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, 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
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 mián 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 qǐ bái sān, a well-known skin whitening herbal prescription. However, its composition varies among different historical dynasties, geographical regions, and environments. For example, different compositions of qǐ bái sān can be found in related prescriptions such as yòng lèi qián fàng, pǔ jì fàng, and tài píng shìng hùi fàng (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.

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 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.

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

Frontiers in Pharmacology | www.frontiersin.org 2 November 2021 | Volume 12 | Article 736370
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):

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

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 | RFCa | Family | Color | Flavor and property | Traditional usage | Literature on skin modern research (PubMed)b |
|---|---|---|---|---|---|---|
| Oral |
| *Poria cocos* (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](#)) |
| *Glycyrrhiza uralensis* Fisch./Glycyrrhizae radix et rhizoma/甘草/CMU2021SWGrr | 0.41 | Leguminosae | brown | Sweet; plain | Tonifying and replenishing | Accelerate wound healing and promote neovascularization ([Iao 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](#)) |
| *Paeonia lactiflora* 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](#)) |
| *Angelica dahurica* (Hoffm.) Benth. & Hook./ex Franch. & Sav./Angelicae dahuricae radix/白芷/CMU2021SWAdr | 0.35 | Apiaceae | white | Pungent; warm | Exterior-releasing | Accelerate wound healing and promote neovascularization ([Iao 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](#)) |
| *Astragalus propinquus* 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](#)) |
| *Angelica sinensis* (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](#)) |
| *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf/Coicis semen/白薏仁/CMU2021SWCs | 0.32 | Poaceae | white | Sweet and plain; cool | Dampness-draining diuretic | Accelerate wound healing ([Kakikihara 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](#)) |
| *Ziziphus jujuba* Mill. (red)/Jujubae fructus (red)/紅棗/CMU2021SWJf | 0.3 | Rhamnaceae | red | Sweet; warm | Tonifying and replenishing | Accelerate wound healing ([Kao et al., 2020](#)); anti-wrinkle ([Son and Lee, 2020](#)); melanoma ([Hung et al., 2012](#)) |
| *Atractylodes macrocephala* 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 | RFCa | Family | Color | Flavor and property | Traditional usage | Literature on skin modern research (PubMed)b |
|---|---|---|---|---|---|---|
| Dioscorea polystachya Turcz./ Dioscorea 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) |
| Lycium chinense 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 (Cenanaru et al., 2021); moisturizing (Meng et al., 2020) |
| Ophiopogon japonicus (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; Manzer et al., 2019; An et al., 2020) |
| Ligusticum striatum DC./Chuanxiong Ligusticum/CPR2021SWDr | 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) |
| Wolfiporia extensa (Peck) Ginna/Poria白茯苓/CPR2021SWP | 0.82 | Polyporaceae | white | Sweet and plain; plain | Dampness-draining diuretic | 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) |
| Bletilla striata (Thunb.) Rchb.f./Bletilae rhizoma/白及/CPR2021SWBr | 0.58 | Orchidaceae | white | Bitter, sweet, and astringent; cold | Hemostatic | 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) |
| Atractylodes macrocephala Koidz./Atractylodis macrocephalae rhizoma/白术/CPR2021SWAr | 0.53 | Compositae | white | Bitter and sweet; warm | Tonifying and replenishing | Hyperpigmentation (Ho et al., 2021); skin itching (Zhu et al., 2019) |
| Ampelopsis japonica (Thunb.) Makino/ Ampelopsis radii/白蔹/CPR2021SWAd | 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) |
| Paeonia lactiflora Pall. (white)/Paeoniae radii alba/白芍/CPR2021SWPa | 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 (Zhu 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) |
| Bombbyx mori Linnaeus/Bombbyx batryticatus/白蠶/CPR2021SWBb | 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.
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 qi bái sán (Figure 8A). Taiwan qi bái sán 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 qi bái sán-related prescriptions in yòng lèi qián fāng, pǔ jì fāng, and tài píng shēng hui fāng found that Taiwan qi bái sán is the addition and subtraction formula from the qi bái sán 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
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 Qing-Cao-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.; Amr, Atractylodes macrocephala Koiz.; 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.Cai); StSp, Dioscorea polyodachya Turch.; Grs, Glycyrrhiza uralensis Fisch.; Jf, Ziziphus jujuba Mill. (red); Lf, Lycium chinense Mill.; Or, Ophiopogon japonicus (Thunb.) Ker Gawl.; P, Wolffdophilia extensa (Peck) Ginns; P, Paeonia lactitiflora Pall. (white).

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 dots represent 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.; Amr, Atractylodes macrocephala Koiz.; 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.Cai); StSp, Dioscorea polyodachya Turch.; Grs, Glycyrrhiza uralensis Fisch.; Jf, Ziziphus jujuba Mill. (red); Lf, Lycium chinense Mill.; Or, Ophiopogon japonicus (Thunb.) Ker Gawl.; P, Wolffdophilia extensa (Peck) Ginns; P, Paeonia lactitiflora Pall. (white).
A 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 (Gilchrest 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 1H-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.
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., *Atractylodes macrocephala* Koidz., *Ampelopsis radix* Batsch, and *Bombyx batryticatus* 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...
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 in inhibition of tyrosinase synthesis, but it does not inhibit tyrosinase activity (Cho et al., 2006). A study highlighted that the extract of Reynoutria multiflora, an immunomodulatory agent, and it can significantly increase phagocytosis and the secretion of cytokines by macrophages (Cho et al., 2006). A study highlighted that the extract of Reynoutria multiflora, an immunomodulatory agent, and it can significantly increase phagocytosis and the secretion of cytokines by macrophages (Cho et al., 2006).

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

"Look alike" or "sound 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.

Astragalus membranaceus (Fisch.) Bunge is a commonly used synonym of Astragalus propinquus Schischkin.

Polygonum multiflorum Thunb. is a commonly used synonym of Reynoutria multiflora (Thunb.) Moldenke.

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 baikalensis Georgi, Pteroxygonum giraldi 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.
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.

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