (0.5 h, 1 h, and 24 hr). Participant characteristics are shown in Table 3 and the total means of irritation scores are presented in Table 4.

The two formulations produced marginal irritation, more so for the formulation containing 0.1% eAC. This may have reflected the effects of other differing ingredients (Table 1). Higher eAC doses at 1% and 5% in water caused mild irritation (Table 3).

Table 3. Characteristics of participants in skin irritation study (n = 33).

Assessment after patch removal	Amount of eAC	Number of participants		
		Erythema	Dryness	Fissures
0.5 hr	0.1% (formulation)	2	1	0
	0.2% (formulation)	1	1	0
	1% (water)	1	1	0
	5% (water)	3	0	0
1 hr	0.1% (formulation)	4	1	0
	0.2% (formulation)	2	0	0
	1% (water)	5	1	0
	5% (water)	6	1	0
24 hr	0.1% (formulation)	4	1	0
	0.2% (formulation)	2	1	0
	1% (water)	3	1	0
	5% (water)	4	0	0
Overall scores				
MCII	0.1% (formulation)	0.084		
	0.2% (formulation)	0.089		
	1% (water)	0.136		
	5% (water)	0.133		
Irritating Potential	0.1% (formulation)	non-irritating		
	0.2% (formulation)	non-irritating		
	1% (water)	Very slight irritation		
	5% (water)	Very slight irritation		

Table 4. Number of participants with erythema, dryness, and fissures, overall scores of MCII, and irritating potentials of eAC in formulations and water from the patch tests.

Parameter	Participants
Female, n (%)	21 (63%)
Mean age, years (SD)	40.1 (6.8)
Range (years)	30-56

3.1.2 Efficacy of formulations

A flow chart of participants for efficacy testing is shown in Fig. 3 of 60 answering the advertisement, 33 fit the selection criteria. Of these, 30 participated in and completed the study (5 males and 25 females). The mean age of study participants was 40.8 years (range 32-55 years), presented in Table 5. Three participants were withdrawn; one unrelated to the intervention and two due to itching from the placebo treated side after 30 min use.

Table 5. Characteristics of participants in efficacy evaluation (n = 30).

Treatment duration	Increase of skin moisture scores%, compared to week 0, n participants				
	< 0 %	10-0%	> 10 – 40%	> 40 – 80%	100%
Placebo mask					
week 4	12	5	13	0	0
week 8	9	3	15	3	0
eAC mask					
week 4	0	7	13	10	0
week 8	0	1	11	10	8

Skin hydration by corneometry: After 4 weeks and 8 weeks of treatment, the face side that used the experimental mask showed significantly higher skin hydration than at the baseline and the placebo groups at those times (Fig. 4). Table 6 shows the number of participants classified according to their increased skin hydration score compared to baseline. The majority of the eAC mask group showed an improvement in skin moisture scores. The 100% increased skin hydration score was only found in the eAC mask group after 8 weeks of treatment (n=8).

Skin elasticity by cutometry: At week 0, both placebo and test masks demonstrated similar elasticity levels. After weeks 4 and 8, elasticity progressively increased while the improvements were negligible (Fig. 5).

Table 6. Number of participants classified according to their increased skin hydration score.

Parameter	Participants
Female, n (%)	25 (83.33)
Mean age, years (SD)	40.8 (5.3)
Age range, years	32 – 55
Skin type, n (%)	
Dry	6 (20)
Oily	10 (33.33)
Dry and oily	7 (23.33)
Normal	7 (23.33)

Self-assessment: The participant questionnaire indicated no perceived differences in skin hydration, firmness, youthfulness, colour, and the useability between eAC and placebo. Grouping all the responses suggested a marginal preference for the eAC treatment although that did not reflect their overall self-assessment (Table 7).

Table 7. The results of self-assessment questionnaire after 8 weeks of treatment[a]. Questions presented here are translated from the Thai language version used in the study.

Question	Placebo score±SD	eAC score±SD	p-value[b]
1. Please estimate your skin hydration. The product can make more your skin moisturized	4.17±0.70	4.23±0.68	0.16
2. The product made your skin firmer	3.93±0.69	3.97±0.67	0.32
3. The product made your skin look younger	3.70±0.75	3.73±0.74	0.57
4. The wrinkles on your face are visibly reduced	3.57±0.73	3.63±0.72	0.33
5. The product made your skin whiter	3.67±0.88	3.70±0.84	0.66
6. This product has a fragrance	3.37±1.10	3.50±1.04	0.10
7. This product does not irritate skin	3.47±1.20	3.57±1.10	0.33
8. This product is suitable for daily use	3.43±0.82	3.53±0.82	0.33
9. This product is gentle on the skin	3.53±0.97	3.57±1.01	0.74
Mean score, questions 1-9	3.65±0.24	3.71±0.23	0.001
10.Overall satisfaction with the products	3.97±0.81	3.97±0.81	null

Note: [a] The responses were given a numerical score of 1 to 5, where 1 = Strongly disagree, 5 = Strongly agree, and 3 = Neutral. [b]p-value determined using Wilcoxon signed rank test (2-tailed).

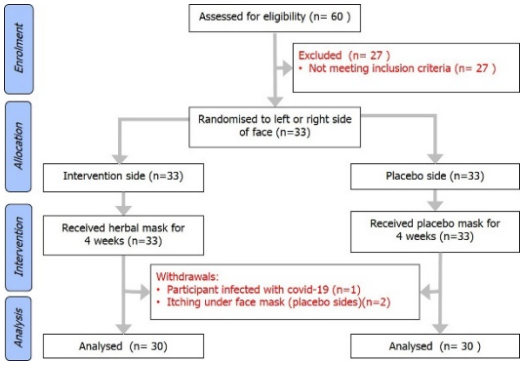

Fig. 3. Flow chart for participants in the efficacy study.

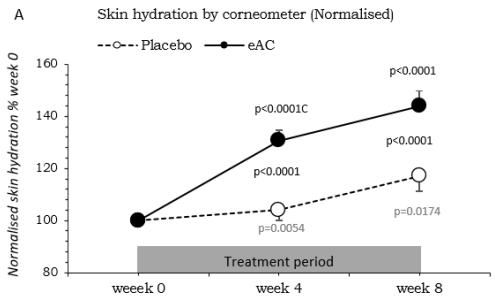

Fig. 4. Changes in skin hydration after treatment for 8 weeks in the eAC mask and placebo mask. Data are shown as mean ± SEM (n = 30, each group) [a]. The responses were given a numerical score of 1 to 5, where 1 = Strongly disagree, 5 = Strongly agree, and 3 = Neutral.

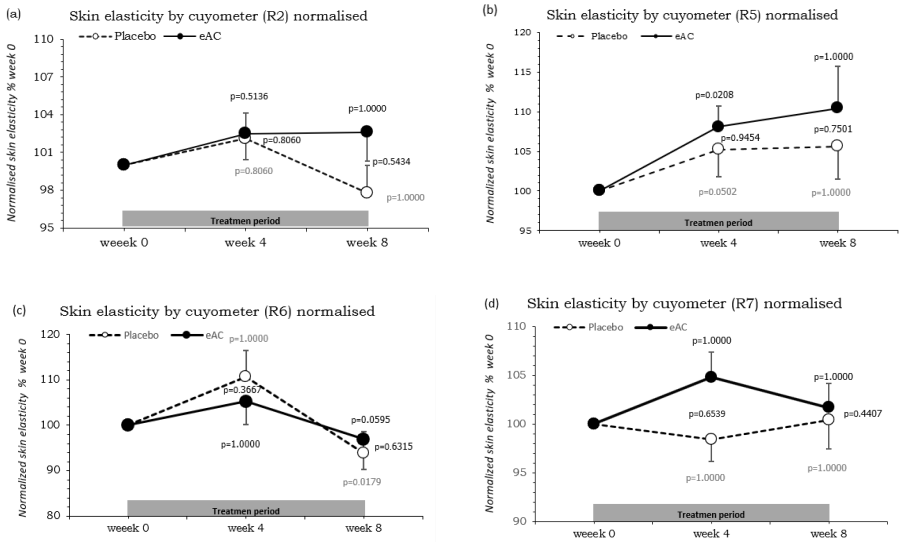

Fig. 5. Changes in skin elastic parameters after treatment for 8 weeks in the eAC mask and placebo mask. (a) R2 parameter. (b) R5 parameter (c) R6 parameter. (d) R7 parameter. Data are shown as mean ± SEM (n=30, each group).

3.2 Discussion

3.2.1 Efficacy

Aging is a multifactorial and complex process, resulting in loss of hydration and elasticity and structural changes of the skin [10]. The main findings were that eAC substantially increased facial skin hydration while the placebo had little effect. The possible mechanisms might be the maintenance of the barrier to water loss and the production of some epidermal thickening. The antioxidant activity of eAC might indirectly improve the function of the viable cell layers [11]. In addition, this hydration creates a physical action on the stratum corneum and reduced cutaneous water loss. Glycosidic compounds in the extract such as mangiferin might perform as natural hydrating agents [12]. The fabric facial mask has been reported to enhance skin permeation of hydrophilic bioactive compounds in eAC including mangiferin [5]. Penetration and permeation of mangiferin through the skin were also studied by another

group [13].

As for the effect on skin elasticity, outcomes for the four parameters extracted from cutometer profiles were unconvincing when comparing placebo and eAC. Those involving fast components of the deformation-recoil cycle (overall suppleness, net elasticity and visco-elasticity) appeared to marginally increase for both eAC and placebo interventions.

Actual cutaneous elasticity largely comes from the dermal connective tissue and remodeling done by rejuvenated fibroblasts. The inability of eAC to promote elasticity is consistent with (a) the recalcitrance of aging fibroblasts [14] as well as the failure of the active ingredients to penetrate the particularly robust human corneal layer. Even if an active ingredient appears at suprathreshold concentrations, it washes into the systemic circulation.

3.2.2 Adverse events

Acute (24 h) challenges had little effect in the patch tests during the 8-week treatments; the skin reaction from the placebo facial masks also suggest that the test formulation was not an irritant.

3.2.3 Limitations

Although mangiferin content was used to standardize eAC, observed reactions probably arise from a combination of several constituents. A major challenge for topically applied drugs is to understand their pharmacokinetics across a barrier that is essentially impermeable to most compounds. While topical compounds may partition into the corneal layer, the skin elastic properties are largely determined by the dermal extracellular matrix, including fibrillin-1 and elastin creating elasticity, various proteoglycans forming a network responsible for viscoelasticity, and collagen (mainly type 1) providing strength and preventing over-stretching[13]. If the topical medicine diffuses into the vascular dermis, it can also be taken into the bloodstream. Accumulation of topically applied compounds then creates the risk of systemically mediated toxicities. These would also need testing. Thus, actions characterized *in vitro* may not necessarily be seen in deeper layers of the skin [15]. Safety testing was limited to 24 hr patch testing and spontaneous reports from healthy participants. Only longer treatments involving many more users having a wide range of conditions will allow the risk/benefit of this treatment to be fully assessed.

4. Conclusion

The fabric facial mask containing 0.2% eAC improved skin hydration and, therefore, eAC has the potential to be developed into cosmetics aiming to increase skin moisture.

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