



Ethnobotanical Survey on Skin Whitening Prescriptions of Traditional Chinese Medicine in Taiwan

Chien-Yu Ko^{1†}, Jung Chao^{2†}, Pei-Yu Chen³, Shan-Yu Su^{4,5}, Tomoji Maeda^{6,7}, Chin-Yu Lin^{7,8}, Hung-Che Chiang^{1,7} and Shyh-Shyun Huang^{1,7,9*}

¹School of Pharmacy, China Medical University, Taichung, Taiwan, ²Chinese Medicine Research Center, Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, Master Program for Food and Drug Safety, China Medical University, Taichung, Taiwan, ³Department of Cosmeceutics, China Medical University, Taichung, Taiwan, ⁴Department of Chinese Medicine, China Medical University Hospital, Taichung, Taiwan, ⁵School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan, ⁶Department of Pharmaceutical Sciences, Nihon Pharmaceutical University, Saitama, Japan, ⁷Tsuzuki Institute for Traditional Medicine, China Medical University, Taichung, Taiwan, ⁸Institute of New Drug Development, China Medical University, Taichung, Taiwan, ⁹Department of Food Nutrition and Health Biotechnology, Asia University, Taichung, Taiwan

OPEN ACCESS

Edited by:

Lie-Fen Shyur,
Academia Sinica, Taiwan

Reviewed by:

Hsing-Yu Chen,
Chang Gung Memorial Hospital,
Taiwan
Linchun Shi,
Chinese Academy of Medical
Sciences and Peking Union Medical
College, China

*Correspondence:

Shyh-Shyun Huang
sshuang@mail.cmu.edu.tw

[†]These authors have contributed
equally to this work and share first
authorship.

Specialty section:

This article was submitted to
Ethnopharmacology,
a section of the journal
Frontiers in Pharmacology

Received: 05 July 2021

Accepted: 10 November 2021

Published: 30 November 2021

Citation:

Ko C-Y, Chao J, Chen P-Y, Su S-Y,
Maeda T, Lin C-Y, Chiang H-C and
Huang S-S (2021) Ethnobotanical
Survey on Skin Whitening
Prescriptions of Traditional Chinese
Medicine in Taiwan.
Front. Pharmacol. 12:736370.
doi: 10.3389/fphar.2021.736370

The increasing interest and demand for skin whitening products globally, particularly in Asia, have necessitated rapid advances in research on skin whitening products used in traditional Chinese medicine (TCM). Herein, we investigated 74 skin whitening prescriptions sold in TCM pharmacies in Taiwan. Commonly used medicinal materials were defined as those with a relative frequency of citation (RFC) > 0.2 and their characteristics were evaluated. Correlation analysis of commonly used medicinal materials was carried out to identify the core component of the medicinal materials. Of the purchased 74 skin whitening prescriptions, 36 were oral prescriptions, 37 were external prescriptions, and one prescription could be used as an oral or external prescription. After analysis, 90 traditional Chinese medicinal materials were obtained. The Apiaceae (10%; 13%) and Leguminosae (9%; 11%) were the main sources of oral and external medicinal materials, respectively. Oral skin whitening prescriptions were found to be mostly warm (46%) and sweet (53%), while external skin whitening prescriptions included cold (43%) and bitter (29%) medicinal materials. Additionally, mainly tonifying and replenishing effects of the materials were noted. Pharmacological analysis indicated that these medicinal materials may promote wound healing, treat inflammatory skin diseases, or anti-hyperpigmentation. According to the Spearman correlation analysis on interactions among medicinal materials with an RFC > 0.2 in the oral skin whitening prescriptions, *Paeonia lactiflora* Pall. (white) and *Atractylodes macrocephala* Koidz. showed the highest correlation (confidence score = 0.93), followed by *Ziziphus jujuba* Mill. (red) and *Astragalus propinquus* Schischkin (confidence score = 0.91). Seven medicinal materials in external skin whitening prescriptions with an RFC > 0.2, were classified as Taiwan *qi bai san* (an herbal preparation), including *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav., *Wolfiporia extensa* (Peck) Ginns, *Bletilla striata* (Thunb.) Rchb. f., *Atractylodes macrocephala* Koidz., *Ampelopsis japonica* (Thunb.) Makino, *Paeonia lactiflora* Pall. (white), and *Bombyx mori* Linnaeus. Skin whitening prescriptions included multiple traditional Chinese medicinal materials. Despite the long history of use, there is a lack of studies concerning skin whitening products, possibly due to the complex composition of

traditional Chinese medicine. Further studies are required to assess the efficacy and safety of these traditional Chinese medicinal materials for inclusion in effective, safe, and functional pharmacological products.

Keywords: skin whitening, ethnobotanical, Taiwan, traditional Chinese medicine pharmacy, traditional Taiwanese medicine

1 INTRODUCTION

The global cosmetics market is undergoing an unprecedented boom due to economic development and growing aesthetic needs. Rapidly expanding Asian cosmetic markets, of which China, Japan, South Korea, and India are major consumer countries, are following in the footsteps of European and American countries with the ubiquitous use of cosmetic products, particularly skin whitening products. Moreover, a recent survey noted the increasing prevalence of males using skin whitening products in addition to females (Pillaiyar et al., 2017; Hu et al., 2020).

Skin whitening prescriptions can not only be used to lighten skin tone, but also clinically treat hyperpigmentary disorders by decreasing melanin synthesis (Gillbro and Olsson, 2011). Melanin, one of the important pigments, is synthesized in melanocytes in the basal layer of epidermis and can protect the skin from ultraviolet-induced damage (Brenner and Hearing, 2008). Epidermal melanin content is intimately associated with anthropological origins. As the level of ultraviolet radiation is higher in low-latitude regions, people in these regions have higher melanin content; conversely, melanin content is lower in people at high-latitude regions, hence they have whiter skin (Slominski et al., 2004). Melanogenesis involves the conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by tyrosinase before further conversion to L-dopaquinone. Finally, L-dopaquinone undergoes a series of chemical reactions to form melanin (**Supplementary Figure S1**). Tyrosinase is a rate-limiting enzyme in melanogenesis and is considered an important target for the development of therapies in treating hyperpigmentation (Sonthalia et al., 2016; Ullah et al., 2019; Zaidi et al., 2019).

At present, there are a variety of skin whitening products on the market classified as either “inhibiting melanogenesis” or “inhibiting melanogenesis and promoting melanin removal.” In Taiwan, only 13 skin whitening components (**Supplementary Table S1**) (Food and Drug Administration, 2014) have been approved for use in cosmetic preparations. While ascorbic acid (vitamin C) is a common component, it is unstable and easily oxidized which limits its direct use. In order to prevent premature degradation, derivatives such as magnesium ascorbyl phosphate, ascorbyl glucoside, and ascorbyl tetraisopalmitate (Balaguer et al., 2008) are often utilized. Caution must be exercised when using various skin whitening components as improper use may lead to dermatitis, erythema, burns, and other skin injuries (Nordin et al., 2021). Thus, manufacturers have begun to seek natural alternatives to develop gentle, hypoallergenic skin whitening products derived from traditional Chinese medicine (TCM).

In traditional Chinese medicine books, many words describe dark skin or spots on the face, such as *miàn gǎn zèng*. In addition, there are ancient descriptions regarding the use of TCM for skin whitening. The *Shennong Materia Medica*, an extant medicinal text published in 100 B.C., recorded that *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav. promotes skin growth and has moisturizing effects. Of additional interest is *qī bái sǎn*, a well-known skin whitening herbal prescription. However, its composition varies among different historical dynasties, geographical regions, and environments. For example, different compositions of *qī bái sǎn* can be found in related prescriptions such as *yǒng lèi qián fāng*, *pǔ jì fāng*, and *tài píng shèng huì fāng* (**Table 1**). To date, there is still no comprehensive study on skin whitening prescriptions in traditional Chinese medicine pharmacies in Taiwan. Therefore, the aim of this study was to examine the composition of skin whitening prescriptions sold in traditional Chinese medicine pharmacies in Taiwan to understand the usage, methods of preparation, and principles of skin whitening prescriptions in Taiwan.

2 MATERIALS AND METHODS

2.1 Ethical Review

The research for this study was conducted from March 2020 to April 2021. The study was approved by the Central Regional Research Ethics Committee of China Medical University (CRREC-109-125) (**Supplementary Figure S2**).

2.2 Research Process

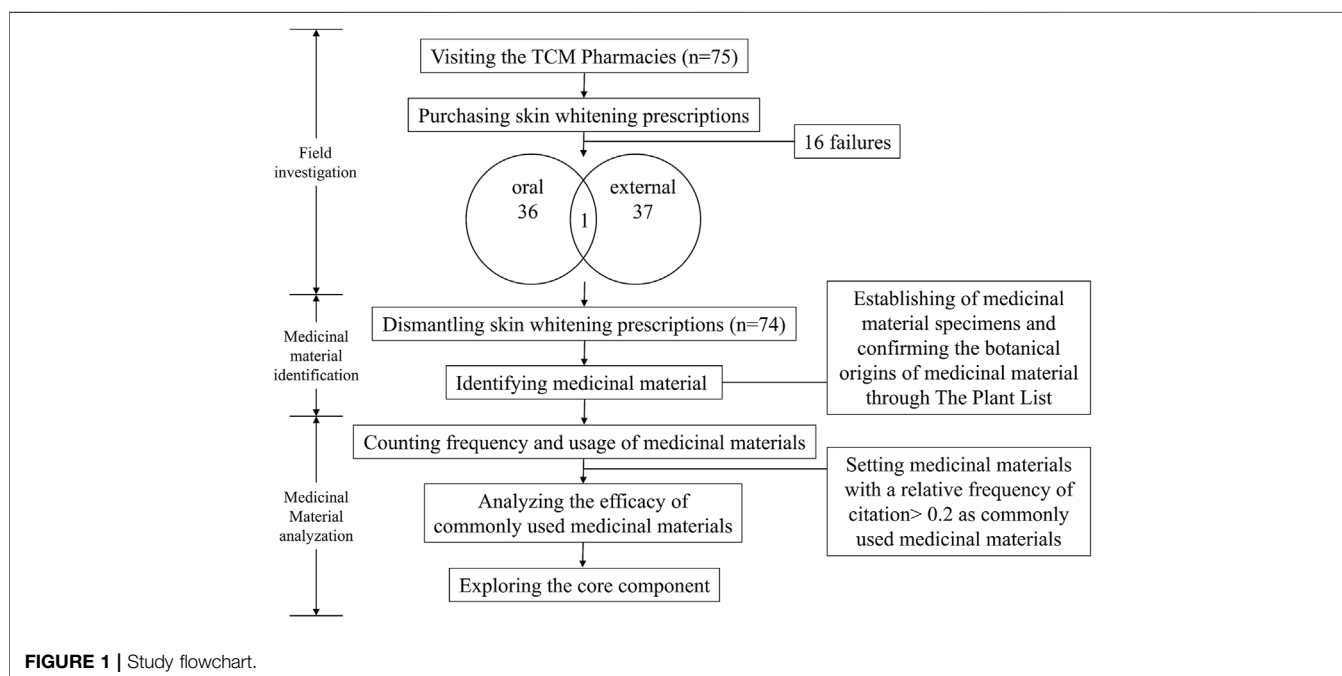
This study complied with the ethnobotanical research guidelines (Rivera et al., 2014; Mullane et al., 2015; Heinrich et al., 2018; Heinrich et al., 2020), and could mainly be divided into field investigation, medicinal material identification, and analysis. The complete study methods are shown in the study flowchart (**Figure 1**).

2.2.1 Field Investigation

Taiwan is an island located at the intersection between Northeast Asia and Southeast Asia and a total area of 36,000 km² (Tourism Bureau, 2021). The study was conducted over 12 months and we randomly visited the TCM pharmacies that appropriately represented the use of TCM medicine in Taiwan. The number of TCM pharmacies selected was directly proportional to the number of TCM pharmacies in each county and city published by the government (Ministry of Health and Welfare, 2015). A total of 75 TCM pharmacies were visited, included 16 pharmacies were visited but no prescription was obtained.

TABLE 1 | Qī bái sǎn-related prescriptions in ancient books.

Name of prescription	Composition	Source
qī bái sǎn (七白散)	<i>Atractylodes macrocephala</i> Koidz., <i>Ampelopsis japonica</i> (Thunb.) Makino, <i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., <i>Bombyx mori</i> Linnaeus, <i>Paeonia lactiflora</i> Pall., <i>Ipomoea nil</i> (L.) Roth, <i>Sauromatum giganteum</i> (Engl.) Cusimano & Hett	yǒng lèi qián fāng (永類鈴方)
qī bái wán (七白丸)	<i>Atractylodes macrocephala</i> Koidz., <i>Ampelopsis japonica</i> (Thunb.) Makino, <i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., <i>Bletilla striata</i> (Thunb.) Rchb.f., <i>Bombyx mori</i> Linnaeus, <i>Wolfiporia extensa</i> (Peck) Ginns, <i>Sauromatum giganteum</i> (Engl.) Cusimano & Hett	pǔ jì fāng (普濟方)
qī bái sǎn xǐ miàn yào (七白散洗面藥)	<i>Atractylodes macrocephala</i> Koidz., <i>Ampelopsis japonica</i> (Thunb.) Makino, <i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., <i>Bombyx mori</i> Linnaeus, <i>Paeonia lactiflora</i> Pall., <i>Ipomoea nil</i> (L.) Roth, <i>Wolfiporia extensa</i> (Peck) Ginns	pǔ jì fāng (普濟方)
qī bái tǐng zǐ gāo (七白挺子膏)	<i>Atractylodes macrocephala</i> Koidz., <i>Ampelopsis japonica</i> (Thunb.) Makino, <i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., <i>Asarum heterotropoides</i> F.Schmidt f. <i>mandshuricum</i> (Maxim.) Kitag., <i>Bletilla striata</i> (Thunb.) Rchb.f., <i>Wolfiporia extensa</i> (Peck) Ginns, <i>Sauromatum giganteum</i> (Engl.) Cusimano & Hett (This prescription must be mixed with egg white for use)	tài píng shèng huì fāng (太平聖惠方)

**FIGURE 1** | Study flowchart.

Overall, 74 skin whitening prescriptions were obtained (with 13 TCM pharmacies providing more than one prescription) (Figure 2), including 36 oral prescriptions, 37 external prescriptions, and one prescription which could be used as an oral or external prescription.

2.2.2 Identification of Medicinal Materials

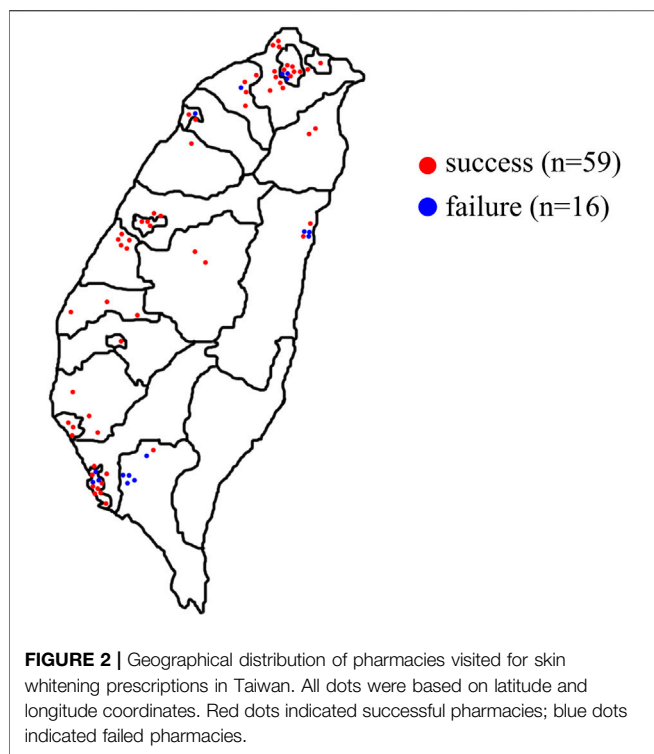
This study examined the purchased medicinal materials and performed the five-sense identification to identify the origins and plant parts of the materials, and compared them with the medicinal material standards to distinguish authentic or misused medicinal materials (Figure 3). We also photographed the materials and recorded the weight of each material. Finally, the materials were numbered and stored in the herbarium of the China Medical University, Taiwan.

2.2.3 Analysis of Medicinal Materials

The various medicinal materials were analyzed and collated based on biological taxonomy, relative frequency of citation (RFC), efficacy of traditional use, and skin-related pharmacological effects. Biological taxonomy included the Scientific name of the crude drug, family, and color. The Plant List (<http://www.theplantlist.org/>) was used as a source of botanical information. Medicinal materials with $RFC > 0.2$ were defined as commonly used medicinal materials. The RFC formula was defined as follows (Vitalini et al., 2013; Dixit and Tiwari, 2020; Abbas et al., 2021):

$$RFC_i = FC_i/N (0 \leq RFC_i \leq 1)$$

Where RFC_i is the relative frequency count of i species and it is commonly used in ethnopharmacology papers. FC_i defines the

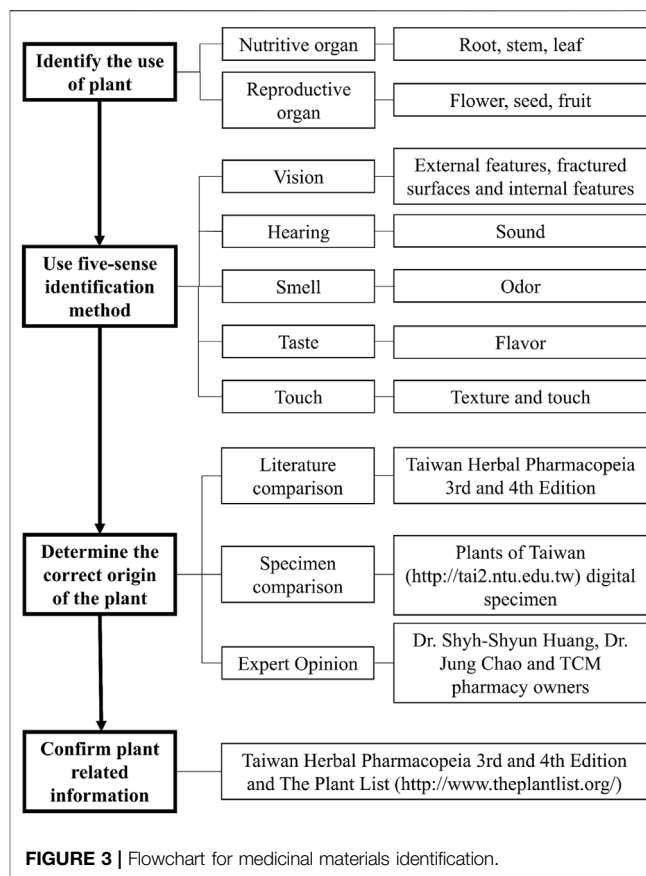


count of prescriptions which used species *i*. *N* denotes the total number of prescriptions.

The medicinal materials were indexed against the Taiwan Herbal Pharmacopeia (3rd, 4th edition) (Taiwan Herbal Pharmacopeia 3rd Edition Committee, 2018; Taiwan Herbal Pharmacopeia 4th Edition Committee, 2021), Pharmacopoeia of the People's Republic of China (Chinese Pharmacopoeia Commission, 2020), and Chinese Materia Medica (State Administration of Traditional Chinese Medicine, 1999). The effects, properties, and flavors of traditional Chinese medicine were cited from the Taiwan Herbal Pharmacopeia (3rd, 4th edition). The PubMed database was systematically searched from Jan 2010 to May 2021 for skin-related pharmacological effects, utilizing keywords such as “skin” and the scientific names of medicinal materials.

2.2.4 Analysis

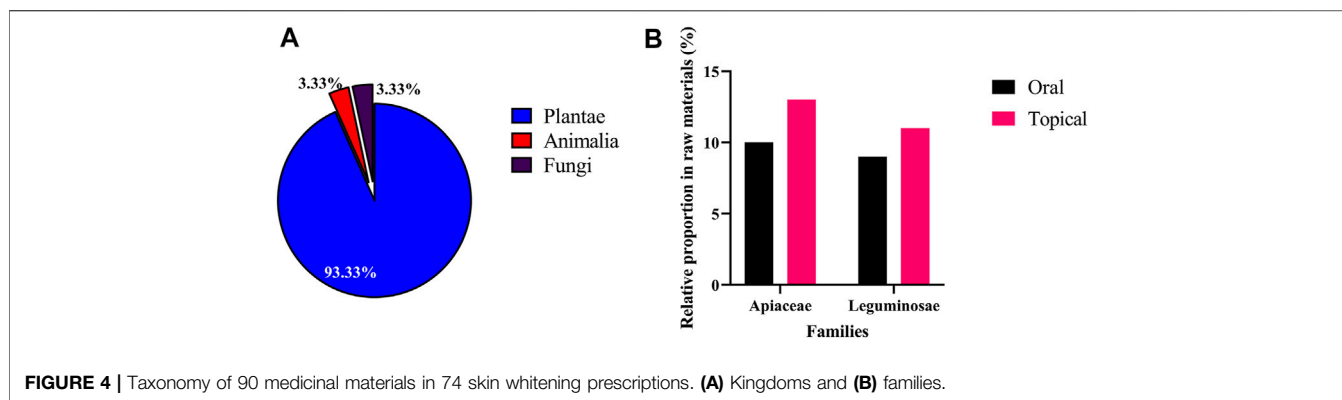
GraphPad Prism 9.0 (GraphPad Prism version 9.0 for Windows, GraphPad Software, San Diego, California, USA) was used to plot a heat map for Spearman correlation analysis of commonly used medicinal materials used in oral skin whitening prescriptions. The colors of the squares in the heat map were based on the visualization of Spearman correlation matrix of the two medicinal materials. The more intense red hue, the higher the correlation between the two medicinal materials. Conversely, the lighter the color, the lower the correlation between the two medicinal materials (Vacanti, 2019).



3 RESULTS

3.1 Biological Taxonomic Characteristics of Medicinal Materials Used in Skin Whitening Prescriptions

During this study, 74 skin whitening prescriptions were purchased from 59 TCM pharmacies in Taiwan, of which 36 were oral prescriptions, 37 were external prescriptions, and one prescription could be used orally or externally. Oral prescription use method is to add appropriate amount of water to decoct; external prescription use method is to mash the medicinal materials, then add water, honey or milk, and apply to the face. Among the oral and external skin whitening prescriptions, 79 and 56 medicinal materials were found respectively. Overall, a total of 90 medicinal materials were obtained from the 74 prescriptions, and 6 misused medicinal materials were found (**Supplementary Table S2**). The majority of these medicinal materials were Plantae (93.33%), 3 medicinal materials (3.33%) were obtained from Animalia [*Bombyx mori* Linnaeus, *Crassostrea gigas* (Thunberg), and *Pteria martensii* (Dunker)] and 3 (3.33%) were from Fungi [*Tremella fuciformis*, *Wolfiporia extensa* (Peck) Ginns cum pini radix, and *Wolfiporia extensa* (Peck) Ginns] (**Figure 4A**).



The most used of medicinal material in oral skin whitening prescriptions was *Wolfiporia extensa* (Peck) Ginns (RFC = 0.51), followed by *Glycyrrhiza uralensis* Fisch. and *Paeonia lactiflora* Pall. (white) (RFC = 0.41), while *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav. (RFC = 0.89) was the most commonly used of medicinal material in external skin whitening prescriptions. When classified by family, the most common families in both oral and external skin whitening prescriptions were Apiaceae (10 and 13% respectively) and Leguminosae (9 and 11% respectively) (Figure 4B).

3.2 Analysis of Traditional Efficacy, Skin-Related Pharmacological Effects and Dosage of Commonly Used Medicinal Materials in Skin Whitening Prescriptions

Commonly used medicinal materials were defined as those with RFC > 0.2. Thirteen and seven commonly used medicinal materials were obtained from oral and external skin whitening prescriptions, respectively (Table 2).

With regards to the properties (Figure 5A), commonly used medicinal materials used in oral skin whitening prescriptions were mostly warm (46%) and plain (31%), while those used in external were mostly cold (43%), followed by warm (29%) and plain (29%). About the flavors (Figure 5B), commonly used medicinal materials used in oral skin whitening prescriptions were mostly sweet (53%), while those used in external were mostly bitter (29%).

About classification by traditional effect (Figures 5C,D), commonly used medicinal materials used in both oral and external skin whitening prescriptions were mostly tonifying and replenishing. Integrated the modern research related to skin, including pharmacological effects, clinical studies and intervention studies, it is found that most of these medicinal materials could promote wound healing, treat inflammatory skin diseases, or anti-hyperpigmentation (Figure 5E).

The analysis of the various medicinal materials dosage used in prescriptions is presented in Supplementary Table S3. In commonly used oral medicinal materials (Figure 6A), the average dose of *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.)

Stapf was the highest and that *Glycyrrhiza uralensis* Fisch. was the lowest. *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf showed the largest dose difference across the various TCM pharmacies, while dose differences of the *Angelica sinensis* (Oliv.) Diels were the smallest. In commonly used external medicinal materials (Figure 6B), the average dosage of *Wolfiporia extensa* (Peck) Ginns was the highest, while the *Bletilla striata* (Thunb.) Rchb. f. and *Paeonia lactiflora* Pall. (white) were the lowest. The dosages of *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav. had the largest differences across various TCM pharmacies, while the dosages of the *Paeonia lactiflora* Pall. (white) exhibited the smallest difference.

3.3 Correlation Analysis of Commonly Used Medicinal Materials Used in Oral Skin Whitening Prescriptions

Spearman correlation analysis was performed for commonly used medicinal materials in oral skin whitening prescriptions and a heatmap was plotted (Figure 7A). The highest correlation was detected between *Paeonia lactiflora* Pall. (white) and *Atractylodes macrocephala* Koidz. (confidence score = 0.93), followed by the correlation between *Ziziphus jujuba* Mill. (red) and *Astragalus propinquus* Schischkin (confidence score = 0.91). In contrast, low correlation was observed between *Dioscorea polystachya* Turcz. and *Glycyrrhiza uralensis* Fisch. (confidence score = -0.7). *Dioscorea polystachya* Turcz. also demonstrated a low correlation with *Paeonia lactiflora* Pall. (white) and *Atractylodes macrocephala* Koidz. Therefore, *Dioscorea polystachya* Turcz. is less likely to be present when *Glycyrrhiza uralensis* Fisch., *Paeonia lactiflora* Pall. (white), or *Atractylodes macrocephala* Koidz. are present. When network analysis was performed on medicinal materials with RFC > 0.2 in oral skin whitening prescriptions (Figure 7B) and two medicinal materials with confidence score >0.6 were connected by lines, it was found that *Paeonia lactiflora* Pall. (white) and *Atractylodes macrocephala* Koidz. frequently appeared together with *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav. or *Wolfiporia extensa* (Peck) Ginns and *Glycyrrhiza uralensis* Fisch.;

TABLE 2 | Medicinal properties and skin-related modern research of commonly used medicinal materials used in skin whitening prescriptions (RFC>0.2).

Scientific name/Latin name of crude drug/Local name/sample number	RFC ^a	Family	Color	Flavor and property	Traditional usage	Literature on skin modern research (PubMed) ^b
Oral						
<i>Wolfiporia extensa</i> (Peck) Ginns/Poria/白茯苓/CMU2021SWP	0.51	Polyporaceae	white	Sweet and plain; plain	Dampness-draining diuretic	Hyperpigmentation (Ho et al., 2021); inhibition of melanogenesis (Lee and Cha, 2018; Kang et al., 2019); moisturizing and increased skin barrier function (Choi et al., 2019); oxidative stress associated skin aging effects and inflammatory skin diseases (Kang et al., 2019; Fang et al., 2021)
<i>Glycyrrhiza uralensis</i> Fisch./Glycyrrhizae radix et rhizoma/甘草/CMU2021SWGr	0.41	Leguminosae	brown	Sweet; plain	Tonifying and replenishing	Accelerate wound healing and promote neovascularization (Hao et al., 2020) anti-photoaging effects (Kim et al., 2017; Xuan et al., 2017); human dermal fibroblasts (Kim et al., 2017); inflammatory skin diseases (Jeong et al., 2015; Cha et al., 2016; Lee et al., 2020); inhibition of melanogenesis (Lim et al., 2018); protection of skin barrier (Cha et al., 2017); viral skin diseases (Wang et al., 2013a)
<i>Paeonia lactiflora</i> Pall. (white)/Paeoniae radix alba/白芍/CMU2021SWPra	0.41	Paeoniaceae	white	Bitter and sour; cold	Tonifying and replenishing	Ameliorated vascular damage (Chen et al., 2013); anti-photoaging effects (Lu et al., 2020); hyperpigmentation (Qiu et al., 2016; Ho et al., 2021); inflammatory skin diseases (Chen et al., 2011; Jeong et al., 2015; Kim et al., 2021); inhibition of melanogenesis (You et al., 2017); psoriasis (Sun et al., 2015a; Choi et al., 2015; Li et al., 2019); skin itching (Zhu et al., 2019)
<i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav./Angelicae dahuricae radix/白芷/CMU2021SWADr	0.35	Apiaceae	white	Pungent; warm	Exterior-releasing	Accelerate wound healing and promote neovascularization (Bai et al., 2012; Yang et al., 2017; Yang et al., 2020a); acne (Hwang et al., 2016); inflammatory skin diseases (Lee et al., 2012; Ku et al., 2017); inhibition of melanogenesis (Kim et al., 2016); melanoma (Hwangbo et al., 2020); skin itching (Zhu et al., 2019)
<i>Astragalus propinquus</i> Schischkin/Astragali radix/黃耆/CMU2021SWApr	0.32	Leguminosae	brown	Sweet; warm	Tonifying and replenishing	Accelerate wound healing (Luo et al., 2016; Zhao et al., 2017); anti-photoaging effects (Hong et al., 2013; Berezutsky et al., 2019; Shan et al., 2019); hyperpigmentation (Tsao et al., 2017); inflammatory skin diseases (Kim et al., 2013; Deng et al., 2019)
<i>Angelica sinensis</i> (Oliv.) Diels/Angelicae sinensis radix/當歸/CMU2021SWAsr	0.32	Apiaceae	brown	Sweet and pungent; warm	Tonifying and replenishing	Accelerate wound healing (Hsiao et al., 2012; Zhao et al., 2012; Wang et al., 2013b); inflammatory skin diseases (Gong et al., 2015; Choi et al., 2016; Lee et al., 2016; Saba et al., 2016; Nam et al., 2021); skin itching (Lee et al., 2016; Zhu et al., 2019); melanoma (Gao et al., 2018)
<i>Coix lacryma-jobi</i> var. <i>ma-yuen</i> (Rom.Caill.) Stapf/Coicis semen/白薏仁/CMU2021SWCs	0.32	Poaceae	white	Sweet and plain; cool	Dampness-draining diuretic	Accelerate wound healing (Kalekhan et al., 2021); anti-photoaging effects (Shan et al., 2012); chapped skin and warts (Chung et al., 2011; Byun et al., 2016; Son et al., 2019); inhibition of melanogenesis (Huang et al., 2014; Amen et al., 2017)
<i>Ziziphus jujuba</i> Mill. (red)/Jujubae fructus (red)/紅棗/CMU2021SWJf	0.3	Rhamnaceae	red	Sweet; warm	Tonifying and replenishing	Accelerate wound healing (Fazio et al., 2020); anti-wrinkle (Son and Lee, 2020); melanoma (Hung et al., 2012)
<i>Atractylodes macrocephala</i> Koidz./Atractylodis macrocephalae rhizoma/白朮/CMU2021SWAmr	0.3	Compositae	white	Bitter and sweet; warm	Tonifying and replenishing	Hyperpigmentation (Ho et al., 2021); skin itching (Zhu et al., 2019)

(Continued on following page)

TABLE 2 | (Continued) Medicinal properties and skin-related modern research of commonly used medicinal materials used in skin whitening prescriptions (RFC>0.2).

Scientific name/Latin name of crude drug/Local name/sample number	RFC ^a	Family	Color	Flavor and property	Traditional usage	Literature on skin modern research (PubMed) ^b
<i>Dioscorea polystachya</i> Turcz./ Dioscoreae rhizoma/白山藥/ CMU2021SWDr	0.24	Dioscoreaceae	white	Sweet; plain	Tonifying and replenishing	Inflammatory skin diseases (Jegal et al., 2017; Jegal et al., 2018); skin cancer (Tsukayama et al., 2018)
<i>Lycium chinense</i> Mill./Lycii fructus/枸杞子/ CMU2021SWLf	0.24	Solanaceae	red	Sweet; plain	Tonifying and replenishing	Anti-photoaging effects (Yi et al., 2013; Im et al., 2016; Li et al., 2017; Liang et al., 2018; Neves et al., 2020; Neves et al., 2021); inflammatory skin diseases (Wu et al., 2020); melanoma (Cenariu et al., 2021); moisturizing (Meng et al., 2020)
<i>Ophiopogon japonicus</i> (Thunb.) Ker Gawl./ Ophiopogonis radix/麥門冬/ CMU2021SWOr	0.24	Asparagaceae	white	Sweet and bitter; cold	Tonifying and replenishing	Inflammatory skin diseases (Kitahiro et al., 2018; Mainzer et al., 2019; An et al., 2020)
<i>Ligusticum striatum</i> DC./ Chuanxiong rhizoma/川芎/ CMU2021SWCr	0.22	Apiaceae	brown	Pungent; warm	Tonifying and replenishing	Inflammatory skin diseases (Lee et al., 2016; Yan et al., 2020); skin itching (Zhu et al., 2019)
External						
<i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav./ Angelicae dahuricae radix/白芷/ CMU2021SWAdr	0.89	Apiaceae	white	Pungent; warm	Exterior-releasing	Accelerate wound healing and promote neovascularization (Bai et al., 2012; Yang et al., 2017; Yang et al., 2020b); acne (Hwang et al., 2016); inflammatory skin diseases (Lee et al., 2012; Ku et al., 2017); inhibition of melanogenesis (Kim et al., 2016); melanoma (Hwangbo et al., 2020); skin itching (Zhu et al., 2019)
<i>Wolfiporia extensa</i> (Peck) Ginns/ Poria/白茯苓/ CMU2021SWP	0.82	Polyporaceae	white	Sweet and plain; plain	Dampness-draining diuretic	Hyperpigmentation (Ho et al., 2021); inhibition of melanogenesis (Lee and cha, 2018; Kang et al., 2019); moisturizing and increased skin barrier function (Choi et al., 2019); oxidative stress associated skin aging effects (Kang et al., 2019; Fang et al., 2021)
<i>Bletilla striata</i> (Thunb.) Rchb.f./ Bletillae rhizoma/白及/ CMU2021SWBr	0.58	Orchidaceae	white	Bitter, sweet, and astringent; cold	Hemostatic	Accelerate wound healing (Yu et al., 2011; He et al., 2017; Song et al., 2017; Zhang et al., 2019; Yang et al., 2020a); chapped skin (He et al., 2017); hyperpigmentation (Ho et al., 2021)
<i>Atractylodes macrocephala</i> Koidz./ Atractylodis macrocephalae rhizoma/白朮/ CMU2021SWAmr	0.53	Compositae	white	Bitter and sweet; warm	Tonifying and replenishing	Hyperpigmentation (Ho et al., 2021); skin itching (Zhu et al., 2019)
<i>Ampelopsis japonica</i> (Thunb.) Makino/ Ampelopsis radix/白藜/ CMU2021SWAr	0.37	Vitaceae	white	Bitter and pungent; cold	Heat-clearing	Accelerate wound healing and promote neovascularization (Lee et al., 2015); hyperpigmentation (Fong and Tong, 2012; Ho et al., 2021)
<i>Paeonia lactiflora</i> Pall. (white)/ Paeoniae radix alba/白芍/ CMU2021SWPra	0.32	Paeoniaceae	white	Bitter and sour; cold	Tonifying and replenishing	Ameliorated vascular damage (Chen et al., 2013); anti-photoaging effect (Lu et al., 2020); hyperpigmentation (Qiu et al., 2016; Ho et al., 2021); inflammatory skin diseases (Chen et al., 2011; Jeong et al., 2015; Kim et al., 2020); inhibition of melanogenesis (You et al., 2017); psoriasis (Sun et al., 2015b; Choi et al., 2015; Li et al., 2019); skin itching (Zhu et al., 2019)
<i>Bombyx mori</i> Linnaeus/ Bombyx batryticatus/白僵蠶/ CMU2021SWBb	0.26	Bombycidae	white	Salty and pungent; plain	Liver-pacifying and wind-extinguishing	Accelerate wound healing (Tariq et al., 2021)

^aRFC, relative frequency of citation.

^bLiterature on skin modern research (PubMed) included pharmacological effects, clinical research and intervention research.

Ziziphus jujuba Mill. (red) and *Astragalus propinquus* Schischkin were used in combination with *Lycium chinense* Mill. or *Ligusticum striatum* DC.; and *Angelica sinensis* (Oliv.) Diels, *Coix lacryma-jobi*

var. *ma-yuen* (Rom.Caill.) Stapf, and *Dioscorea polystachya* Turcz. was a prescription. These combinations could be used as a reference for oral skin whitening prescriptions.

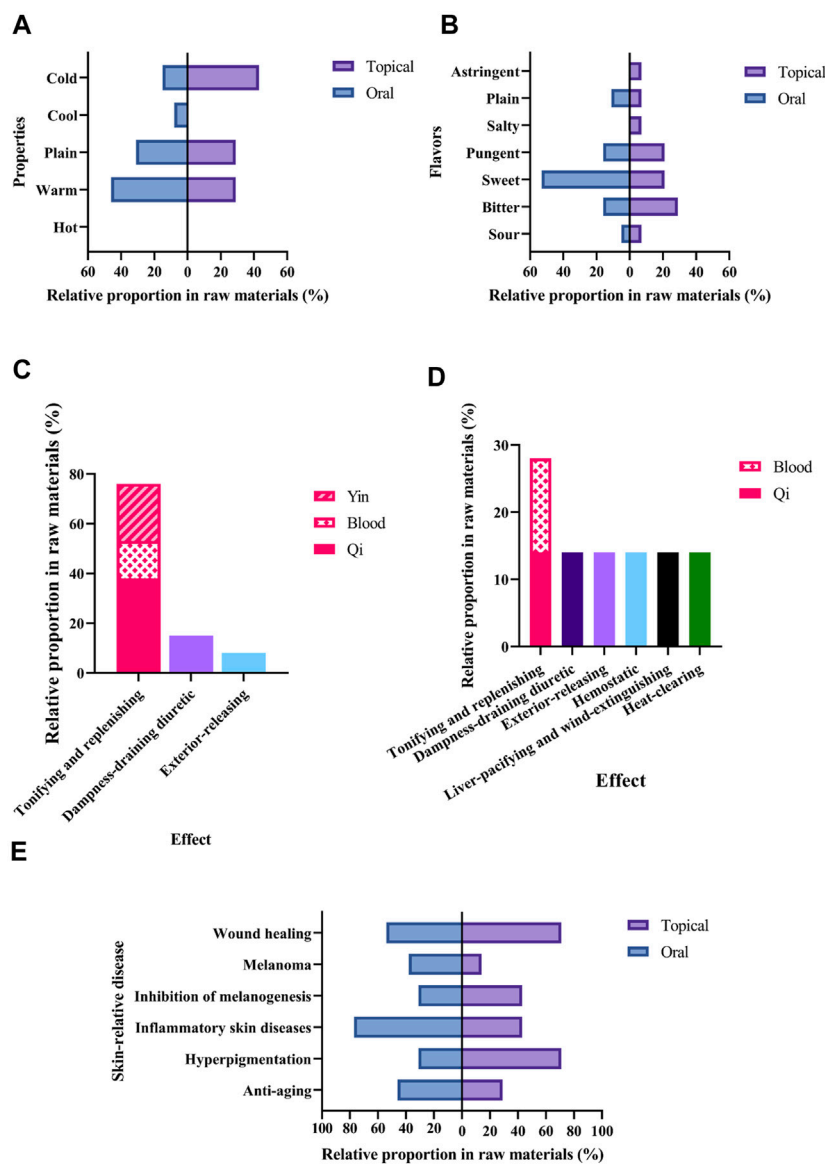


FIGURE 5 | Characteristics of medicinal materials with an RFC > 0.2 in skin whitening prescriptions. **(A)** Properties and **(B)** Flavors. Histogram of traditional efficacy classifications. **(C)** oral prescriptions and **(D)** external prescriptions. **(E)** Modern research related to skin.

3.4 Venn Diagram Analysis of Commonly Used Medicinal Materials Used in External Skin Whitening Prescriptions

In this study, medicinal materials with RFC > 0.2 in external skin whitening prescriptions were defined as Taiwan *qī bái sǎn* (Figure 8A). Taiwan *qī bái sǎn* consists of *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav., *Wolfiporia extensa* (Peck) Ginns, *Bletilla striata* (Thunb.) Rchb. f., *Atractylodes macrocephala* Koidz., *Ampelopsis japonica* (Thunb.) Makino, *Paeonia lactiflora* Pall. (white), and *Bombyx mori* Linnaeus. Venn diagram analysis of these medicinal materials with *qī bái sǎn*-related prescriptions in *yǒng lèi qián fāng*, *pǔ jì fāng*, and *tài píng shèng huì fāng* found that Taiwan *qī bái sǎn* is the addition

and subtraction formula from the *qī bái sǎn* mentioned in ancient books (Figure 8B).

3.5 Misuse of Medicinal Materials in Skin Whitening Prescriptions

Due to the wide variety of traditional Chinese medicinal materials, some medicinal materials may have the same vernacular name but are composed of different materials, whereas some medicinal materials may have different names but same origin. During integration and analysis of medicinal materials used in skin whitening prescriptions, it was found that *Ampelopsis japonica* (Thunb.) Makino, *Astragalus propinquus* Schischkin, *Reynoutria multiflora* (Thunb.) Moldenke, *Rosa*

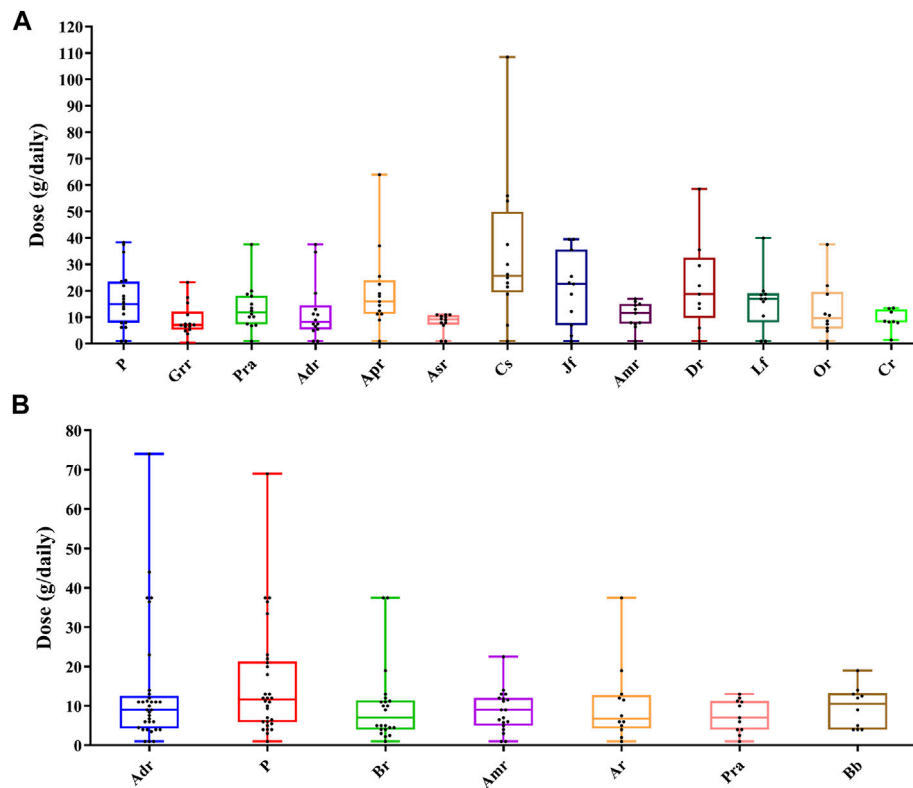


FIGURE 6 | Box plots of dose ranges of commonly used medicinal materials. The top line represents the maximum value, and the bottom line represents the minimum value; the bottom of each box represents the first quartile (Q1), the middle line represents the second quartile (Q2), and the top of each box represents the third quartile (Q3). The black dots represent the doses in the collected samples. **(A)** Oral prescriptions and **(B)** external prescriptions. *Adr*, *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav.; *Grr*, *Glycyrrhiza uralensis* Fisch.; *Pra*, *Paeonia lactiflora* Pall. (white); *Apr*, *Astragalus propinquus* Schischkin; *Ar*, *Ampelopsis japonica* (Thunb.) Makino; *Asr*, *Angelica sinensis* (Oliv.) Diels; *Cr*, *Ligusticum striatum* DC.; *Cs*, *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf; *Dr*, *Dioscorea polystachya* Turcz.; *Lf*, *Lycium chinense* Mill.; *Or*, *Ophiopogon japonicus* (Thunb.) Ker Gawl.; *P*, *Wolfiporia extensa* (Peck) Ginns; *Cx*, *Citrus xanthocarpa* (L.) Sw.

rugosa Thunb., *Scutellaria baicalensis* Georgi, and *Tribulus terrestris* L. had misused sound alike or look alike medicinal materials (Table 3).

4 DISCUSSION

4.1 Field Investigation Sites

In this study, field investigation was employed to study skin whitening prescriptions sold in TCM pharmacies in Taiwan. Field investigations are mostly used in sociology, geography, or cultural studies and was previously employed to examine the drug treatment habits for certain diseases in some regions, such as traditional Chinese medicine composition used in galactagogues prescriptions (Chao et al., 2020), herbal composition of Qīng-Cāo-Chá tea (Huang et al., 2020), and medicinal materials used for hypertension (Baharvand-Ahmadi et al., 2016). Traditional Chinese Medicine, the mainstay of Asian culture, is a form of experience-based therapies, and is a medical care system for diagnosing, preventing, and treating diseases (Xu et al., 2013). Therefore, traditional Chinese pharmacies in Taiwan are important sites for retaining TCM culture.

4.2 Types and Biological Taxonomic Characteristics of Medicinal Materials in Skin Whitening Prescriptions

This study on the composition of skin whitening prescriptions used in Taiwan found that most medicinal materials were from Apiaceae, including *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav., *Angelica sinensis* (Oliv.) Diels and *Ligusticum striatum* DC., followed by Leguminosae, including *Glycyrrhiza uralensis* Fisch. and *Astragalus propinquus* Schischkin. Apiaceae and Leguminosae plants can inhibit tyrosinase activity, thereby reducing melanogenesis. These plants are rich in phenolic compounds and flavonoids that are proven to have significant antioxidant activity. The previous experiments also showed that they can inhibit matrix metalloproteinases (MMPs), delay skin photoaging, and stimulate keratinocyte and fibroblast migration, which has significant effects on skin regeneration (Tundis et al., 2015; Waqas et al., 2015; Zofia et al., 2020).

Melanin is an important pigment that determines skin, hair, and eye colors, and can be mainly divided into pheomelanin and eumelanin (Zanetti et al., 2001). Melanin synthesis is intimately associated with tyrosinase. Pigmentation is an important

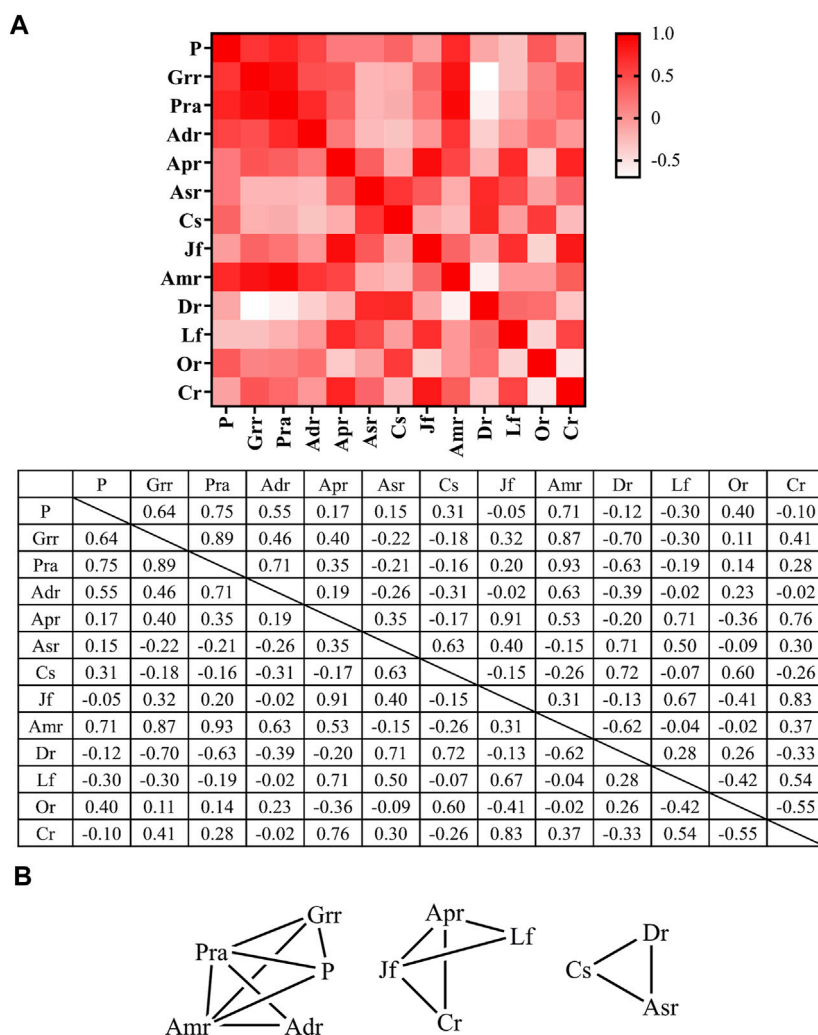


FIGURE 7 | Spearman correlation analysis of commonly used medicinal materials used in oral skin whitening prescriptions. **(A)** Heat map and **(B)** Network map.

Adr, *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav.; Amr, *Atractylodes macrocephala* Koidz.; Apr, *Astragalus propinquus* Schischkin; Asr, *Angelica sinensis* (Oliv.) Diels; Cr, *Ligusticum striatum* DC.; Cs, *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf; Dr, *Dioscorea polystachya* Turcz.; Grr, *Glycyrrhiza uralensis* Fisch.; Jf, *Ziziphus jujuba* Mill. (red); Lf, *Lycium chinense* Mill.; Or, *Ophiopogon japonicus* (Thunb.) Ker Gawl.; P, *Wolfiporia extensa* (Peck) Ginns; Pra, *Paeonia lactiflora* Pall. (white).

photoprotective factor, and its regulatory mechanism is extremely complex and still not completely understood. However, a large volume of data shows that ultraviolet-induced DNA damage and its repair will activate tyrosinase in melanocytes, resulting in melanogenesis (Gilcrest and Eller, 1999; Brenner and Hearing, 2008; Lai et al., 2018). Therefore, inhibition of tyrosinase can inhibit melanogenesis.

4.3 Analysis of Effects and Pharmacology of Commonly Used Medicinal Materials Used in Skin Whitening Prescriptions

TCM has a unique theory where medicinal materials are classified by properties (hot, warm, plain, cool, and cold) and flavors (sour, bitter, sweet, pungent, salty, plain, and astringent). Most TCM materials comprise a combination of flavors (Liao et al., 2008). The $^1\text{H-NMR}$

spectrum was used to identify the properties of the medicinal materials, and it was found that their ingredients were very different (Zhang et al., 2020). A previous report showed that warm and hot medicinal materials can regulate the immune system; cold and cool medicinal materials can inhibit cell growth and proliferation (Liang et al., 2013); sweet medicinal materials have supplementation, moderation, and harmonization effects (He et al., 2012), while bitter medicinal materials mostly contain alkaloids with anti-inflammatory effects (Chen et al., 2015). The results of this study found that commonly used medicinal materials used in oral skin whitening prescriptions are mostly warm and sweet while those used in external skin whitening prescriptions are mostly cold and bitter. In combination with previous studies, it can be deduced that oral skin whitening prescriptions mostly focus on immune regulation while external skin whitening prescriptions focus on inflammation alleviation.

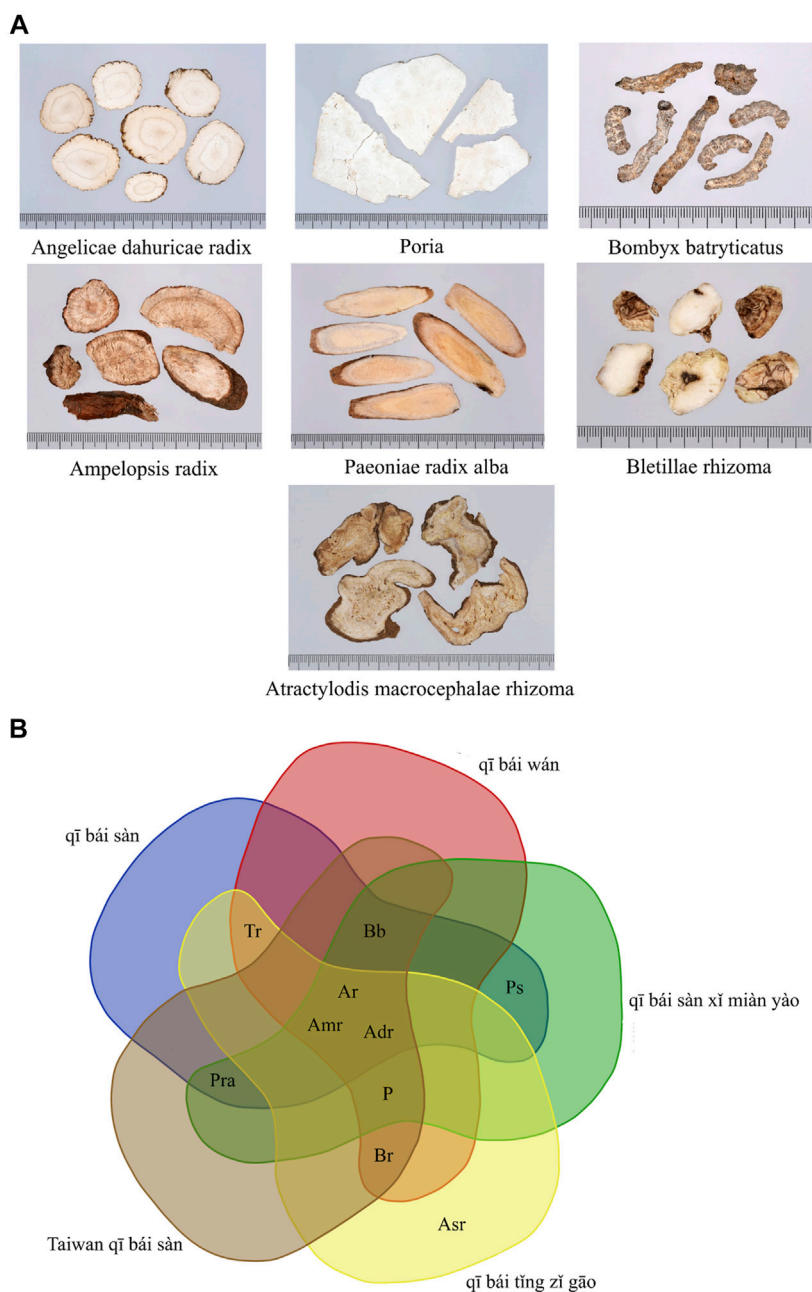


FIGURE 8 | (A) Pictures of medicinal materials of Taiwan *qī bái sǎn*. **(B)** Venn diagram of *qī bái sǎn*-related prescriptions in ancient books and Taiwan *qī bái sǎn*. Adr, *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav.; Amr, *Atractylodes macrocephala* Koidz.; Ar, *Ampelopsis japonica* (Thunb.) Makino; Asr, *Asarum heterotropoides* F. Schmidt f. *mandshuricum* (Maxim.) Kitag.; Bb, *Bombyx mori* Linnaeus; Br, *Bletilla striata* (Thunb.) Rchb. f.; P, *Wolfiporia extensa* (Peck) Ginns; Pra, *Paeonia lactiflora* Pall. (white); Ps, *Ipomoea nil* (L.) Roth; Tr, *Sauromatum giganteum* (Engl.) Cusimano & Hett.

4.4 Analysis of Commonly Used Medicinal Materials Used in Oral and External Skin Whitening Prescriptions

Wolfiporia extensa (Peck) Ginns, *Paeonia lactiflora* Pall. (white), *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav., and *Atractylodes macrocephala* Koidz. are commonly used medicinal materials used in oral and external skin whitening

prescriptions. *Wolfiporia extensa* (Peck) Ginns regulates tyrosinase activity to inhibit melanogenesis (Lee and Cha, 2018). In past studies had found that *Paeonia lactiflora* Pall. (white) can be used to treat allergic dermatitis and reduce facial wrinkles. Paeoniflorin in *Paeonia lactiflora* Pall. (white) can reduce the expression of microphthalmia-associated transcription factor (MITF) and melanogenic enzymes (including tyrosinase, TRP-1, and TRP-2) by regulating the p38 MAPK pathway, thereby inhibiting

TABLE 3 | Summary of medicinal materials that tend to be misused in skin whitening prescriptions.

Latin name of crude drug	Authentic or misused	Scientific name	Family	Look alike or sound alike ^a	Frequency/Use ratio (%)
Ampelopsis radix	authentic	<i>Ampelopsis japonica</i> (Thunb.) Makino	Vitaceae	look alike	11/73%
	misused	<i>Momordica cochinchinensis</i> (Lour.) Spreng	Cucurbitaceae		4/27%
Astragali radix	authentic	<i>Astragalus propinquus</i> Schischkin [<i>Astragalus membranaceus</i> (Fisch.) Bunge] ^b	Leguminosae	look alike	1/7%
	misused	<i>Hedysarum polybotrys</i> Hand. -Mazz	Leguminosae		13/93%
Reynoutria multiflorae radix	authentic	<i>Reynoutria multiflora</i> (Thunb.) Moldenke [<i>Polygonum multiflorum</i> Thunb.] ^c	Polygonaceae	look alike	0/0%
Rosae rugosae flos	misused	<i>Pteroxygonum giraldii</i> Dammer and Diels	Polygonaceae		1/100%
	authentic	<i>Rosa rugosa</i> Thunb	Rosaceae	look alike	1/50%
Scutellariae radix	misused	<i>Rosa chinensis</i> Jacq	Rosaceae		1/50%
	authentic	<i>Scutellaria baicalensis</i> Georgi	Lamiaceae	look alike	3/60%
Tribuli fructus	misused	<i>Scutellaria amoena</i> C.H.Wright	Lamiaceae		2/40%
	authentic	<i>Tribulus terrestris</i> L.	Zygophyllaceae	sound	5/83%
	misused	<i>Astragalus complanatus</i> Bunge	Leguminosae	alike	1/17%

^a“Look alike” refers to the similar appearance of two confusing medicinal materials, thus causing misuse. “Sound alike” means that the local names of two confusing medicinal materials are similar in pronunciation, which causes misuse.

^b*Astragalus membranaceus* (Fisch.) bunge is a commonly used synonym of *astragalus propinquus schischkin*.

^c*Polygonum multiflorum* Thunb. is a commonly used synonym of *Reynoutria multiflora* (Thunb.) moldenke.

melanogenesis (Qiu et al., 2016). *Angelica dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav. is a good immunomodulatory agent, and it can significantly increase phagocytosis and the secretion of cytokines by macrophages (Wang et al., 2021). It can also inhibit melanogenesis. It is involved inhibition of tyrosinase synthesis, but it does not inhibit tyrosinase activity (Cho et al., 2006). A study highlighted that the extract of *Atractylodes macrocephala* Koidz. has immune-enhancing activities (Sun et al., 2015a). Its active ingredients are Atractylenolide I and 14-acetoxy-12-seneciolyoxytetradeca-2E, 8E, 10E-trien-4,6-diyn-1-ol. They are both alkaloids that demonstrate anti-inflammatory effects and are tyrosinase inhibitors (Li et al., 2007; Ye et al., 2010).

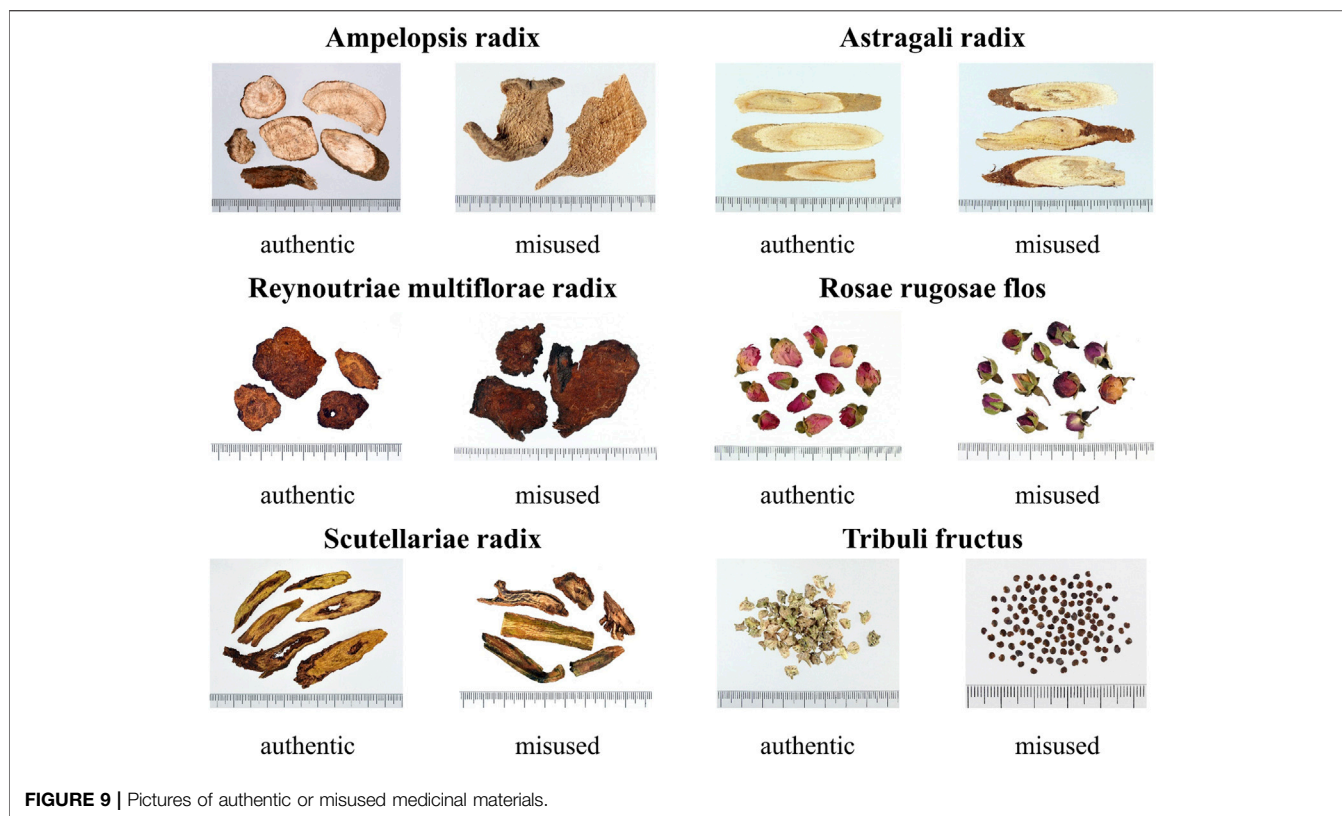
4.5 Misuse of Medicinal Materials in Skin Whitening Prescriptions

The Taiwan Herbal Pharmacopeia is a codex of management regulations for TCM in Taiwan. The medicinal materials recorded in monographs should comply with the pharmacopeia standards before being manufactured, sold, and dispensed for medical treatment and health care. Medicinal materials recorded in the Taiwan Herbal Pharmacopeia are defined as authentic medicinal materials, while the origins of medicinal materials not included in the pharmacopeia are regarded as misused or fake medicinal materials (Taiwan Herbal Pharmacopeia 3rd Edition Committee, 2018; Taiwan Herbal Pharmacopeia 4th Edition Committee, 2021). Although the government releases information about authentic medicinal materials every year, medicinal materials' misuse is still commonly seen in markets in Taiwan. Such misused materials were also found in skin whitening prescriptions that were collected in this study, including medicinal materials that look alike, which refers to the similar appearance of two confusing medicinal materials, thus causing misuse, such as *Momordica cochinchinensis*

(Lour.) Spreng. that was used instead of *Ampelopsis japonica* (Thunb.) Makino, *Hedysarum polybotrys* Hand-Mazz. that was used instead of *Astragalus propinquus* Schischkin, *Scutellaria amoena* C.H.Wright that was used instead of *Scutellaria baicalensis* Georgi, *Pteroxygonum giraldii* Dammer & Diels that was used instead of *Reynoutria multiflora* (Thunb.) Moldenke, and *Rosa chinensis* Jacq. that was used instead of *Rosa rugosa* Thunb.; and medicinal materials that sound alike, which means that the local names of two confusing medicinal materials are similar in pronunciation, thus causing misuse, such as *Astragalus complanatus* Bunge that was used instead of *Tribulus terrestris* L. (Figure 9). Even though misused medicinal materials in skin whitening prescriptions do not seem to cause immediate harm to the human body, there is no way to prove whether they will have adverse interactions with other medicinal materials. Therefore, simple and clear pictures showing that appearance and properties of medicinal materials should be created, and rapid, simple, and convenient identification methods should be developed to disseminate knowledge for identification of misused medicinal materials and remind traditional Chinese medicine users to be cautious and prevent misuse of medicinal materials.

4.6 Limitations and Future Directions

This study had certain limitations that should be addressed in future research. The first limitation is that this study was a field survey study, which only investigated skin whitening prescriptions sold in Chinese medicine stores in Taiwan. The skin whitening prescriptions investigated in this study reflect local usage in Taiwan. Further research will be needed to examine the whitening prescriptions used in traditional Chinese medicine in other regions. The second limitation is that this study only analyzed the core medicinal materials and dosages of the prescriptions but not the efficacy of these botanical drugs. Therefore, animal or cell experiments can be used in future



research to verify the effectiveness of the skin whitening medicinal materials or prescriptions. The last limitation is that the Spearman correlation analysis only shows the correlations between prescription drugs and not the drug interactions between them. When discussing prescriptions in future research, we may have to consider both the theoretical significance of traditional Chinese medicine and the practical significance. We should also conduct *in vivo* and *in vitro* experiments to further explore the efficacy and the interactions between the medicinal materials.

5 CONCLUSION

In Asian countries, whiter skin color is synonymous with beauty for women and many Asian women look for natural and without side effects skin whitening products in order to reduce cutaneous pigmentation. This study is the first ethnobotanical survey on skin whitening prescriptions collected from TCM pharmacies in Taiwan. The purpose is to preserve the use of TCM for skin whitening in Taiwan. Although the use of TCM in skin whitening has been widely recorded and many skin whitening medicinal materials were collected from TCM pharmacies in this study, the ingredients of TCM are extremely complex and tends to be affected by many factors, may also be used in misused medicinal materials. Moreover, the efficacy and safety of most medicinal materials have not been scientifically validated. Further studies are needed to support the conversion of traditional skin whitening prescriptions to effective functional products. Thus,

the results of this study may provide significant foundational data for subsequent studies The Royal Botanic Gardens, 2013, Li et al., 2017, Institute of Ecology et al., 2021.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the CRREC-109-125. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

C-YK, P-YC, JC, and S-SH performed the field investigation and organized and analyzed the database. C-YK, JC, S-SH, TM, and C-YL contributed conception and design of the study. S-SH and S-YS identified the botanical materials. C-YK, S-SH, JC, S-YS, TM, and C-YL drafted the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

S-SH, JC, S-YS, and H-CC provided guidance for the project and supervised the experiment and manuscript review.

FUNDING

This research was funded by the Tsuzuki Institute for Traditional Medicine, Grant numbers 108727B8, 109727B8 and 110727B8; China Medical University, Grant numbers CMU108-MF-116 and CMU108-N-22; the Ministry of Science and Technology, Grant number MOST 107-2320-B-039-030-MY3 and 109-2813-C-039-061-B. The China Medical University under the Higher Education Sprout Project and Teaching Practice Research Program, Grant number 1077170A, of the Ministry of Education of Taiwan.

REFERENCES

- Abbas, Z., Kousar, S., Aziz, M. A., Pieroni, A., Aldosari, A. A., Bussmann, R. W., et al. (2021). Comparative Assessment of Medicinal Plant Utilization Among Balti and Shina Communities in the Periphery of Deosai National Park, Pakistan. *Biology (Basel)* 105, 434. doi:10.3390/biology10050434
- Amen, Y., Arung, E. T., Afifi, M. S., Halim, A. F., Ashour, A., Fujimoto, R., et al. (2017). Melanogenesis Inhibitors from Coix Lacryma-Jobi Seeds in B16-F10 Melanoma Cells. *Nat. Prod. Res.* 31, 2712–2718. doi:10.1080/14786419.2017.1292270
- An, E. J., Kim, Y., Lee, S. H., Choi, S. H., Chung, W. S., and Jang, H. J. (2020). Ophiopogonin D Ameliorates DNCB-Induced Atopic Dermatitis-like Lesions in BALB/c Mice and TNF- α Inflamed HaCaT Cell. *Biochem. Biophys. Res. Commun.* 522, 40–46. doi:10.1016/j.bbrc.2019.10.190
- Baharvand-Ahmadi, B., Bahmani, M., Tajeddini, P., Rafeian-Kopaei, M., and Naghdi, N. (2016). An Ethnobotanical Study of Medicinal Plants Administered for the Treatment of Hypertension. *J. Ren. Inj Prev* 5, 123–128. doi:10.15171/jrip.2016.26
- Bai, X. Z., Hu, D. H., Wang, Y. C., Liu, J. Q., Shi, J. H., and Tang, C. W. (2012). Effects of Angelica Dahurica Extract on Biological Behavior of Dermal Fibroblasts. *Zhonghua Wai Ke Za Zhi* 50, 357–360.
- Balaguer, A., Chisvert, A., and Salvador, A. (2008). Environmentally Friendly LC for the Simultaneous Determination of Ascorbic Acid and its Derivatives in Skin-Whitening Cosmetics. *J. Sep. Sci.* 31, 229–236. doi:10.1002/jssc.200700414
- Berezutsky, M. A., Durnova, N. A., and Vlasova, I. A. (2019). Experimental and Clinical Studies of Mechanisms of the Anti-aging Effects of Chemical Compounds in Astragalus Membranaceus (Review). *Adv. Gerontol.* 32, 702–710. doi:10.1134/S2079057020020046
- Brenner, M., and Hearing, V. J. (2008). The Protective Role of Melanin against UV Damage in Human Skin. *Photochem. Photobiol.* 84, 539–549. doi:10.1111/j.1751-1097.2007.00226.x
- Byun, A. R., Kwon, S., and Kim, S. (2016). Administration of Herbal Complexes, Dangguijakyak-San (TJ-23) and Coix Seeds, for Treating Verruca Planae: A Case Report. *Explore (NY)* 12, 65–67. doi:10.1016/j.explore.2015.10.003
- Cenariu, D., Fischer-Fodor, E., Tigu, A. B., Bunea, A., Virág, P., Perde-Schrepler, M., et al. (2021). Zeaxanthin-Rich Extract from Superfood Lycium Barbarum Selectively Modulates the Cellular Adhesion and MAPK Signaling in Melanoma versus Normal Skin Cells *In Vitro*. *Molecules* 26, 333. doi:10.3390/molecules26020333
- Cha, H. Y., Ahn, S. H., Cheon, J. H., Park, I. S., Kim, J. T., and Kim, K. (2016). Hataedock Treatment Has Preventive Therapeutic Effects in Atopic Dermatitis-Induced NC/Nga Mice under High-Fat Diet Conditions. *Evid. Based Complement. Alternat Med.* 2016, 1739760. doi:10.1155/2016/1739760
- Cha, H. Y., Ahn, S. H., Cheon, J. H., Park, S. Y., and Kim, K. (2017). Hataedock Treatment Has Preventive Therapeutic Effects for Atopic Dermatitis through Skin Barrier protection in Dermatophagoides Farinae-Induced NC/Nga Mice. *J. Ethnopharmacol.* 206, 327–336. doi:10.1016/j.jep.2017.06.001
- Chao, J., Ko, C. Y., Lin, C. Y., Tomoji, M., Huang, C. H., Chiang, H. C., et al. (2020). Ethnobotanical Survey of Natural Galactagogues Prescribed in Traditional Chinese Medicine Pharmacies in Taiwan. *Front. Pharmacol.* 11, 625869. doi:10.3389/fphar.2020.625869
- Chen, H., Guo, J., Pang, B., Zhao, L., and Tong, X. (2015). Application of Herbal Medicines with Bitter Flavor and Cold Property on Treating Diabetes Mellitus. *Evid. Based Complement. Alternat Med.* 2015, 529491. doi:10.1155/2015/529491
- Chen, T., Guo, Z. P., Jiao, X. Y., Jia, R. Z., Zhang, Y. H., Li, J. Y., et al. (2011). Peoniflorin Suppresses Tumor Necrosis Factor- α Induced Chemokine Production in Human Dermal Microvascular Endothelial Cells by Blocking Nuclear Factor-Kb and ERK Pathway. *Arch. Dermatol. Res.* 303, 351–360. doi:10.1007/s00403-010-1116-6
- Chen, T., Guo, Z. P., Wang, L., Qin, S., Cao, N., Li, M. M., et al. (2013). Paeoniflorin Suppresses Vascular Damage and the Expression of E-Selectin and ICAM-1 in a Mouse Model of Cutaneous Arthus Reaction. *Exp. Dermatol.* 22, 453–457. doi:10.1111/exd.12174
- Chinese Pharmacopoeia Commission (2020). *Pharmacopoeia of the People's Republic of China*. China: China Medical Science Press.
- Cho, Y. H., Kim, J. H., Park, S. M., Lee, B. C., Pyo, H. B., and Park, H. D. (2006). New Cosmetic Agents for Skin Whitening from Angelica Dahurica. *J. Cosmet. Sci.* 57, 11–21.
- Choi, E., Kang, Y. G., Hwang, S. H., Kim, J. K., Hong, Y. D., Park, W. S., et al. (2019). *In Vitro* Effects of Dehydrotrametenolic Acid on Skin Barrier Function. *Molecules* 24, 4583. doi:10.3390/molecules24244583
- Choi, M. R., Choi, D. K., Sohn, K. C., Lim, S. K., Kim, D. I., Lee, Y. H., et al. (2015). Inhibitory Effect of Paeonia Lactiflora Pallas Extract (PE) on Poly (I:C)-induced Immune Response of Epidermal Keratinocytes. *Int. J. Clin. Exp. Pathol.* 8, 5236–5241.
- Choi, Y. Y., Kim, M. H., Hong, J., Kim, K., and Yang, W. M. (2016). Effect of Dangguibohuyul-Tang, a Mixed Extract of Astragalus Membranaceus and Angelica Sinensis, on Allergic and Inflammatory Skin Reaction Compared with Single Extracts of Astragalus Membranaceus or Angelica Sinensis. *Evid. Based Complement. Alternat Med.* 2016, 5936354. doi:10.1155/2016/5936354
- Chung, C. P., Hsia, S. M., Lee, M. Y., Chen, H. J., Cheng, F., Chan, L. C., et al. (2011). Gastroprotective Activities of Adlay (Coix Lacryma-Jobi L. Var. Ma-Yuen Stapf) on the Growth of the Stomach Cancer AGS Cell Line and Indomethacin-Induced Gastric Ulcers. *J. Agric. Food Chem.* 59, 6025–6033. doi:10.1021/jf2009556
- Deng, G., Chen, W., Wang, P., Zhan, T., Zheng, W., Gu, Z., et al. (2019). Inhibition of NLRP3 Inflammasome-Mediated Pyroptosis in Macrophage by Cycloastragenol Contributes to Amelioration of Imiquimod-Induced Psoriasis-like Skin Inflammation in Mice. *Int. Immunopharmacol.* 74, 105682. doi:10.1016/j.intimp.2019.105682
- Dixit, S., and Tiwari, S. (2020). Investigation of Anti-diabetic Plants Used Among the Ethnic Communities of Kanpur Division, India. *J. Ethnopharmacol.* 253, 112639. doi:10.1016/j.jep.2020.112639
- Fang, C. L., Paul, C. R., Day, C. H., Chang, R. L., Kuo, C. H., Ho, T. J., et al. (2021). Poria Cocos (Fuling) Targets TGF β /Smad7 Associated Collagen Accumulation and Enhances Nrf2-Antioxidant Mechanism to Exert Anti-skin Aging Effects in

ACKNOWLEDGMENTS

The authors thank the herbarium of China Medical University for providing us with space to store the medicinal materials for this study. Also, we would like to thank the 63rd pharmacy students of China Medical University for their assistance in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.736370/full#supplementary-material>

- Human Dermal Fibroblasts. *Environ. Toxicol.* 36, 729–736. doi:10.1002/tox.23075
- Fazio, A., La Torre, C., Caroleo, M. C., Caputo, P., Plastina, P., and Cione, E. (2020). Isolation and Purification of Glucans from an Italian Cultivar of *Ziziphus Jujuba* Mill. And *In Vitro* Effect on Skin Repair. *Molecules* 25, 968. doi:10.3390/molecules25040968
- Fong, P., and Tong, H. H. (2012). In Silico prediction of the Cosmetic Whitening Effects of Naturally Occurring lead Compounds. *Nat. Prod. Commun.* 7, 1287–1294. doi:10.1177/1934578x1200701010
- Food and Drug Administration (2014). *Know Cosmetic Whitening Ingredients*. [Online]. Available: <https://www.mohw.gov.tw/cp-3205-21666-1.html> (Accessed Jun 17, 2021).
- Gao, H. W., Chang, K. F., Huang, X. F., Lin, Y. L., Weng, J. C., Liao, K. W., et al. (2018). Antitumor Effect of N-Butylideneephthalide Encapsulated on B16/F10 Melanoma Cells *In Vitro* with a Polycationic Liposome Containing PEI and Polyethylene Glycol Complex. *Molecules* 23, 3224. doi:10.3390/molecules23123224
- Gilchrest, B. A., and Eller, M. S. (1999). DNA Photodamage Stimulates Melanogenesis and Other Photoprotective Responses. *J. Investig. Dermatol. Symp. Proc.* 4, 35–40. doi:10.1038/sj.jidsp.5640178
- Gillbro, J. M., and Olsson, M. J. (2011). The Melanogenesis and Mechanisms of Skin-Lightening Agents-Existing and New Approaches. *Int. J. Cosmet. Sci.* 33, 210–221. doi:10.1111/j.1468-2494.2010.00616.x
- Gong, P., Lu, Z., Xing, J., Wang, N., and Zhang, Y. (2015). Traditional Chinese Medicine Xuebijing Treatment Is Associated with Decreased Mortality Risk of Patients with Moderate Paraquat Poisoning. *PLoS One* 10, e0123504. doi:10.1371/journal.pone.0123504
- Hao, B., Wang, X., Ma, X., Jin, Y., Fan, W., Laba, C., et al. (2020). Preparation of Complex Microcapsules of Soluble Polysaccharide from *Glycyrrhiza Uralensis* and its Application in Wound Repair and Scar Inhibition. *Int. J. Biol. Macromol.* 156, 906–917. doi:10.1016/j.ijbiomac.2020.03.121
- He, X., Wang, X., Fang, J., Zhao, Z., Huang, L., Guo, H., et al. (2017). *Bletilla Striata*: Medicinal Uses, Phytochemistry and Pharmacological Activities. *J. Ethnopharmacol.* 195, 20–38. doi:10.1016/j.jep.2016.11.026
- He, Y., Zheng, X., Sit, C., Loo, W. T., Wang, Z., Xie, T., et al. (2012). Using Association Rules Mining to Explore Pattern of Chinese Medicinal Formulae (Prescription) in Treating and Preventing Breast Cancer Recurrence and Metastasis. *J. Transl. Med.* 10 (1), S12. doi:10.1186/1479-5876-10-S1-S12
- Heinrich, M., Appendino, G., Efferth, T., Fürst, R., Izzo, A. A., Kayser, O., et al. (2020). Best Practice in Research - Overcoming Common Challenges in Phytopharmacological Research. *J. Ethnopharmacol.* 246, 112230. doi:10.1016/j.jep.2019.112230
- Heinrich, M., Lardos, A., Leonti, M., Weckerle, C., Willcox, M., Applequist, W., et al. (2018). Best Practice in Research: Consensus Statement on Ethnopharmacological Field Studies - ConSEFS. *J. Ethnopharmacol.* 211, 329–339. doi:10.1016/j.jep.2017.08.015
- Ho, C. C., Ng, S. C., Chuang, H. L., Chen, J. Y., Wen, S. Y., Kuo, C. H., et al. (2021). Seven Traditional Chinese Herbal Extracts Fermented by *Lactobacillus Rhamnosus* Provide Anti-pigmentation Effects by Regulating the CREB/MITF/tyrosinase Pathway. *Environ. Toxicol.* 36, 654–664. doi:10.1002/tox.23069
- Hong, M. J., Ko, E. B., Park, S. K., and Chang, M. S. (2013). Inhibitory Effect of *Astragalus Membranaceus* Root on Matrix Metalloproteinase-1 Collagenase Expression and Procollagen Destruction in Ultraviolet B-Irradiated Human Dermal Fibroblasts by Suppressing Nuclear Factor Kappa-B Activity. *J. Pharm. Pharmacol.* 65, 142–148. doi:10.1111/j.2042-7158.2012.01570.x
- Hsiao, C. Y., Hung, C. Y., Tsai, T. H., and Chak, K. F. (2012/2012). A Study of the Wound Healing Mechanism of a Traditional Chinese Medicine, *Angelica Sinensis*, Using a Proteomic Approach. *Evid. Based Complement. Alternat Med.* 2012, 467531. doi:10.1155/2012/467531
- Hu, Y., Zeng, H., Huang, J., Jiang, L., Chen, J., and Zeng, Q. (2020). Traditional Asian Herbs in Skin Whitening: The Current Development and Limitations. *Front. Pharmacol.* 11, 982. doi:10.3389/fphar.2020.00982
- Huang, H. C., Hsieh, W. Y., Niu, Y. L., and Chang, T. M. (2014). Inhibitory Effects of Adlay Extract on Melanin Production and Cellular Oxygen Stress in B16F10 Melanoma Cells. *Int. J. Mol. Sci.* 15, 16665–16679. doi:10.3390/ijms150916665
- Huang, S. S., Chen, T. Y., Deng, J. S., Pao, L. H., Cheng, Y. C., and Chao, J. (2020). An Ethnobotanical Study on Qing-Cào-Chá Tea in Taiwan. *Front. Pharmacol.* 11, 931. doi:10.3389/fphar.2020.00931
- Hung, C. F., Hsu, B. Y., Chang, S. C., and Chen, B. H. (2012). Antiproliferation of Melanoma Cells by Polysaccharide Isolated from *Ziziphus Jujuba*. *Nutrition* 28, 98–105. doi:10.1016/j.nut.2011.05.009
- Hwang, Y. L., Im, M., Lee, M. H., Roh, S. S., Choi, B. W., Kim, S. J., et al. (2016). Inhibitory Effect of Imperatorin on Insulin-like Growth Factor-1-Induced Sebom Production in Human Sebocytes Cultured *In Vitro*. *Life Sci.* 144, 49–53. doi:10.1016/j.lfs.2015.11.027
- Hwangbo, H., Choi, E. O., Kim, M. Y., Kwon, D. H., Ji, S. Y., Lee, H., et al. (2020). Suppression of Tumor Growth and Metastasis by Ethanol Extract of *Angelica Dahurica Radix* in Murine Melanoma B16F10 Cells. *Biosci. Trends* 14, 23–34. doi:10.5582/bst.2019.01230
- Im, A. R., Lee, H. J., Youn, U. J., Hyun, J. W., and Chae, S. (2016). Orally Administered Betaine Reduces Photodamage Caused by UVB Irradiation through the Regulation of Matrix Metalloproteinase-9 Activity in Hairless Mice. *Mol. Med. Rep.* 13, 823–828. doi:10.3892/mmr.2015.4613
- Institute of Ecology and Evolutionary Biology, NTU (2021). *Plants of Taiwan*. [Online]. Available: <http://tai2.ntu.edu.tw> (Accessed May 6, 2021).
- Jegal, J., Park, N. J., Bong, S. K., Jegal, H., Kim, S. N., and Yang, M. H. (2017). *Dioscorea Quinqueloba* Ameliorates Oxazolone- and 2,4-Dinitrochlorobenzene-Induced Atopic Dermatitis Symptoms in Murine Models. *Nutrients* 9, 1324. doi:10.3390/nu9121324
- Jegal, J., Park, N. J., Jo, B. G., Bong, S. K., Jegal, H., Yang, M. H., et al. (2018). Anti-Atopic Properties of Gracillin Isolated from *Dioscorea Quinqueloba* on 2,4-Dinitrochlorobenzene-Induced Skin Lesions in Mice. *Nutrients* 10, 1205. doi:10.3390/nu10091205
- Jeong, S. J., Lim, H. S., Seo, C. S., Kim, J. H., Jin, S. E., Yoo, S. R., et al. (2015). Traditional Herbal Formula Jakyakgamcho-Tang (*Paeonia Lactiflora* and *Glycyrrhiza Uralensis*) Impairs Inflammatory Chemokine Production by Inhibiting Activation of STAT1 and NF-Kb in HaCaT Cells. *Phytomedicine* 22, 326–332. doi:10.1016/j.phymed.2014.12.002
- Kalekhan, F., Kudva, A. K., Raghu, S. V., Rao, S., Hegde, S. K., Simon, P., et al. (2021). Traditionally Used Natural Products in Preventing Ionizing Radiation-Induced Dermatitis: First Review on the Clinical Studies. *Anticancer Agents Med. Chem.* 21. doi:10.2174/1871520621666210405093236
- Kang, K. Y., Hwang, Y. H., Lee, S. J., Jang, H. Y., Hong, S. G., Mun, S. K., et al. (2019). Verification of the Functional Antioxidant Activity and Antimelanogenic Properties of Extracts of *Poria Cocos Mycelium* Fermented with Freeze-Dried Plum Powder. *Int. J. Biomater.* 2019, 9283207. doi:10.1155/2019/9283207
- Kim, J. H., Kim, M. H., Yang, G., Huh, Y., Kim, S. H., and Yang, W. M. (2013). Effects of Topical Application of *Astragalus Membranaceus* on Allergic Dermatitis. *Immunopharmacol Immunotoxicol.* 35, 151–156. doi:10.3109/08923973.2012.733708
- Kim, K. H., Shim, J. S., Kim, H. J., and Son, E. D. (2020). Penta-O-galloyl-β-D-glucose from *Paeonia Lactiflora* Pall. Root Extract Enhances the Expression of Skin Barrier Genes via EGR3. *J. Ethnopharmacol.* 248, 112337. doi:10.1016/j.jep.2019.112337
- Kim, K. J., Xuan, S. H., and Park, S. N. (2017). Licoricidin, an Isoflavonoid Isolated from *Glycyrrhiza Uralensis* Fisher, Prevents UVA-Induced Photoaging of Human Dermal Fibroblasts. *Int. J. Cosmet. Sci.* 39, 133–140. doi:10.1111/ics.12357
- Kim, M. K., Bang, C. Y., Kim, M. Y., Lee, J. H., Ro, H., Choi, M. S., et al. (2016). Traditional Herbal Prescription LASAP-C Inhibits Melanin Synthesis in B16F10 Melanoma Cells and Zebrafish. *BMC Complement. Altern. Med.* 16, 223. doi:10.1186/s12906-016-1209-7
- Kitahiro, Y., Koike, A., Sonoki, A., Muto, M., Ozaki, K., and Shibano, M. (2018). Anti-inflammatory Activities of *Ophiopogon Radix* on Hydrogen Peroxide-Induced Cellular Senescence of normal Human Dermal Fibroblasts. *J. Nat. Med.* 72, 905–914. doi:10.1007/s11418-018-1223-9
- Ku, J. M., Hong, S. H., Kim, H. L., Seo, H. S., Shin, Y. C., and Ko, S. G. (2017). Effects of *Angelica Dahurica Radix* on 2, 4-Dinitrochlorobenzene-Induced Atopic Dermatitis-like Skin Lesions in Mice Model. *BMC Complement. Altern. Med.* 17, 98. doi:10.1186/s12906-017-1584-8

- Lai, X., Wichers, H. J., Soler-Lopez, M., and Dijkstra, B. W. (2018). Structure and Function of Human Tyrosinase and Tyrosinase-Related Proteins. *Chemistry* 24, 47–55. doi:10.1002/chem.201704410
- Lee, H., and Cha, H. J. (2018). Poria Cocos Wolf Extracts Represses Pigmentation *In Vitro* and *In Vivo*. *Cel Mol Biol (Noisy-le-grand)* 64, 80–84. doi:10.14715/cmb/2018.64.5.13
- Lee, H., Lee, J. K., Ha, H., Lee, M. Y., Seo, C. S., and Shin, H. K. (2012). Angelica Dahuricae Radix Inhibits Dust Mite Extract-Induced Atopic Dermatitis-like Skin Lesions in NC/Nga Mice. *Evid. Based Complement. Alternat Med.* 2012, 743075. doi:10.1155/2012/743075
- Lee, J., Choi, Y. Y., Kim, M. H., Han, J. M., Lee, J. E., Kim, E. H., et al. (2016). Topical Application of Angelica Sinensis Improves Pruritus and Skin Inflammation in Mice with Atopic Dermatitis-like Symptoms. *J. Med. Food* 19, 98–105. doi:10.1089/jmf.2015.3489
- Lee, J. H., Lim, J. Y., Jo, E. H., Noh, H. M., Park, S., Park, M. C., et al. (2020). Chiyabuyupi-Tang Inhibits Pro-inflammatory Cytokines and Chemokines via the Nrf2/HO-1 Signaling Pathway in TNF- α /ifn- γ -Stimulated HaCaT Cells and Ameliorates 2,4-Dinitrochlorobenzene-Induced Atopic Dermatitis-like Skin Lesions in Mice. *Front. Pharmacol.* 11, 1018. doi:10.3389/fphar.2020.01018
- Lee, K., Lee, B., Lee, M. H., Kim, B., Chinannai, K. S., Ham, I., et al. (2015). Effect of Ampelopsis Radix on Wound Healing in Scalded Rats. *BMC Complement. Altern. Med.* 15, 213. doi:10.1186/s12906-015-0751-z
- Li, B., He, S., Liu, R., Huang, L., Liu, G., Wang, R., et al. (2019). Total Glucosides of Paeony Attenuates Animal Psoriasis Induced Inflammatory Response through Inhibiting STAT1 and STAT3 Phosphorylation. *J. Ethnopharmacol* 243, 112121. doi:10.1016/j.jep.2019.112121
- Li, C. Q., He, L. C., Dong, H. Y., and Jin, J. Q. (2007). Screening for the Anti-inflammatory Activity of Fractions and Compounds from Atractylodes Macrocephala Koidz. *J. Ethnopharmacol* 114, 212–217. doi:10.1016/j.jep.2007.08.002
- Li, H., Li, Z., Peng, L., Jiang, N., Liu, Q., Zhang, E., et al. (2017). Lycium Barbarum Polysaccharide Protects Human Keratinocytes against UVB-Induced Photodamage. *Free Radic. Res.* 51, 200–210. doi:10.1080/10715762.2017.1294755
- Liang, B., Peng, L., Li, R., Li, H., Mo, Z., Dai, X., et al. (2018). Lycium Barbarum Polysaccharide Protects HSF Cells against Ultraviolet-Induced Damage through the Activation of Nrf2. *Cell Mol Biol Lett* 23, 18. doi:10.1186/s11658-018-0084-2
- Liang, F., Li, L., Wang, M., Niu, X., Zhan, J., He, X., et al. (2013). Molecular Network and Chemical Fragment-Based Characteristics of Medicinal Herbs with Cold and Hot Properties from Chinese Medicine. *J. Ethnopharmacol* 148, 770–779. doi:10.1016/j.jep.2013.04.055
- Liao, H., Banbury, L. K., and Leach, D. N. (2008). Antioxidant Activity of 45 Chinese Herbs and the Relationship with Their TCM Characteristics. *Evid. Based Complement. Alternat Med.* 5 (4), 429–434. doi:10.1093/ecam/nem054
- Lim, J. W., Ha, J. H., Jeong, Y. J., and Park, S. N. (2018). Anti-melanogenesis Effect of Dehydroglyasperin C through the Downregulation of MITF via the Reduction of Intracellular cAMP and Acceleration of ERK Activation in B16F1 Melanoma Cells. *Pharmacol. Rep.* 70, 930–935. doi:10.1016/j.pharep.2018.02.024
- Lu, Y. S., Jiang, Y., Yuan, J. P., Jiang, S. B., Yang, Y., Zhu, P. Y., et al. (2020). UVA Induced Oxidative Stress Was Inhibited by Paeoniflorin/Nrf2 Signaling or PLIN2. *Front. Pharmacol.* 11, 736. doi:10.3389/fphar.2020.00736
- Luo, X., Huang, P., Yuan, B., Liu, T., Lan, F., Lu, X., et al. (2016). Astragaloside IV Enhances Diabetic Wound Healing Involving Upregulation of Alternatively Activated Macrophages. *Int. Immunopharmacol* 35, 22–28. doi:10.1016/j.intimp.2016.03.020
- Mainzer, C., Le Guillou, M., Vyumvuhore, R., Chadoutaud, B., Bordes, S., and Closs, B. (2019). Clinical Efficacy of Oligofructans from Ophiopogon Japonicus in Reducing Atopic Dermatitis Flare-Ups in Caucasian Patients. *Acta Derm Venereol.* 99, 858–864. doi:10.2340/00015555-3224
- Meng, H., Li, J., Dong, Y., He, Y., Ren, H., Liu, Y., et al. (2020). Poly Traditional Chinese Medicine Formulation Prepared with Skin Moisturizing Properties. *Dermatol. Ther.* 33, e14105. doi:10.1111/dth.14105
- Ministry of Health and Welfare (2015). *Drug Administration*. [Online]. Available: <https://dep.mohw.gov.tw/DOS/cp-1729-2939-113.html> (Accessed May 6, 2021).
- Mullane, K., Enna, S. J., Piette, J., and Williams, M. (2015). Guidelines for Manuscript Submission in the Peer-Reviewed Pharmacological Literature. *Biochem. Pharmacol.* 97, 225–235. doi:10.1016/j.bcp.2015.06.023
- Nam, Y. K., Kim, M. H., Ha, I. J., and Yang, W. M. (2021). Derma-Hc, a New Developed Herbal Formula, Ameliorates Cutaneous Lichenification in Atopic Dermatitis. *Int. J. Mol. Sci.* 22, 2359. doi:10.3390/ijms22052359
- Neves, L. M. G., Parizotto, N. A., Tim, C. R., Floriano, E. M., Lopez, R. F. V., Venâncio, T., et al. (2020). Polysaccharide-rich Hydrogel Formulation Combined with Photobiomodulation Repairs UV-Induced Photodamage in Mice Skin. *Wound Repair Regen.* 28, 645–655. doi:10.1111/wrr.12826
- Neves, L. M. G., Tim, C. R., Floriano, E. M., da Silva de Avó, L. R., Fernandes, J. B., Parizotto, N. A., et al. (2021). Lycium Barbarum Polysaccharide Fraction Associated with Photobiomodulation Protects from Epithelium Thickness and Collagen Fragmentation in a Model of Cutaneous Photodamage. *Lasers Med. Sci.* 36, 863–870. doi:10.1007/s10103-020-03132-w
- Nordin, F. N. M., Aziz, A., Zakaria, Z., and Wan Mohamed Radzi, C. W. J. (2021). A Systematic Review on the Skin Whitening Products and Their Ingredients for Safety, Health Risk, and the Halal Status. *J. Cosmet. Dermatol.* 20, 1050–1060. doi:10.1111/jocd.13691
- Pillaiyar, T., Manickam, M., and Namasivayam, V. (2017). Skin Whitening Agents: Medicinal Chemistry Perspective of Tyrosinase Inhibitors. *J. Enzyme Inhib. Med. Chem.* 32, 403–425. doi:10.1080/14756366.2016.1256882
- Qiu, J., Chen, M., Liu, J., Huang, X., Chen, J., Zhou, L., et al. (2016). The Skin-Depigmenting Potential of Paeonia Lactiflora Root Extract and Paeoniflorin: *In Vitro* Evaluation Using Reconstructed Pigmented Human Epidermis. *Int. J. Cosmet. Sci.* 38, 444–451. doi:10.1111/ics.12309
- Rivera, D., Allkin, R., Obón, C., Alcaraz, F., Verpoorte, R., and Heinrich, M. (2014). What Is in a Name? the Need for Accurate Scientific Nomenclature for Plants. *J. Ethnopharmacol* 152, 393–402. doi:10.1016/j.jep.2013.12.022
- Saba, E., Lee, C. H., Jeong, da. H., Lee, K., Kim, T. H., Roh, S. S., et al. (2016). Fermented rice Bran Prevents Atopic Dermatitis in DNCB-Treated NC/Nga Mice. *J. Biomed. Res.* 30, 334–343. doi:10.7555/JBR.30.2016K0001
- Shan, H., Zheng, X., and Li, M. (2019). The Effects of Astragalus Membranaceus Active Extracts on Autophagy-Related Diseases. *Int. J. Mol. Sci.* 20, 1904. doi:10.3390/ijms20081904
- Shan, S. J., Xiao, T., Chen, J., Geng, S. L., Li, C. P., Xu, X., et al. (2012). Kanglaite Attenuates UVB-Induced Down-Regulation of Aquaporin-3 in Cultured Human Skin Keratinocytes. *Int. J. Mol. Med.* 29, 625–629. doi:10.3892/ijmm.2011.873
- Slominski, A., Tobin, D. J., Shibahara, S., and Wortsman, J. (2004). Melanin Pigmentation in Mammalian Skin and its Hormonal Regulation. *Physiol. Rev.* 84, 1155–1228. doi:10.1152/physrev.00044.2003
- Son, E. S., Kim, S. H., Kim, Y. O., Lee, Y. E., Kyung, S. Y., Jeong, S. H., et al. (2019). Coix Lacryma-Jobi Var. Ma-Yuen Stapf Sprout Extract Induces Cell Cycle Arrest and Apoptosis in Human Cervical Carcinoma Cells. *BMC Complement. Altern. Med.* 19, 312. doi:10.1186/s12906-019-2725-z
- Son, J., and Lee, S. Y. (2020). Ursonic Acid Exerts Inhibitory Effects on Matrix Metalloproteinases via ERK Signaling Pathway. *Chem. Biol. Interact* 315, 108910. doi:10.1016/j.cbi.2019.108910
- Song, Y., Zeng, R., Hu, L., Maffucci, K. G., Ren, X., and Qu, Y. (2017). *In Vivo* Wound Healing and *In Vitro* Antioxidant Activities of Bletilla Striata Phenolic Extracts. *Biomed. Pharmacother.* 93, 451–461. doi:10.1016/j.biopha.2017.06.079
- Sonthalia, S., Daulatabad, D., and Sarkar, R. (2016). Glutathione as a Skin Whitening Agent: Facts, Myths, Evidence and Controversies. *Indian J. Dermatol. Venereol. Leprol.* 82, 262–272. doi:10.4103/0378-6323.179088
- State Administration of Traditional Chinese Medicine (1999). *Chinese Materia Medica* Editorial Board (1999). *Chinese Materia Medica*. Shanghai: Shanghai Scientific & Technical Publishers.
- Sun, W., Meng, K., Qi, C., Yang, X., Wang, Y., Fan, W., et al. (2015a). Immune-enhancing Activity of Polysaccharides Isolated from Atractylodes Macrocephalae Koidz. *Carbohydr. Polym.* 126, 91–96. doi:10.1016/j.carbpol.2015.03.034
- Sun, Y., Zhang, J., Huo, R., Zhai, T., Li, H., Wu, P., et al. (2015b). Paeoniflorin Inhibits Skin Lesions in Imiquimod-Induced Psoriasis-like Mice by Downregulating Inflammation. *Int. Immunopharmacol* 24, 392–399. doi:10.1016/j.intimp.2014.12.032
- Taiwan Herbal Pharmacopeia 3rd Edition Committee (2018). *Taiwan Herbal Pharmacopeia*. Republic of China: Ministry of Health and Welfare.
- Taiwan Herbal Pharmacopeia 4th Edition Committee (2021). *Taiwan Herbal Pharmacopeia*. Republic of China: Ministry of Health and Welfare.

- Tariq, M., Tahir, H. M., Butt, S. A., Ali, S., Ahmad, A. B., Raza, C., et al. (2021). Silk Derived Formulations for Accelerated Wound Healing in Diabetic Mice. *PeerJ* 9, e10232. doi:10.7717/peerj.10232
- The Royal Botanic Gardens (2013). *The Plant List*. [Online]. Available: <http://www.theplantlist.org/> (Accessed May 7, 2021).
- Tourism Bureau (2021). *General Information*. [Online]. Available: <https://www.taiwan.net.tw/m1.aspx?No=0027009> (Accessed May 6, 2021).
- Tsao, Y. T., Kuo, C. Y., Kuan, Y. D., Lin, H. C., Wu, L. H., and Lee, C. H. (2017). The Extracts of Astragalus Membranaceus Inhibit Melanogenesis through the ERK Signaling Pathway. *Int. J. Med. Sci.* 14, 1049–1053. doi:10.7150/ijms.20335
- Tsukayama, I., Toda, K., Takeda, Y., Mega, T., Tanaka, M., Kawakami, Y., et al. (2018). Preventive Effect of Dioscorea Japonica on Squamous Cell Carcinoma of Mouse Skin Involving Down-Regulation of Prostaglandin E2 Synthetic Pathway. *J. Clin. Biochem. Nutr.* 62, 139–147. doi:10.3164/jcfn.17-54
- Tundis, R., Loizzo, M. R., Bonesi, M., and Menichini, F. (2015). Potential Role of Natural Compounds against Skin Aging. *Curr. Med. Chem.* 22, 1515–1538. doi:10.2174/0929867322666150227151809
- Ullah, S., Park, C., Ikram, M., Kang, D., Lee, S., Yang, J., et al. (2019). Tyrosinase Inhibition and Anti-melanin Generation Effect of Cinnamide Analogues. *Bioorg. Chem.* 87, 43–55. doi:10.1016/j.bioorg.2019.03.001
- Vacanti, N. M. (2019). The Fundamentals of Constructing and Interpreting Heat Maps. *Methods Mol. Biol.* 1862, 279–291. doi:10.1007/978-1-4939-8769-6_20
- Vitalini, S., Iriti, M., Puricelli, C., Ciuchi, D., Segale, A., and Fico, G. (2013). Traditional Knowledge on Medicinal and Food Plants Used in Val San Giacomo (Sondrio, Italy)—an alpine Ethnobotanical Study. *J. Ethnopharmacol.* 145, 517–529. doi:10.1016/j.jep.2012.11.024
- Wang, H., Wang, X., Zhou, L., Zhang, S., An, L., Bao, J., et al. (2021). Structural Characteristics and *In Vitro* and *In Vivo* Immunoregulatory Properties of a Gluco-Arabinan from Angelica Dahurica. *Int. J. Biol. Macromol.* 183, 90–100. doi:10.1016/j.ijbiomac.2021.04.077
- Wang, J., Chen, X., Wang, W., Zhang, Y., Yang, Z., Jin, Y., et al. (2013a). Glycyrrhizic Acid as the Antiviral Component of Glycyrrhiza Uralensis Fisch. Against Coxsackievirus A16 and Enterovirus 71 of Hand Foot and Mouth Disease. *J. Ethnopharmacol.* 147, 114–121. doi:10.1016/j.jep.2013.02.017
- Wang, R., Lechtenberg, M., Sendker, J., Peterleit, F., Deters, A., and Hensel, A. (2013b). Wound-healing Plants from TCM: *In Vitro* Investigations on Selected TCM Plants and Their Influence on Human Dermal Fibroblasts and Keratinocytes. *Fitoterapia* 84, 308–317. doi:10.1016/j.fitote.2012.12.020
- Waqas, M. K., Akhtar, N., Mustafa, R., Jamshaid, M., Khan, H. M., and Murtaza, G. (2015). Dermatological and Cosmeceutical Benefits of Glycine max (Soybean) and its Active Components. *Acta Pol. Pharm.* 72, 3–11.
- Wu, P. Y., Li, T. M., Chen, S. L., Chen, C. J., Chiou, J. S., Lin, M. K., et al. (2020). Complementary Chinese Herbal Medicine Therapy Improves Survival in Patients with Pemphigus: A Retrospective Study from a Taiwan-Based Registry. *Front. Pharmacol.* 11, 594486. doi:10.3389/fphar.2020.594486
- Xu, Q., Bauer, R., Hendry, B. M., Fan, T. P., Zhao, Z., Duez, P., et al. (2013). The Quest for Modernisation of Traditional Chinese Medicine. *BMC Complement. Altern. Med.* 13, 132. doi:10.1186/1472-6882-13-132
- Xuan, S. H., Park, Y. M., Ha, J. H., Jeong, Y. J., and Park, S. N. (2017). The Effect of Dehydroglyasperin C on UVB-Mediated MMPs Expression in Human HaCaT Cells. *Pharmacol. Rep.* 69, 1224–1231. doi:10.1016/j.pharep.2017.05.012
- Yan, N., Tang, Z., Xu, Y., Li, X., and Wang, Q. (2020). Pharmacokinetic Study of Ferulic Acid Following Transdermal or Intragastric Administration in Rats. *AAPS PharmSciTech* 21, 169. doi:10.1208/s12249-020-01709-w
- Yang, L., Han, Z., Chen, C., Li, Z., Yu, S., Qu, Y., et al. (2020a). Novel Probiotic-Bound Oxidized Bletilla Striata Polysaccharide-Chitosan Composite Hydrogel. *Mater. Sci. Eng. C Mater. Biol. Appl.* 117, 111265. doi:10.1016/j.msec.2020.111265
- Yang, W. T., Ke, C. Y., Wu, W. T., Harn, H. J., Tseng, Y. H., and Lee, R. P. (2017). Effects of Angelica Dahurica and Rheum Officinale Extracts on Excisional Wound Healing in Rats. *Evid. Based Complement. Alternat Med.* 2017, 1583031. doi:10.1155/2017/1583031
- Yang, W. T., Ke, C. Y., Wu, W. T., Tseng, Y. H., and Lee, R. P. (2020b). Antimicrobial and Anti-inflammatory Potential of Angelica Dahurica and Rheum Officinale Extract Accelerates Wound Healing in Staphylococcus Aureus-Infected Wounds. *Sci. Rep.* 10, 5596. doi:10.1038/s41598-020-62581-z
- Ye, Y., Chu, J. H., Wang, H., Xu, H., Chou, G. X., Leung, A. K., et al. (2010). Involvement of P38 MAPK Signaling Pathway in the Anti-melanogenic Effect of San-Bai-tang, a Chinese Herbal Formula, in B16 Cells. *J. Ethnopharmacol.* 132, 533–535. doi:10.1016/j.jep.2010.09.007
- Yi, R., Liu, X. M., and Dong, Q. (2013). A Study of Lycium Barbarum Polysaccharides (LBP) Extraction Technology and its Anti-aging Effect. *Afr. J. Tradit. Complement. Altern. Med.* 10, 171–174. doi:10.4314/ajtcam.v10i4.27
- You, O. H., Shin, E. A., Lee, H., Kim, J. H., Sim, D. Y., Kim, J. H., et al. (2017). Apoptotic Effect of Astragalus in Melanoma Skin Cancers via Activation of Caspases and Inhibition of Sry-Related HMg-Box Gene 10. *Phytother Res.* 31, 1614–1620. doi:10.1002/ptr.5895
- Yu, L., Nie, X., Pan, H., Ling, S., Zhang, D., and Bian, K. (2011). Diabetes Mellitus Ulcers Treatment with Bletilla Striata Polysaccharide. *Zhongguo Zhong Yao Za Zhi* 36, 1487–1491. doi:10.4268/cjcm.201111118
- Zaidi, K. U., Ali, S. A., Ali, A., and Naaz, I. (2019). Natural Tyrosinase Inhibitors: Role of Herbals in the Treatment of Hyperpigmentary Disorders. *Mini Rev. Med. Chem.* 19, 796–808. doi:10.2174/1389557519666190116101039
- Zanetti, R., Prota, G., Napolitano, A., Martinez, C., Sancho-Garnier, H., Østerlind, A., et al. (2001). Development of an Integrated Method of Skin Phenotype Measurement Using the Melanins. *Melanoma Res.* 11, 551–557. doi:10.1097/00008390-200112000-00001
- Zhang, C., He, Y., Chen, Z., Shi, J., Qu, Y., and Zhang, J. (2019). Effect of Polysaccharides from Bletilla Striata on the Healing of Dermal Wounds in Mice. *Evid. Based Complement. Alternat Med.* 2019, 9212314. doi:10.1155/2019/9212314
- Zhang, J., Guo, W., Li, Q., Sun, F., Xu, X., and Xu, H. (2020). Discriminant Analysis of Traditional Chinese Medicinal Properties Based on Holistic Chemical Profiling by 1H-NMR Spectrometry. *Evid. Based Complement. Alternat Med.* 2020, 3141340. doi:10.1155/2020/3141340
- Zhao, B., Zhang, X., Han, W., Cheng, J., and Qin, Y. (2017). Wound Healing Effect of an Astragalus Membranaceus Polysaccharide and its Mechanism. *Mol. Med. Rep.* 15, 4077–4083. doi:10.3892/mmr.2017.6488
- Zhao, H., Deneau, J., Che, G. O., Li, S., Vagnini, F., Azadi, P., et al. (2012). Angelica Sinensis Isolate SBD.4: Composition, Gene Expression Profiling, Mechanism of Action and Effect on Wounds, in Rats and Humans. *Eur. J. Dermatol.* 22, 58–67. doi:10.1684/ejd.2011.1599
- Zhu, C. S., Nie, A. Z., Zhang, B., and Lin, Z. J. (2019). Medication Rules of Professor Zhang Bing in Treatment of Skin Itching Based on Data Mining. *Zhongguo Zhong Yao Za Zhi* 44, 597–601. doi:10.19540/j.cnki.cjcm.20181128.001
- Zofia, N. L., Martyna, Z. D., Aleksandra, Z., and Tomasz, B. (2020). Comparison of the Antiaging and Protective Properties of Plants from the Apiaceae Family. *Oxid Med. Cel Longev* 2020, 5307614. doi:10.1155/2020/5307614

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Ko, Chao, Chen, Su, Maeda, Lin, Chiang and Huang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.