

Assessment of Skin Photoallergy Risk in Cosmetics Containing Herbal Extract Ingredients

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Keywords

Photoallergy · Herbs · Herbal extracts · Photopatch test · Cosmetics · Adverse events · *Coptis* · *Phellodendron amurense* · Curcumin · Shikonin

Abstract

Background/Objective: In recent years, herbal extracts are becoming increasingly popular ingredients added in cosmetics; however, the assessment of their potential adverse effects on the skin remains unclear. As *Coptis*, *Phellodendron amurense*, curcumin, and shikonin are herbs currently used in cosmetic ingredients, the aim of this study was to assess their skin photoallergy (PA) potential and the concentrations at which they could safely be used. **Methods:** In the patch test, *Coptis*, *P. amurense*, curcumin, and shikonin with 5, 10, 25, and 50% concentration were applied on 33 healthy Chinese subjects using the T.R.U.E. TEST[®] patch test system for 48 h. Photopatch testing was performed on 206 Chinese subjects with predisposed photosensitivity history using the Scandinavian photopatch series, and subjects were irradiated by 50% UVA minimum erythema dose. Photopatch testing of herbal extracts was then performed on subjects diagnosed with PA. **Results:** Thirty-three subjects (14 with

type III skin and 19 with type IV skin) completed contact patch testing of herbal extracts. *Coptis* induced a contact allergy (CA) reaction on 2 subjects at 25% concentration and on 2 subjects at 10% concentration. *P. amurense* induced a CA reaction on 1 subject at 10% concentration and on 1 subject at 5% concentration. Shikonin induced a stimulating reaction on 1 subject at 10% concentration. Curcumin induced a stimulating reaction on 1 subject at 10% concentration. Of the 206 Chinese subjects predisposed for photosensitivity, 10.19% had PA, 16.5% showed CA, and 1.45% had both PA + CA. PA-induced substances were promethazine hydrochloride (15%, $n = 31$), chlorpromazine hydrochloride (10.84%, $n = 19$), perfume mix (5.82%, $n = 12$), atranorin (3.39%, $n = 7$), 6-methyl coumarin (3.39%, $n = 7$), balsam Peru (1.94%, $n = 4$), fenchlor (1.94%, $n = 4$), 3,3',4',5-tetrachloro salicylanilide (0.97%, $n = 2$), hexachlorophene (0.97%, $n = 2$), chlorhexidine digluconate (0.97%, $n = 2$), and 4-aminobenzoic acid 2-hydroxy-4-methoxybenzophenone (0.97%, $n = 2$). *Coptis* at 25, 10, and 5% concentration and *P. amurense*, shikonin, and

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curcumin each at 10 and 5% concentration induced negative photopatch test results in all 10 photosensitive subjects.

Conclusion: We have shown that *Coptis*, shikonin, or curcumin at 5% concentration in cosmetics could be applied safely without inducing contact allergic and photosensitive reactions on the skin. These findings advance the understanding of herbal extract use in cosmetic ingredients as related to the fields of dermatopharmacology and dermatotoxicology.

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Introduction

The broad pharmacological use of naturally derived Chinese herbs such as *Coptis*, *Phellodendron amurense*, curcumin, and shikonin has been reported. Traditionally, these roots are used to treat several diseases such as cancer. In recent years, herbal extracts have become increasingly popular ingredients in skin care products because of their function in improvement of skin conditions. Some phytoconstituents from the herbal extract were suggested to be used for fighting against the deleterious photosensitization reactions [1]. However, there is limited research on the use of topically applied herbal extracts and their potential side effects on the skin.

Previous studies have shown that herbs such as *Arnica*, *Elecampagne*, and tea tree oil have induced contact dermatitis [2–5]. Besides contact allergic dermatitis and irritant dermatitis, photosensitive dermatitis is also a common adverse effect induced by cosmetics. As cosmetics are topically used on the skin, they are inevitably exposed to UV radiation from the sun after being applied, and the potential photosensitivity of the ingredients within these cosmetics needs to be thoroughly assessed.

It has been reported that plant extracts may cause photosensitivity [6–9]. Inbaraj et al. [6] found that UVA irradiation of HaCaT keratinocytes in the presence of 50 μ M berberine resulted in an 80% decrease in cell viability and a 3-fold increase in DNA damage. Pietkiewicz et al. [7] revealed that sesquiterpene lactones extracted from *Jacobaea vulgaris* could induce contact allergy (CA) and phototoxic dermatitis. Furniss et al. [8] reported a case of acute phytophotodermatitis with systemic upset after contact with the herb *Ruta graveolens*. Eickhorst et al. [9] reported that rue induced phytophotodermatitis when psoralens from rue came in contact with human skin that was subsequently exposed to ultraviolet A light.

Coptis, *P. amurense*, curcumin, and shikonin have been widely used, including as cosmetic ingredients. *Cop-*

tis plants (Ranunculaceae) which could upregulate skin antioxidant enzymes and immunity activities [10–12] has been used in the prevention and treatment of many human diseases in Chinese history. Curcumin, a yellow-orange compound derived from the root of *Curcuma longa* (Zingiberaceae family), has been used as a medicine, spice, and coloring agent. *P. amurense* is usually found in China, Korea, and Japan and widely used in traditional medicine to treat pneumonia, diarrhea, and circulation system disease [13]. Shikonin has had pharmacological effects in skin wound healing, immune modulation, skin cancers, and skin scars. However, the safety concentration of preparations for external use and photoallergy (PA) risk of these herbal extract ingredients contained in cosmetics still lack enough assessment.

This study focuses on the herbal extracts of *Coptis*, *P. amurense*, curcumin, and shikonin, which are commonly used as cosmetic ingredients and approved for use by the Chinese government. Therefore, the aim of this study was to assess the potential phototoxicity of *Coptis*, *P. amurense*, curcumin, and shikonin, as well as test the concentrations at which these herbal extracts could safely be used on human skin.

Materials and Methods

Chemicals

The following chemicals were tested in our study: *Coptis* (Zelang Pharmaceutical Technology Co. Ltd., Nanjing, China), *P. amurense* (Zelang Pharmaceutical Technology Co. Ltd., Nanjing, China), and curcumin and shikonin (Kishida chemical Co. Ltd., Osaka, Kishida, Japan). The preparation of the herbal extracts and the concentrations used are summarized in Table 1.

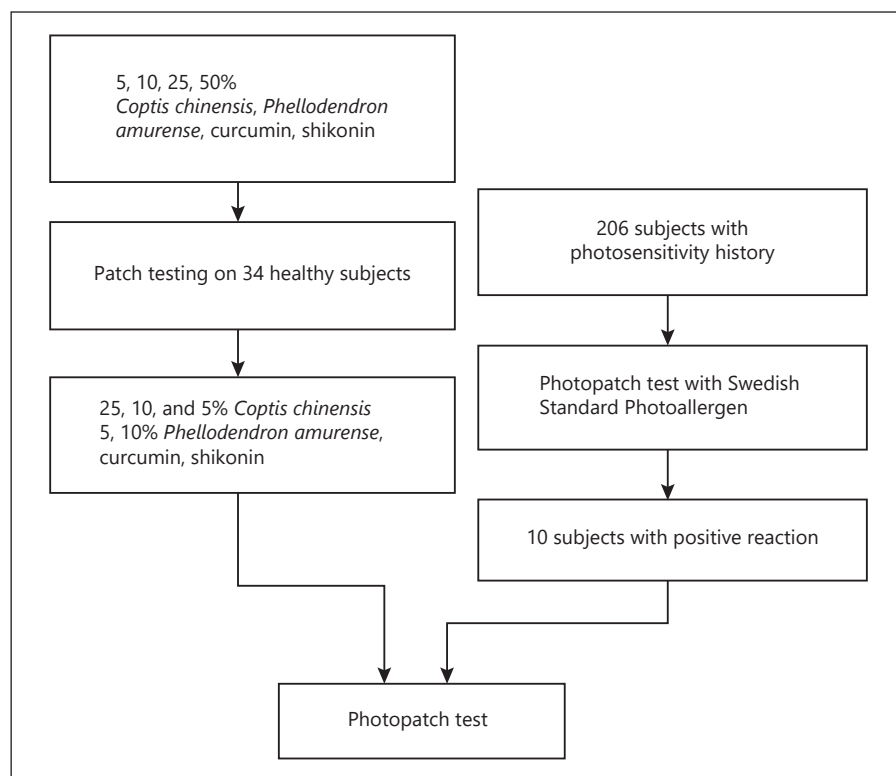
Radiation Source

Multiport solar simulators 601-300 W (Solar Light Company, Inc., Glenside, PA, USA) were used to take the measurements. The solar simulator included a 300-W xenon lamp and a dichroic mirror. Radiation was filtered to deliver a continuous UV spectrum of 320–400 nm by solar light (Solar Light Company, Inc., Glenside, PA, USA). The irradiances at skin level were monitored with a calibrated PMA2100 digital spectroradiometer (Solar Light Company, Inc., Glenside, PA, USA).

The Study Design and Procedure

Thirty-four healthy subjects were accepted for the patch testing of *Coptis chinensis*, *P. amurense*, curcumin, and shikonin. Basing on the path testing results, 25, 10, and 5% *C. chinensis* and 5 and 10% *P. amurense*, curcumin, and shikonin were selected and applied on 10 subjects who presented positive reaction in Swedish Standard Photoallergen photopatch testing. Then, photopatch testing of *C. chinensis*, *P. amurense*, curcumin, and shikonin was processed on these 10 photosensitivity subjects (Fig. 1).

Fig. 1. Study design and process. Thirty-four healthy subjects were accepted for the patch testing of *Coptis chinensis*, *Phellodendron amurense*, curcumin, and shikonin. Basing on the path testing results, 25, 10, and 5% *C. chinensis* and 5 and 10% *P. amurense*, curcumin, and shikonin were selected and applied on 10 subjects who presented positive reaction in Swedish Standard Photoallergen photopatch testing. Then, photopatch testing of *C. chinensis*, *P. amurense*, curcumin, and shikonin was processed on these 10 photosensitivity subjects.



Patch Testing Subjects

Thirty-three healthy subjects (Fitzpatrick III-IV) were selected for patch testing. Subjects were without obvious skin diseases or known history of atopic dermatitis. The subjects did not have any previous dermatological issues, history of drug hypersensitivity, or abnormal reaction to sunlight. Subjects went without drug intake for 1 month and did not receive phototherapy on their backs for 6 months prior to the study. For the duration of the study, subjects were required to avoid medical treatments and sun exposure on their backs. The study protocol and informed consent form were approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Subjects provided informed written consent.

Photopatch Testing on Photosensitivity Subjects

Two hundred six Chinese subjects with predisposed photosensitivity history completed photopatch testing. Exclusion criteria included (1) subjects who used antihistamines in the past week or an immunosuppressant in the past month; (2) subjects who used anti-inflammatory drugs on the test site within the past 2 months; (3) subjects with clinically unhealed inflammatory skin disease; (4) subjects with insulin-dependent diabetes; (5) subjects currently receiving treatments for asthma or other chronic respiratory diseases; (6) subjects who received anticancer chemotherapy within 6 months; (7) subjects with immunodeficiency or autoimmune diseases; (8) lactating or pregnant women; (9) subjects with bilateral mastectomy and bilateral axillary lymph node resection; and (10) subjects with scars, pigment, atrophy, or nevus flammeus on the tested skin regions.

Table 1. Herbal extract preparation

Herbal extracts	Concentration, %	Vessel
<i>Coptis chinensis</i>	25	Distilled water
<i>Coptis chinensis</i>	10	Distilled water
<i>Coptis chinensis</i>	5	Distilled water
Cortex <i>Phellodendri</i>	10	Distilled water
Cortex <i>Phellodendri</i>	5	Distilled water
Shikonin	10	Vaseline
Shikonin	5	Vaseline
Curcumin	10	Vaseline
Curcumin	5	Vaseline

Patch Testing Procedures

In the patch test, 5, 10, 25, and 50% of *Coptis*, *P. amurense*, curcumin, or shikonin were applied on 30 healthy Chinese subjects (15 males and 15 females; mean age 30–50 years) using the T.R.U.E. TEST® patch test system (True Test Technology Inc., Mineral Wells, TX, USA) for 48 h. Products were placed directly on the upper back of the skin, within small disks (True Test Technology Inc.). The prepared reagent was placed in the patch tester at a dose of 0.020 g (solid or semisolid) or 0.020 mL (liquid) [14]. The substances were applied to the back of the subjects as shown in Table 1. Controls were designed as matrix control (distilled water or vaseline) or blank control (no substance added into the T.R.U.E. TEST®).

Table 2. Positive rate of the photopatch test with Scandinavian Photopatch series

Reaction	Subjects (rate %)
Nonallergy	155 (75.24)
Allergic contact dermatitis	34 (16.5)
Photoallergic dermatitis	21 (10.19)
Photoallergic dermatitis and allergic contact dermatitis	3 (1.45)

Table 3. Results of the photopatch test with Scandinavian Photopatch series

Antigen series	Positive, %	Antigen series	Positive, %
3,4,4-Trichlorocarbaniide	0	Atranorin	3.39
Promethazine hydrochloride	15	Wood mix	0
4-Aminobenzoic acid	1	Evernic acid	0
3,4,5-Tribromosalicylanilide	0	Balsam Peru	1.94
Chlorpromazine hydrochloride	10.84	3,3',4',5'-Tetrachloro salicylanilide	0.97
2-Hydroxy-4-methoxybenzophenone	0.97	Hexachlorophene	0.97
6-Methyl coumarine	3.39	Chlorhexidine digluconate	0.97
Bithionol	0	Triclosan	0
Fenticlor	1.94	Diphenhydramine hydrochloride	2
Utric acid	0	Perfume mix	5.82

patch test system). Adhesive tape was used to fix the patches in place, and test sites were marked. The patches were left in place for 48 h, during which time the subjects were not allowed to wash the area or play vigorous sports. After 48 h, patches were removed, and an initial reading was taken 1 h later. Twenty-four, 48, and 72 h after removing patches, skin reactions were determined according to the International Contact Dermatitis scoring system [15].

Photopatch Testing Procedures

Photopatch test number and concentration were designed and listed as 25% *Coptis* (No. 1), 10% *Coptis* (No. 2), 5% *Coptis* (No. 3), 10% *P. amurense* (No. 4), 5% *P. amurense* (No. 5), 10% shikonin (No. 6), 5% shikonin (No. 7), 10% curcumin (No. 8), and 5% curcumin (No. 9). Vessel (vaseline [No. 10] and distilled water [No. 11]) was used as control. The Scandinavian photopatch series (Yuan Kang Company, Chemotechnique Diagnose, Sweden) was used as the standard antigen. Each subject underwent the UVA-MED test, and 2 identical photoallergens were applied to the left and right sides of the back for 24 h via the T.R.U.E. TEST® patch test system. Immediately after photoallergen patches on the back were removed, 1 side was irradiated by broadband UVA with 50% UVA-MED and the other side was covered with opaque material. The results were read before irradiation, immediately after irradiation, and then 48, 72, and 96 h after irradiation. The subjects diagnosed with PA were selected and continued with PA testing of *Coptis*, *P. amurense*, curcumin, and shikonin at different concentrations. The results of the photopatch test were recorded as nonallergy: the irradiation site and the nonirradiation site were both negative reactions; PA: the irradiation site was a positive reaction,

and the nonirradiation site was a negative reaction; CA: the irradiation site and the nonirradiation site were both positive reactions, and the degree of positive reaction was consistent; and PA + CA: the irradiation site and the nonirradiation site were positive reactions, and the degree of positive reaction on the irradiation site was greater than that of the nonirradiated site.

Results

Photosensitivity of Healthy Subjects

Two hundred six Chinese subjects with predisposed photosensitivity history underwent photopatch testing using the Scandinavian photopatch series. The rate of PA was 10.19%, the rate of CA was 16.5% (7.28% males and 9.22% females), and the positive rate of PA + CA was 1.45% (Table 2). PA-induced substances were promethazine hydrochloride (15%, $n = 31$), chlorpromazine hydrochloride (10.84%, $n = 19$), perfume mix (5.82%, $n = 12$), atranorin (3.39%, $n = 7$), 6-methyl coumarine (3.39%, $n = 7$), balsam Peru (1.94%, $n = 4$), fenticlor (1.94%, $n = 4$), 3,3',4',5'-tetrachloro salicylanilide (0.97%, $n = 2$), hexachlorophene (0.97%, $n = 2$), chlorhexidine digluconate (0.97%, $n = 2$), and 4-aminobenzoic acid 2-hydroxy-4-methoxybenzophenone (0.97%, $n = 2$) (Table 3).



Fig. 2. Skin sensitizing potency of *Coptis*, *Phellodendron amurense*, curcumin, and shikonin. Five, 10, 25, and 50% of *Coptis*, *P. amurense*, curcumin, or shikonin were applied separately on 30 healthy Chinese subjects using the T.R.U.E. TEST[®] patch test system (True Test Technology Inc., Mineral Wells, TX, USA) for 48 h and then removed. Results were read at 24, 48, and 72 h after the patch test

system removal. **a** Patch test of *Coptis* and *P. amurense*. *Coptis* induced a contact allergic reaction at 10 and 25% concentration. *P. amurense* induced a contact allergic reaction at 5 and 10% concentration. **b** Patch test of curcumin and shikonin. Shikonin induced a stimulating reaction at 10% concentration. Curcumin induced a stimulating reaction at 10% concentration.

Skin-Sensitizing Potency of Coptis, P. amurense, Curcumin, and Shikonin

Thirty-three healthy subjects (2 males and 32 females, aged 23–48 years, 14 with type III skin and 19 with type IV skin) completed the contact patch test of herbal extracts. *Coptis* induced a contact allergic reaction on 2 sub-

jects at 25% concentration and on 2 subjects at 10% concentration. *P. amurense* induced a contact allergic reaction on 1 subject at 10% concentration and on 1 subject at 5% concentration. Shikonin induced a stimulating reaction on 1 subject at 10% concentration. Curcumin induced a contact stimulating reaction on 1 subject at 10%

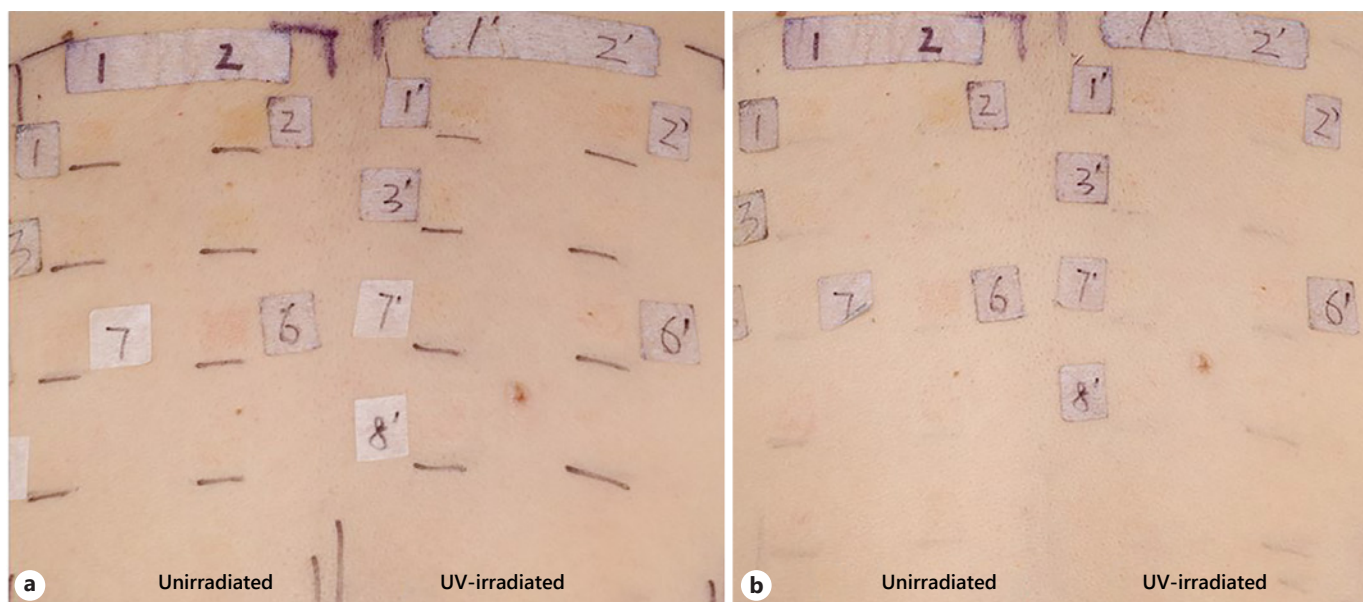


Fig. 3. Photosensitivity assessment of *Coptis*, *Phellodendron amurense*, curcumin, and shikonin. Photosensitive subjects were administered *Coptis*, *P. amurense*, curcumin, and shikonin photosensitivity assessment using the contact patch for 24 h and then underwent irradiation by 50% UVA-MED of 320–400 nm UV. Patched substances were 25% *Coptis* (No. 1), 10% *Coptis* (No. 2), 5% *Coptis* (No. 3), 10% *P. amurense* (No. 4), 5% *P. amurense* (No. 5), 10% shikonin (No. 6), 5% shikonin (No. 7), 10% curcumin (No.

8), and 5% curcumin (No. 9). Vessel (vaseline [No. 10] and distilled water [No. 11]) was used as control. Results were read before UV irradiation and immediately and 48 and 72 h after UV irradiation. **a** Unirradiation and 48 h after UV irradiation. **b** Unirradiation and 72 h after irradiation. The reactions of 25, 10, and 5% *Coptis*, 10 and 5% *P. amurense*, 10 and 5% shikonin, and 10 and 5% curcumin were all negative in 48- and 72-h readings in photopatch testing.

Table 4. Subjects who received the photopatch test of herbal extracts

Subjects	Clinical manifestation	Positive substance in photopatch test
F/53Y	Drug photosensitive dermatitis	Promethazine hydrochloride
F/32Y	Chronic eczema on sun-exposed skin	Chlorpromazine hydrochloride
		Thiodichlorophenol
F/56Y	Chronic eczema on sun-exposed skin	Aromatic blend
M/60Y	Chronic actinic dermatitis	Aromatic blend
		2-Hydroxyl-4-methoxybenzophenone
M/50Y	Contact dermatitis on sun-exposed skin	6-Methylcoumarin diphenhydramine hydrochloride
M/76Y	Chronic actinic dermatitis	Balsam of Peru
		Glucose chlorhexidine
M/24Y	Polymorphous light eruption	Chlorpromazine hydrochloride bithionol, fenticlor
F/54Y	Chronic eczema on sun-exposed skin	Atonin
M/42Y	Contact dermatitis on sun-exposed skin	Aromatic blend
M/60Y	Chronic actinic dermatitis	Aromatic blend

F, female; M, male; Y, year old.

concentration (Fig. 2). At 5% concentration, *Coptis*, shikonin, and curcumin did not induce contact allergic reactions; however, *P. amurense* did induce a contact allergic reaction at 5% concentration.

Skin-Photosensitizing Potency of Coptis, P. amurense, Curcumin, and Shikonin on Photosensitive Subjects
Ten subjects (aged 24–76 years, 6 males and 4 females; 2 with Fitzpatrick type III skin and 8 with type IV skin),

who previously presented positive photopatch test reactions using the Scandinavian photopatch series and were diagnosed as photosensitive, completed the herbal extract photopatch test. The clinical characteristics of these 10 subjects are listed in Table 4. Results were read immediately and 48 and 72 h after UV irradiation; *Coptis* at 25, 10, and 5% concentration and *P. amurense*, shikonin, and curcumin each at 10 and 5% concentration induced negative reactions in the photopatch test of all photosensitive subjects (Fig. 3).

Discussion

Adverse effects commonly reported from cosmetic ingredients include immediate type reactions (mostly non-immune immediate contact reactions and contact urticaria), photosensitivity, respiratory disorders, and miscellaneous adverse effects including irritant contact dermatitis, depigmentation, and systemic adverse effects [16, 17]. In the patch test of this study, we found that the highest concentration that could induce irritant or contact allergic dermatitis on healthy human skin is 25% for *C. chinensis* and 10% for *P. amurense*, curcumin, and shikonin via patch testing. On the basis of the above patch test results, we selected 25% *C. chinensis* and 10% *P. amurense*, curcumin, and shikonin to carry out photopatch testing on 10 photosensitive subjects.

Photoallergic reactions can commonly occur when a photosensitizing chemical (cosmetic agents or topical drugs) absorbs radiation from the sun (UVA or UVB) and is transformed into a photoactivated compound that can induce type IV hypersensitivity. Phototoxic reactions can occur within minutes or hours after cosmetic application, are nonimmunological, and directly induce skin injury [18]. In this study, we have found that 10.19% of healthy subjects presented positive photosensitive reactions from photopatch tests. The Swedish standard photoallergen series was used for photopatch testing, of which the main photoreactive dermatitis-causing substances were perfume, antiseptic, and sunscreen. The incidence of photosensitivity was higher in females than that in males. And, we also found that 25% *Coptis*, 10% *P. amurense*, 10% shikonin, and 10% curcumin did not induce phototoxicity on photosensitivity subjects' skin via the photopatch test, while *Coptis* at 25% concentration or higher as well as curcumin, shikonin, and *P. amurense* at 10% concentration or higher could induce irritative reactions on the human skin in contact patch testing.

Wang et al. [11] found that the *Coptis* extract presented radioprotective effects against radiation-induced skin damage in rats by modulating oxidative stress in skin. We found that *Coptis* induced a stimulating reaction at 25 and 10% concentration on healthy subjects' skin using contact patch testing. These results indicate that *Coptis* can be safely used externally as a cosmetic ingredient and topical medicines at concentrations <10%.

Dahl et al. [19] found that curcumin had phototoxic effects on basophilic leukocytes in rats. Curcumin could also exert potential phototoxic effects when illuminated. The mechanisms of curcumin phototoxicity may require hydrogen peroxide production. We found that curcumin induced a stimulating reaction at 10, 25, and 50% concentration on healthy subjects' skin using contact patch testing, but curcumin did not induce a photosensitive reaction at 10 and 5% concentration. These results indicate that curcumin does not present phototoxicity to the human skin at 10% concentration or lower.

P. amurense has many functions [20, 21]. Park et al. [22] found that synergistic topical application of salt-processed *P. amurense* and *Sanguisorba officinalis* Linne could reduce IgE and proinflammatory cytokines, as well as alleviate atopic dermatitis in mice models. Surprisingly, we found that *P. amurense* induced a stimulating reaction at 5% concentration but did not induce a photosensitive reaction. Further experimental research and evaluations are necessary to determine if *P. amurense* can be safely used as a cosmetic ingredient.

Yamashita et al. [23] found that shikonin could produce serious reactions even at a very low concentration of 0.5% by testing 10 natural organic chemicals contained in foods and/or cosmetic ingredients. We found that shikonin did not induce contact allergic and stimulating reaction at 5% concentration on healthy subjects' skin. And, we also found that shikonin did not induce a photosensitive reaction even in photosensitive subjects at 5 and 10% concentration. The role of shikonin in reducing allergic reaction [24], inhibiting melanoma cells [25], modulating oxidative stress [26], suppressing inflammation [27], and promoting skin repair [28] has been reported. It was also considered as a potential antineoplastic agent [29, 30]. We suggested that shikonin at 5% or lower concentration could be used externally for skin repair, anti-inflammation, and antioxidation, as well as for prevention of skin photoaging and skin cancer.

Although previous studies have reported that *Coptis*, *P. amurense*, curcumin, and shikonin which have been used as cosmetic ingredients presented potential phototoxicity, they are still not included in the commercial

True Test. Our study found that the initial concentration that can cause irritating contact dermatitis is 10% for *Coptis*, 5% for *P. amurense*, 10% for curcumin, and 10% for shikonin. These data suggest the recommended initial concentrations to be used externally for healthy people and thus should be included in the commercial True Test. As 25% concentration for *Coptis* and 10% concentration for *P. amurense*, shikonin, and curcumin did not induce phototoxicity, even on photosensitive subjects' skin, the research and development of new agents using the photopatch patch test system could start at 10% concentration or higher for phototoxicity detection.

The limitations of this study include the skin photobiological classification (skin phototype), system that was considered when subjects were enrolled, and the ratio of male and female which was disproportionate (the best ratio is 1:2 for male and female in cosmetic patch testing), and due to the small sample size, there is no statistical significance in different age groups. To further determine the concentration of *Coptis*, *P. amurense*, curcumin, and shikonin that can induce a CA and skin photosensitivity, additional research with a larger sample size must be conducted.

In this study, we found that the minimum concentration that can cause CA on healthy volunteers' skin was 10% for *Coptis*, curcumin, and shikonin and 5% for *P. amurense* and suggested that combining herbal agents in cosmetics at a concentration of 5% for *Coptis*, shikonin, and curcumin could be safely applied without inducing contact allergic and photosensitive reactions as well as potentially provide beneficial skin care effects. These findings may help to better understand the potential risks

of using herbs in cosmetics, especially in combination with UV lights, and to promote the research and development of cosmetics containing Chinese herbal extracts as related to the fields of dermatopharmacology and dermatotoxicology.

Statement of Ethics

The study protocol and informed consent form were approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Experiments on humans were performed in compliance with the Declaration of Helsinki Principles. Subjects provided informed written consent.

Conflict of Interest Statement

There are no conflicts of interest.

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Author Contributions

Nannan Pan and Yue Xia contributed equally to this work. Wei Lai and Yue Zheng contributed equally to this work as the co-correspondent author.

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