Clinical Trial/Experimental Study

Medicine

OPEN

A real-world study to observe the efficacy and safety of Lutai Danshen Baishao Granules for improving melasma

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Abstract

Background: Traditional Chinese Medicine categorizes melasma into various syndromes, one of which is the kidney-deficiency and blood-stasis syndrome. Different Chinese medicines are used for each syndrome to achieve a personalized treatment approach, resulting in a more effective outcome. The study aimed to investigate the efficacy and safety of Lutai Danshen Baishao Granules (LDBG) in alleviating melasma and to compare the effects of LDBG in patients with and without kidney-deficiency and blood-stasis syndrome through a real-world, large-sample investigation.

Methods: A multicenter, prospective, nonrandomized, observational trial was conducted from December 2021 to May 2023, recruiting 1000 female participants with melasma. After enrollment, participants were divided into Group A (kidney-deficiency and blood-stasis syndrome) and group B (non-kidney-deficiency and blood-stasis syndrome) based on the traditional Chinese medicine (TCM) syndrome scale. General physical signs, melasma indicators, Dermatology Life Quality Index, and TCM syndrome scores were recorded before and after the intervention. The long-term effectiveness was assessed 2 months after the intervention ended.

Results: Following the intervention, melasma-related indicators and TCM syndrome scores were significantly lower than those before the intervention ($P < .001$). Compared to Group B, Group A showed a more significant reduction in the total area of melasma and the Melasma Area and Severity Index score ($P < .05$). The reduction in melasma area was also more pronounced in Group A (group A: 425.00 vs group B: 312.50, $P < .001$). Two months after the intervention, intergroup and intragroup comparisons revealed that LDBG had a long-term effect with a lower tendency for recurrence, and the long-term effect in Group A was better than in group B ($P < .05$). The overall incidence of adverse events during the trial was 1.2%.

Conclusion: LDBG can reduce facial melasma and improve TCM syndromes, particularly in cases of melasma associated with kidney-deficiency and blood-stasis syndrome, with high safety and low risk of relapse.

Abbreviations: DLQI = Dermatology Life Quality Index, LDBG = Lutai Danshen Baishao Granules, MASI = Melasma Area and Severity Index, TCM = traditional Chinese medicine.

Keywords: melasma, multicenter prospective study, precision health care, real-world study, syndrome differentiation and treatment, traditional Chinese medicine

1. Introduction

Melasma is a common chronic, acquired facial pigmentation disorder, with a reported prevalence ranging from 1% to 50% in various populations.[1] It is more prevalent in women, with an incidence 9 to 10 times higher than in men, and 41% of women experience onset after pregnancy but before menopause.[2,3] Clinically, melasma is characterized by light brown to dark brown patches of varying depths with indistinct borders, typically appearing on the cheeks, forehead, and jaw.[4] Based on the

This study was funded by the National Key Research and Development Plan of the Traditional Chinese Medicine Modernization Research Key Project (Grant/Award Number: 2018YFC1706800).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study has been reviewed by the Ethics Committee of the Beijing University of Chinese Medicine (No. 2021BZYLL0408), and informed consent was obtained from all subjects involved in the study.

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How to cite this article: Lv M-Y, Yang Y, Fei W-T, Liu J-L, Zhang R, Zhou L-H, Zhang F-H, Wang C, Wang L-Y, Zhang J-J. A real-world study to observe the efficacy and safety of Lutai Danshen Baishao Granules for improving melasma. Medicine 2025;104:6(e41394).

Received: 27 August 2024 / Received in final form: 31 December 2024 / Accepted: 10 January 2025

http://dx.doi.org/10.1097/MD.0000000000041394

location of the lesions, melasma can be classified into 3 types: midface, buccal, and mandibular. Various etiological factors contribute to the development of melasma, including chronic ultraviolet radiation exposure, hormonal changes, and genetic predisposition.[5] Because melasma commonly affects the face, it can have a significant impact on emotional well-being, causing disfiguring lesions that severely affect patients' quality of life.[6]

Common treatments for melasma include chemical peels, laser and light therapies, oral and topical agents, as well as combination approaches.[7–9] However, these treatments often provide only temporary relief and may lead to side effects such as contact dermatitis, depigmentation, and impaired skin barrier function.[10,11] Due to the complex pathogenesis of melasma, there has been a shift in research towards exploring traditional Chinese medicine (TCM) and dietary supplements as alternative treatment options.[12]

TCM has a long history and extensive experience, with a wide variety of medicinal species used in dermatology. The core principle of TCM is syndrome differentiation and treatment, which allows doctors to more accurately diagnose the disease and create personalized treatment plans. Without this approach, individual patient differences and the dynamic nature of the condition may be overlooked, leading to wasted medical resources and reduced effectiveness. TCM products offer numerous benefits in beauty and health care, including the prevention of chronic diseases, due to their multi-component, multi-target, and multi-pathway characteristics.[13] However, there is currently a lack of comprehensive research on the effectiveness of TCM health foods available on the market for improving melasma. Additionally, the core principle of syndrome differentiation and treatment, central to TCM, has not been adequately studied in relation to these health products.

Lutai Danshen Baishao Granules (LDBG), approved by the China Food and Drug Administration (G20100485), is a TCM formulation used to tonify the kidney and essence, promote blood circulation, remove blood stasis, and improve melasma based on the principles of TCM syndrome differentiation and treatment. It is particularly indicated for individuals with kidney-deficiency and blood-stasis syndrome. LDBG is a compound health granule consisting of *Cervus elaphus*, *Salvia miltiorrhiza*, *Paeonia lactiflora*, *Pueraria lobata*, and soybean isoflavones. The quality standard of LDBG has been improved upon by improving the original active ingredients: soybean isoflavone (3.50 mg/g), daidzein (1.60 mg/g), daidzein (1 mg/g), genistein (0.015 mg/g), genistein (0.12 mg/g), and protein (50 mg/g). The HPLC conditions for puerarin, paeoniflorin, and salvianolic acid B have also been established, with their content determined at 18.94, 10.15, and 9.25 mg/g, respectively.[14] Previous research indicates that LDBG regulates the expression of antioxidant enzymes via the Keap1/Nrf2 pathway, increasing the levels of CAT and GSH-px in the bloodstream while decreasing MDA and LPF levels, thus reducing TYR oxidation and consequently melanin formation.[15]

Although LDBG has been marketed as a TCM health product, the available research evidence on its effectiveness remains limited. Large-sample studies are commonly employed in scientific research, market investigations, medical experiments and other fields, providing more reliable and accurate results. However, due to the constraints of research funding, resource limitations, the complexity of implementation, and the lack of sharing and collaboration, Large-scale studies are relatively scarce, and research on TCM health products is even more limited. To set a benchmark in China's TCM health products industry and provide solid evidence, we conducted a prospective observational study involving 1000 participants at dermatology clinics across 9 hospitals. This study not only observed the efficacy of LDBG in treating melasma but also compared its effects between patients with kidney-deficiency and blood-stasis syndrome and those without, highlighting the significance of syndrome differentiation and treatment in TCM health products.

2. Methods

2.1. Study design

This multicenter, nonrandomized, prospective observational study began in December 2021 and was conducted at 4 dermatology hospitals and 5 general hospitals (Fig. 1). A total of 1000 participants diagnosed with melasma were recruited. After receiving a comprehensive explanation of the benefits and risks of participating in the study, participants who voluntarily signed a written informed consent form were screened for compliance with the inclusion and exclusion criteria during their initial visit. Eligible participants were then enrolled in the registry. LDBG was administered continuously for 60 days, with follow-up visits occurring at the end of the intervention and 2 months later. The study employed a natural grouping method, where participants were not pre-assigned to groups. Upon entering the study, participants were divided into Group A (kidney-deficiency and blood-stasis syndrome) and group B (non-kidney-deficiency and blood-stasis syndrome) based on their responses to the TCM syndrome scale. The efficacy of melasma treatment in the 2 groups will be analyzed from various perspectives.

2.2. Ethics and trial registration

Ethical approval for this study was obtained from the Ethics Committee of the Beijing University of Chinese Medicine (No. 2021BZYLL0408). The trial protocol adhered to the provisions of the Declaration of Helsinki, ensuring the protection of participants' rights and interests. All participants provided written informed consent before enrollment. The study was registered on December 28, 2021, with the Chinese Clinical Trial Registry (ChiCTR2100054827, http://www.chictr.org).

2.3. Participants

2.3.1. Inclusion criteria. Women aged 18 to 65 years; participants must have stable melasma, characterized by pale brown to dark brown, well-defined patches that are usually symmetrically distributed, without signs of inflammation or scaling; absence of noticeable subjective symptoms; all participants provided voluntary, informed written consent.

2.3.2. Exclusion criteria. Exclusion criteria included melasma attributed to medical conditions; women who were pregnant or breastfeeding; individuals predisposed to allergies or allergic to health supplement products; patients with significant cardiovascular, cerebrovascular, liver, kidney, or hematopoietic system disorders, endocrine diseases, or mental health conditions; alcoholics or smokers; participants who had used or applied products for freckle lightening within 4 weeks prior to the trial's commencement, or had undergone laser treatment or used alpha-hydroxy acids, potentially influencing outcome assessment.

2.4. Recruitment

Participants were recruited from December 2021 to May 2023 at several hospitals, including Beijing Jingcheng Skin Hospital, Tangshan Jingcheng Skin Hospital, Henan Zhongdu TCM Skin Hospital, Xuzhou Jingcheng Skin Hospital, Tianjin Integrated Traditional Chinese and Western Medicine Nankai Hospital, Tianjin Third Central Hospital, 983 Hospital of the Chinese People's Liberation Army Joint Logistic Support Force, the Second Affiliated Hospital of Tianjin University of Chinese Medicine, and Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital. Recruitment efforts included the placement of posters in each hospital and advertisements on the Internet. For participants who met the inclusion and exclusion

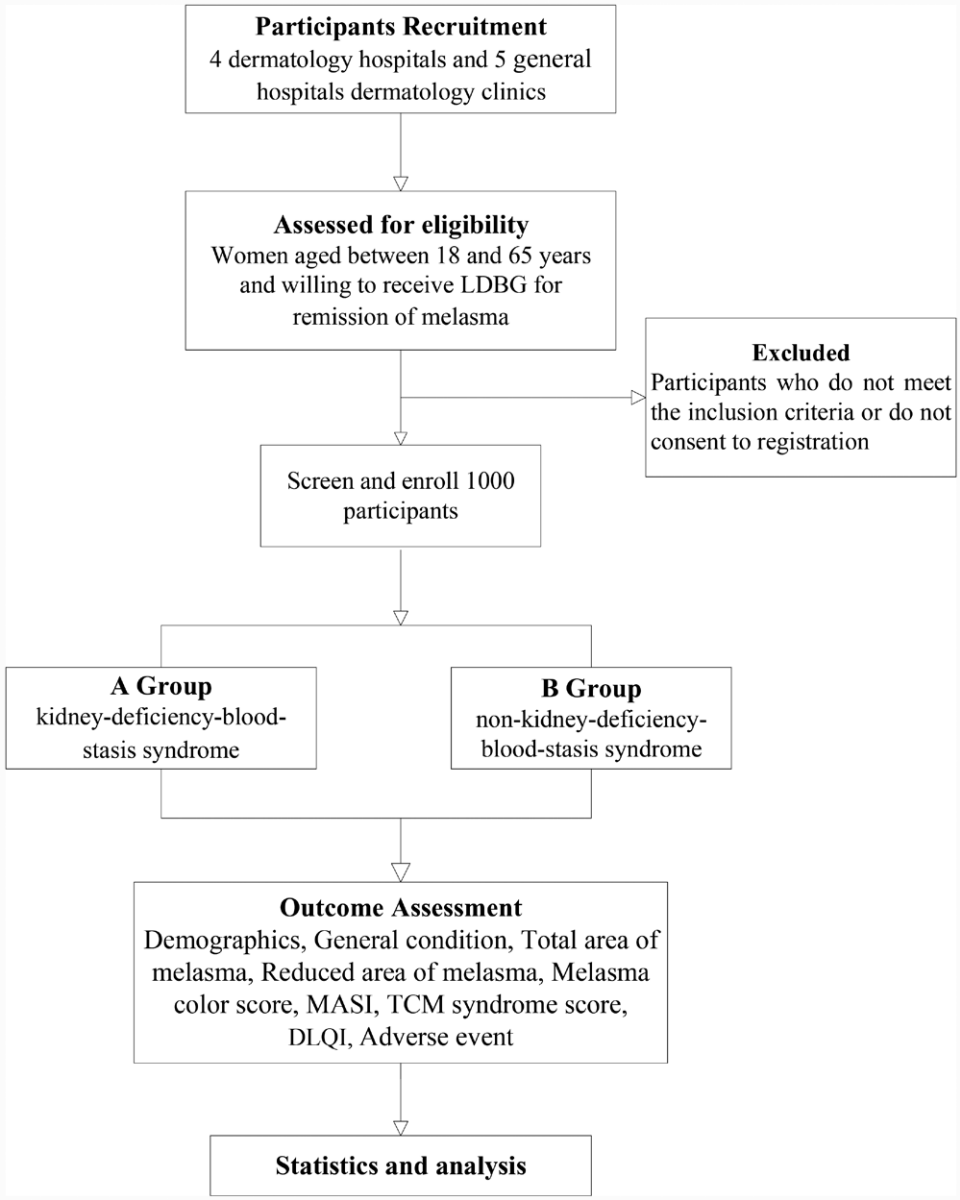

Figure 1. Flow chart of study. Recruitment and eligibility assessment were carried out through 4 dermatology hospitals and 5 general hospitals' dermatology clinics. A total of 1000 participants were screened and included, divided into Group A (kidney-deficiency–blood-stasis syndrome) and Group B (non-kidney-deficiency–blood-stasis syndrome). Statistics and analysis of outcome indicators. DLQI = Dermatology Life Quality Index, LDBG = Lutai Danshen Baishao Granules, MASI = Melasma Area and Severity Index, TCM = traditional Chinese medicine.

criteria, we provided a thorough explanation of the study's purpose, process, and precautions. After ensuring that the potential participants fully understood the study, they were asked to sign an informed consent form. Additionally, professional clinicians were available to assess the participants' status and provide medical assistance as needed.

2.5. Sample size calculation

According to China's "Drug Registration Administration Measures" and the "Practical Guide for Drug Clinical Trials and GCP" (second edition), the number of cases required for biological products trials ranges from 20 to 30 cases in phase I, 100 to 500 cases in phase II, and 200 to 1000 cases in phase III. Relevant studies suggest that for commonly consumed health products, the sample size often needs to exceed 500 participants to ensure a comprehensive test group.[16] Since this trial product is a marketed health food and we are applying methodologies similar to those used in drug clinical trials, we ultimately aimed to enroll 1000 participants in this study.

2.6. Interventions

Participants will receive the LDBG intervention (Hebei Baixiaodan Pharmaceutical Co., Lot Number: 20211201, Hebei, China) twice daily (1 hour after lunch and 1 hour after dinner). Each LDBG packet contains 5.0 g and is prepared by brewing 1 packet at a time. The product is certified by the China Food and Drug Administration under certification number G20100485.

During the trial, participants will maintain their usual diet, water intake, exercise routine, and sleep patterns. It is important to maintain a positive mood, avoid impatience, depression, and anxiety, and minimize emotional stress. Adequate sleep should be prioritized, avoiding late nights and irregular schedules. Participants should reduce sun exposure by using umbrellas or sun hats when outdoors, and apply sunscreen or

wear protective clothing (sunscreen with PSF30 PA+++ rating) during outdoor activities. A light diet consisting of fruits, vegetables, and other non-greasy, non-spicy foods is recommended. Participants should avoid using cosmetics that may cause allergies or adverse reactions and maintain basic skin hydration. They should also refrain from taking health foods or drugs with similar effects, using external freckle whitening products, or undergoing laser or alpha-hydroxy acid treatments during the trial.

2.7. Adverse event management

All adverse reactions that occur during the trial, including their symptoms, severity, onset time, treatment measures, and progression, must be documented in the "Study Report Form" to evaluate their relationship with the test products. Researchers are required to record these details thoroughly, sign, and date the entries.

For mild adverse reactions, follow-up is necessary until the symptoms resolve. In the case of serious adverse reactions, participants must immediately discontinue the product and seek medical attention. The trial unit is responsible for covering any resulting treatment costs and providing appropriate compensation.

2.8. Outcome measurements

The researchers collected the following data to assess the efficacy and safety of LDBG in improving melasma and developed a detailed study plan as outlined in Table 1.

2.8.1. Demographic characteristics. Before the study began, demographic data such as occupation, age, and educational background were collected from the participants.

2.8.2. General condition. Vital signs including systolic blood pressure, diastolic blood pressure, pulse rhythm, and pulse rate were recorded, along with data on mental status, sleep quality, and urinary and bowel function. These measures served both as indicators of general health and as part of the safety analysis.

2.8.3. Melasma area. A transparent mask was used to outline the affected areas of facial melasma. The mask was placed on a 0.5 cm × 0.5 cm grid plate to calculate the melasma area. This assessment was performed independently by 3 physicians, and the average of their measurements was used.

2.8.4. Melasma color. The color of the melasma was scored on a scale from 0 to 4: 0 indicates none, 1 is mild, 2 is moderate, 3 is pronounced, and 4 is the most severe. Higher scores correspond to worse skin conditions.

Table 1

Research schedule of the study.

	Baseline level	End of intervention	The 2nd month after the end
Sign informed consent	√		
Eligibility screening	√		
Demographic characteristics	√		
General condition	√	√	
Melasma area	√	√	√
Melasma color	√	√	√
MASI	√	√	√
DLQI	√	√	√
TCM Syndrome Scale	√	√	√
Adverse events		√	√

2.8.5. Melasma Area and Severity Index (MASI). MASI is a reliable measure of melasma severity, with a confidence level of 0.991.[17] MASI scores range from 0 to 48, with 48 representing the most severe condition. The MASI score was independently assessed by 2 physicians using the following formula[18]:

MASI = forehead[0.3A(D + H)] + right malar[0.3A(D + H)] + left malar[0.3A(D + H)] + chin[0.1A(D + H)]

(A: area of involvement; D: darkness score; H: homogeneity)

2.8.6. Dermatology Life Quality Index (DLQI)[19]. The DLQI questionnaire consists of 10 questions addressing various aspects of patients' experiences, including symptoms, physical sensations, psychological well-being, daily activities, and social relationships and others. Each question is scored using a 4-point scale: 0, 1, 2, and 3 points. The total score ranges from 0 to 30 points, with higher scores indicating a more severe impact on the patient's quality of life.

2.8.7. TCM Syndrome Scale. This scale is specifically designed for assessing kidney-deficiency and blood-stasis syndrome. At the beginning of the study, the scale was used to determine if participants met the criteria for this TCM syndrome, which informed their group assignment. Participants were asked to complete the TCM syndrome scale again at the end of the intervention and 2 months afterward.

2.8.8. Adverse events. In the event of adverse reactions, the decision to continue or terminate observation will be based on the severity of the reaction. Participants will receive appropriate treatment according to clinical guidelines, and their condition will be monitored regularly thereafter.

2.9. Quality control and assurance

Researchers underwent pretest training to thoroughly understand the specific details of the study protocol and its indicators. The reporting of subjective symptoms should remain objective, without leading or prompting the participants. Specified objective indicators must be assessed at the times and using the methods outlined in the protocol. Special attention should be given to monitoring adverse reactions or unexpected side effects, with appropriate follow-up as necessary. Participants were grouped according to TCM syndromes by qualified TCM physicians, and the researchers involved in the trial were kept consistent throughout the study.

Researchers should explain the study procedures clearly to participants to ensure their full understanding and cooperation. Instructions on how to take the product and how to fill out the record card should be communicated effectively, ensuring participants accurately follow medical advice. Participants were informed about potential adverse reactions and were advised to contact the researcher or visit a hospital immediately if any adverse reactions occur.

Supervisors, appointed by the project leader, are responsible for ensuring the quality of the trial and protecting the rights and interests of the participants. The monitors oversee the accuracy and completeness of the recorded and reported data, the adherence to the study protocol, and compliance with relevant regulations and standards.

2.10. Statistical analysis

Data were recorded using an Excel spreadsheet program, and statistical analysis was conducted using SPSS v27 (IBM Corp., Armonk, NY). Descriptive statistics were presented as means (standard deviations) or medians (P25, P75) for continuous variables. For continuous variables that met the assumptions of normality and homogeneity of variance, an independent sample *t* test was used for intergroup comparisons, and a paired sample

t test was used for intragroup comparisons. If the assumptions of normality or homogeneity of variance were not met, nonparametric tests were applied. For the clinical outcomes of melasma, 2 independent sample nonparametric tests (Mann–Whitney *U* test) were used for intergroup comparisons, and 2 paired sample nonparametric tests (Wilcoxon signed rank test) were used for intragroup comparisons before and after the trial. The TCM syndromes before and after the intervention were compared using paired samples nonparametric tests. Categorical variables were described using efficiencies, frequencies, and percentiles, and the chi-square test was used to calculate differences between groups. A *P*-value of < .05 was considered statistically significant.

3. Results

A total of 1043 participants were enrolled in the trial. In group A, 44 participants were excluded from the analysis: 5 due to adverse events that led them to discontinue the trial, 11 for not adhering to the product administration schedule, which impacted the trial results, and 28 for failing to complete their visits on time due to personal reasons. Consequently, 999 participants (856 in Group A and 143 in Group B) were included in the final efficacy and safety analyses. For the long-term efficacy assessment, 35 participants from Group A were excluded due to incomplete data, leaving 964 participants (821 from Group A and 143 from Group B) included in the long-term efficacy analysis.

3.1. Demographics and basic physical examination

Before the study commenced, there were no statistically significant differences between Group A and Group B in terms of demographic characteristics, such as occupation, age, and educational background, or in basic physical examination results, including blood pressure and heart rate ($P > .05$), as detailed in Table 2.

3.2. Effectiveness

Before the trial, no significant differences were observed between the 2 groups in terms of the total area of melasma, melasma color score, MASI score, or DLQI score ($P > .05$), as shown in Table 3. After the 2-month intervention, intragroup comparisons revealed that the total area of melasma, melasma color score, MASI score, and DLQI score in both groups were significantly lower than those recorded before the intervention ($P < .001$), as presented in Table 4.

Intergroup comparisons (Table 5) demonstrated that Group A showed greater improvement than Group B in both the total area of melasma and the MASI score (Group A: 2750.00 vs Group B: 3125.00, $P = .014$; Group A: 7.20 vs Group B: 10.20, $P < .001$). Although the total area of melasma decreased in both groups compared to baseline, the reduction was significantly more pronounced in Group A (Group A: 425.00 vs Group B: 312.50, $P < .001$). However, there were no significant differences between the 2 groups in melasma color or DLQI score. Overall, LDBG was shown to significantly improve melasma.

As shown in Table 6, both groups exhibited significant reductions in symptoms such as dark lips and nails, dark tongue, tongue ecchymosis, waist soreness, leg weakness, forgetfulness, hair loss, dark menstruation, and skin discoloration by the end of the intervention (Group A: $P < .001$; Group B: $P < .05$). Following the 2-month intervention with LDBG, the total score of TCM symptoms decreased markedly ($P < .001$). These results suggest that LDBG can effectively alleviate the various TCM syndromes associated with kidney-deficiency and blood-stasis syndrome.

3.3. Long-term effectiveness

As shown in Table 7, 2 months after the intervention ended, both groups continued to exhibit significant improvements in total melasma area, melasma color score, and MASI score when compared to their baseline measurements ($P < .001$). While the

Table 2

Demographic characteristics and general physical examination.

	Group A (n = 856)	Group B (n = 143)	X^2/Z	*P*-value
Occupation				
Retiree	548 (64.0%)	99 (69.2%)	1.459	.227*
Employee	308 (36.0%)	44 (30.8%)		
Educational background				
Under Junior college	134 (93.7%)	9 (6.3%)	0.069	.792*
Junior college	797 (93.1%)	59 (6.9%)		
Age, M (P25, P75)	53 (46–60)	54 (49–60)	-0.745	.456†
Systolic blood pressure (mm Hg)				
M (P25, P75)	134.00 (121.00, 145.00)	132.00 (121.00, 145.00)	-0.435	.663†
Diastolic blood pressure (mm Hg)				
M (P25, P75)	77.00 (70.00, 85.00)	78.00 (69.00, 86.00)	-0.373	.709†
Heart rate (times/min)				
M (P25, P75)	73.00 (66.25, 81.00)	74.00 (66.00, 80.00)	-0.086	.931†

* Chi-square test.

† Mann–Whitney *U* test.

Table 3

Baseline levels of melasma characteristics.

	Group A (n = 856)	Group B (n = 143)	Z	*P*-value
Total area of melasma (mm^2) M (P25, P75)	3225.00 (2125.00, 4200.00)	3187.50 (2425.00, 4087.50)	-0.441	.659
Melasma color score M (P25, P75)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	-0.057	.955
Melasma MASI score M (P25, P75)	9.80 (7.20, 14.40)	9.60 (7.20, 14.40)	-0.008	.993
Melasma DLQI score M (P25, P75)	7.00 (6.00, 9.00)	7.00 (5.00, 9.00)	-1.313	.189

DLQI score in Group B did not show a significant difference from its pre-intervention level, Group A maintained a significant improvement, with results that were superior to those of Group B (Group A: $P < .001$; Group B: $P < .05$). These findings suggest that LDBG effectively improves melasma with no signs of recurrence, and participants in Group A reported higher satisfaction with their skin condition post-intervention.

Two months after the intervention, intergroup comparisons indicated that there were no statistically significant differences between Group A and Group B in terms of melasma color score and DLQI score ($P > .05$). However, the difference in DLQI scores in Group A was significantly better than in Group B ($P = .044$), as shown in Table 8. Additionally, compared to Group B, Group A experienced significantly greater reductions in melasma area, area reduction, and MASI score ($P < .05$) (Table 8). Therefore, the long-term efficacy of LDBG in participants with melasma in Group A was notably better than in Group B.

As indicated in Table 9, the total TCM syndrome evaluation scores in both groups decreased significantly 2 months after the intervention ended, compared to baseline levels ($P < .001$). Symptoms associated with TCM syndromes, such as dark lips and nails, dark tongue, tongue ecchymosis, waist soreness, leg weakness, forgetfulness, hair loss, dark menstruation, and dark complexion, also showed significant reductions from baseline (Group A: $P < .001$; Group B: $P < .05$). This suggests that LDBG has a sustained effect on kidney-deficiency and blood-stasis syndrome, with a low likelihood of recurrence.

Table 4

Intragroup comparison of melasma outcomes after intervention.

	Group A (n = 856)	Group B (n = 143)
Total area of melasma (mm^2)		
Before trial M (P25, P75)	3225.00 (2125.00, 4200.00)	3187.50 (2425.00, 4087.50)
After trial M (P25, P75)	2750.00 (1806.25, 3784.38)	3125.00 (2350.00, 3875.00)
Z	-16.049	-4.985
P-value	<.001	<.001
Melasma color scores		
Before trial, M (P25, P75)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)
After trial, M (P25, P75)	2.00 (2.00, 3.00)	2.00 (2.00, 2.00)
Z	-12.752	-5.759
P-value	<.001	<.001
MASI scores		
Before trial, M (P25, P75)	9.80 (7.20, 14.400	9.60 (7.20, 14.40)
After trial, M (P25, P75)	7.20 (5.40, 10.80)	10.20 (6.90, 13.80)
Z	-22.385	-3.303
P-value	<.001	<.001
DLQI score		
Before trial, M (P25, P75)	7.00 (6.00, 9.00)	7.00 (5.00, 9.00)
After trial, M (P25, P75)	7.00 (5.00, 8.00)	5.00 (5.00, 8.00)
Z	-19.135	-7.825
P-value	<.001	<.001

3.4. Safety

Following the intervention, there were no significant differences in general signs between Group A and Group B ($P > .05$), as shown in Table 10. A total of 12 adverse events occurred during the trial, as detailed in Table 11. These included 1 case of eczema (0.1%), 1 case of dizziness (0.1%), 1 case of diarrhea (0.1%), 1 case of injury (0.1%), 2 cases of cold (0.2%), 1 case of cough (0.1%), 1 case of gum swelling and pain (0.1%), 1 case of rhinitis recurrence (0.1%), 1 case of red rash (0.1%), and 1 case of mouth ulcer (0.1%). The overall incidence of adverse events during the trial was 1.2%. Of the 12 adverse events, 11 were deemed unrelated to the test product, based on the assessments of both the participants and the clinical physician. One adverse event was considered by the clinician to be possibly related to the trial product, as shown in Table 11.

4. Discussion

This study represents the first real-world, large-scale investigation into the effectiveness of LDBG in alleviating melasma associated with kidney-deficiency and blood-stasis syndrome. Large-sample research improves the accuracy and reliability of findings, offering more convincing evidence, uncovering additional patterns and phenomena, and increasing the generalizability and practical value of the results. Compared to baseline levels, participants who received LDBG showed significant reductions in melasma area, melasma color score, MASI score, and DLQI score. In terms of long-term efficacy, 2 months after the intervention concluded, participants' melasma-related indicators remained significantly improved compared to pre-intervention levels. Thus, the effects of LDBG on melasma are substantial, long-lasting, and do not easily result in recurrence after cessation of intervention. The notable effectiveness of LDBG is closely linked to the active ingredients contained in this traditional Chinese medicine compound. After improving the detection quality standards for LDBG, its active components were identified as including soybean isoflavones, daidzin, daidzein, puerarin, paeoniflorin, salvianolic acid B, and protein.[14] These ingredients may be the material basis of its function. Research indicates that the metabolite of daidzein primarily acts by suppressing MITF expression and CREB phosphorylation, thereby reducing the expression of tyrosinase, TYRP-1, and TYRP-2, which inhibits melanin production.[20] Additionally, puerarin and daidzein significantly downregulate the expression of tyrosinase mRNA, providing anti-pigmentation benefits.[21] Wen SY et al found that paeoniflorin, a natural anti-melanogenic compound, inhibits α-MSH-induced pigmentation in B16F10 cells by suppressing CREB activation and TRP-1, TRP-2, and

Table 5

Intergroup comparison of melasma outcomes after intervention.

	Group A (n = 856)	Group B (n = 143)	*Z*	*P*-value
Total area of melasma (mm^2)				
M (P25, P75)	2750.00 (1806.25, 3784.38)	3125.00 (2350.00, 3875.00)	-2.465	.014
Reduced area of melasma (mm^2)				
M (P25, P75)	425.00 (-37.50, 875.00)	312.50 (-100.00, 512.50)	-3.853	<.001
Melasma color score				
M (P25, P75)	2.00 (2.00, 3.00)	2.00 (2.00, 2.00)	-1.019	.308
MASI score				
M (P25, P75)	7.20 (5.40, 10.80)	10.20 (9.60, 13.80)	-5.180	<.001
DLQI score				
M (P25, P75)	7.00 (5.00, 8.00)	6.00 (5.00, 8.00)	-1.018	.309

Table 6

Intragroup comparison of TCM syndrome outcomes after intervention.

TCM syndrome score	Group A (n = 856)	Group B (n = 143)
Waist soreness		
Before trial, M (P25, P75)	2.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-15.934	-2.236
P-value	<.001	.025
Leg weakness		
Before trial, M (P25, P75)	2.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-15.601	-2.449
P-value	<.001	.014
Dark tongue		
Before trial, M (P25, P75)	2.00 (0.00, 4.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-16.044	-3.000
P-value	<.001	.003
Tongue ecchymosis		
Before trial, M (P25, P75)	2.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-15.199	-3.317
P-value	<.001	<.001
Forgetfulness		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-15.762	-3.000
P-value	<.001	.003
Hair loss		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	1.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-16.279	-4.690
P-value	<.001	<.001
Dark lips and nails		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-15.660	-2.449
P-value	<.001	.014
Dark complexion		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	1.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-16.369	-4.000
P-value	<.001	<.001
Dark menstruation		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-15.372	-3.464
P-value	<.001	<.001
Syndromes total score		
Before trial, M (P25, P75)	13.00 (10.00, 16.00)	2.00 (1.00, 2.00)
After trial, M (P25, P75)	8.00 (6.00, 11.00)	0.00 (0.00, 1.00)
Z	-24.791	-8.368
P-value	<.001	<.001

Table 7

Intragroup comparison of long-term outcomes of melasma.

	Group A (n = 821)	Group B (n = 143)
Total area of melasma (mm^2)		
Before trial M (P25, P75)	3175.00 (2100.00, 4143.75)	3187.50 (2425.00, 4087.50)
After trial M (P25, P75)	2550.00 (1743.75, 3393.75)	2900.00 (2137.50, 3575.00)
Z	-17.717	-7.419
P-value	<.001	<.001
Melasma color scores		
Before trial, M (P25, P75)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)
After trial, M (P25, P75)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)
Z	-17.640	-7.568
P-value	<.001	<.001
MASI scores		
Before trial, M (P25, P75)	10.20 (7.20, 14.40)	9.60 (7.20, 14.40)
After trial, M (P25, P75)	7.20 (4.80, 8.40)	9.60 (6.90, 12.00)
Z	-22.669	-4.550
P-value	<.001	<.001
DLQI score		
Before trial, M (P25, P75)	7.00 (6.00, 9.00)	7.00 (5.00, 9.00)
After trial, M (P25, P75)	7.00 (5.00, 9.00)	5.00 (5.00, 9.00)
Z	-7.812	-0.874
P-value	<.001	.382

MITF expression.[22] Furthermore, studies have shown that a complex of 3 branched-chain amino acids (isoleucine, leucine, and valine) inhibits melanin production without altering intracellular tyrosinase activity.[23] These components of LDBG work synergistically to effectively reduce melasma.

LDBG not only effectively reduced melasma but also significantly improved symptoms of kidney-deficiency and blood-stasis syndrome in participants, demonstrating the efficacy of syndrome differentiation and treatment in TCM. Syndrome differentiation and treatment is a unique diagnostic and therapeutic approach in TCM, forming the core of its practice, it enables physicians to accurately assess a patient's condition and create personalized treatment plans. The results of this study showed that the TCM syndrome scores of participants were significantly reduced following LDBG intervention, LDBG effectively alleviated various symptoms associated with kidney-deficiency and blood-stasis syndrome. Compared with the baseline, LDBG had a long-term effect on kidney-deficiency and blood-stasis syndrome. LDBG is composed of *C elaphus*, *S miltiorrhiza*, *P lobata*, *P lactiflora*, and soybean isoflavones, which collectively work to tonify the kidney and essence, promote blood circulation, and remove blood stasis. According to TCM theory, "shen jing" (kidney essence) nourishes the entire body and supports normal life activities. Studies have shown that *C elaphus* has nourishing properties, improves physical fitness, and comprehensively improves physiological functions.[24] Soybean isoflavones exhibit estrogen-like effects, regulating the neuroendocrine system, preventing and improving osteoporosis, and improving spatial working memory in men.[25,26] Together, these ingredients nourish kidney essence and alleviate symptoms such as waist soreness, leg weakness, memory loss, and hair loss caused by kidney deficiency. *S miltiorrhiza* and its derivatives are widely used in Asia to promote blood circulation, remove blood stasis, and improve microcirculation.[27] *P lactiflora* is known for its ability to improve blood circulation and disperse ecchymosis,[28] and *P lobata* inhibits platelet aggregation, possesses anticoagulant properties, regulates the secretion of vasoactive substances, and protects endothelial function.[29] These components activate blood circulation, remove blood stasis, and improve symptoms such as dark lips and nails, dark tongue, poor complexion, dark menstrual color, and ecchymosis. Each ingredient in LDBG contributes to the improvement of kidney-deficiency and blood-stasis syndrome, supporting internal conditioning that fundamentally strengthens patients' physiques and improves their recovery prospects.

In this trial, a notable finding was that participants in the kidney-deficiency and blood-stasis syndrome group experienced a significantly greater reduction in melasma area and color score compared to those in the non-kidney-deficiency and blood-stasis syndrome group. Regarding long-term efficacy, participants with

Table 8

Intergroup comparison of long-term outcomes of melasma.

	Group A (n = 821)	Group B (n = 143)	*Z*	*P*-value
Total area of melasma (mm^2)				
Mean (SD)	2591.02 (1202.09)	2856.64 (1125.10)	-2.461	.014
Reduced area of melasma (mm^2)				
M (P25, P75)	575.00 (-25.00, 1150.00)	425.00 (12.50, 875.00)	-2.136	.033
Melasma color score				
M (P25, P75)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	-0.195	.845
MASI score				
M (P25, P75)	7.20 (4.80, 8.40)	9.60 (6.00, 12.00)	-6.625	<.001
DLQI score				
M (P25, P75)	7.00 (5.00, 9.00)	7.00 (5.00, 9.00)	-0.298	.766
Reduced DLQI score				
M (P25, P75)	0.00 (0.00, 1.00)	0.00 (-1.00, 1.00)	-2.014	.044

Table 9

Intragroup comparison of long-term efficacy of TCM syndrome.

TCM syndrome score	Group A (n = 821)	Group B (n = 143)
Waist soreness		
Before trial, M (P25, P75)	2.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-17.376	-2.236
P-value	<.001	.025
Leg weakness		
Before trial, M (P25, P75)	2.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-16.474	-2.449
P-value	<.001	.014
Dark tongue		
Before trial, M (P25, P75)	2.00 (0.00, 4.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-17.004	-3.000
P-value	<.001	.003
Tongue ecchymosis		
Before trial, M (P25, P75)	2.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)
Z	-15.982	-3.317
P-value	<.001	<.001
Forgetfulness		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	1.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-18.700	-3.000
P-value	<.001	.003
Hair loss		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	1.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-18.560	-4.690
P-value	<.001	<.001
Dark lips and nails		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-17.616	-2.449
P-value	<.001	.014
Dark complexion		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	1.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-18.728	-4.000
P-value	<.001	<.001
Dark menstruation		
Before trial, M (P25, P75)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)
After trial, M (P25, P75)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)
Z	-17.661	-3.464
P-value	<.001	<.001

kidney-deficiency and blood-stasis syndrome reported higher satisfaction with skin quality improvement than those without this syndrome. In summary, LDBG shows greater efficacy and better long-term results in improving melasma associated with kidney-deficiency and blood-stasis syndrome, LDBG is suitable for melasma patients with kidney-deficiency and blood-stasis syndrome. The results of this study highlight the importance of TCM compound health products tailored to specific syndromes, allowing for more precise syndrome differentiation and targeted healthcare.

Following the intervention, there were no significant differences in general signs (such as heart rate and blood pressure) between the 2 groups. During the trial, 12 participants developed various symptoms, including eczema, dizziness, diarrhea, injuries, colds, cough, swollen and painful gums, recurrent rhinitis, red rashes, and oral ulcers. Of these, 11 adverse events were deemed unrelated to the trial product, while 1 was possibly related, based on the assessments of both the patient and the clinician. The overall incidence of adverse events was 1.2%, with product-related adverse events accounting for 0.1% during the trial. These adverse reactions were effectively managed during follow-up. Overall, LDBG demonstrated a good safety profile.

However, this study has limitations. The TCM classification of melasma focused on only 1 syndrome type, rather than all possible types. Additionally, due to the multicenter nature of the study, the most common measurement methods were used to control variables, which could be refined in future research.

5. Conclusion

LDBG effectively improves melasma, with benefits including tonifying the kidney, nourishing essence, promoting blood circulation, and removing blood stasis. It provides more precise and effective intervention for melasma patients with kidney-deficiency and blood-stasis syndrome, offering long-lasting results with a low risk of recurrence, and demonstrates a high level of safety.

Acknowledgments

We thank all the people who have been involved in our study.

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Table 10

Intergroup comparison of safety outcomes after intervention.

	Group A (n = 856)	Group B (n = 143)	*Z*	*P*-value
Systolic blood pressure (mm Hg)				
M (P25, P75)	134.00 (122.00, 144.00)	132.00 (121.00, 144.00)	-0.444	.657
Diastolic blood pressure (mm Hg)				
M (P25, P75)	77.00 (70.00, 85.00)	78.00 (70.00, 86.00)	-0.741	.458
Heart rate (times/min)				
M (P25, P75)	73.00 (66.00, 81.00)	74.00 (66.00, 80.00)	-0.021	.984

Table 11

Analysis of adverse events between the 2 groups.

Participant number	Adverse event	Time of adverse reaction	Product relevance	Treatment measure	Whether to continue the trial
001015	Eczema	17th day	No	Discontinued product	No
001019	Dizziness	7th day	No	Discontinued product	No
001146	Diarrhea	7th day	No	No	Yes
001147	Injury	8th day	No	No	Yes
001173	Catch a cold	16th day	No	No	Yes
001228	Catch a cold	20th day	No	No	Yes
001230	Cough	10th day	No	No	Yes
001232	Swollen and painful gum	30th day	No	No	Yes
001319	Rhinitis recurrence	15th day	No	No	Yes
002015	Red rash	3th day	Possibly related	Discontinued product	No
002030	Mouth ulcer	7th day	No	Discontinued product	No
002031	Hypothyroidism	60th day	No	Discontinued product	No

References

[1] Ogbechie-Godec OA, Elbuluk N. Melasma: an Up-to-Date comprehensive review. Dermatol Ther (Heidelb). 2017;7:305–18.
[2] Ortonne JP, Arellano I, Berneburg M, et al. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. J Eur Acad Dermatol Venereol. 2009;23:1254–62.
[3] Ghasemiyeh P, Fazlinejad R, Kiafar MR, Rasekh S, Mokhtarzadegan M, Mohammadi-Samani S. Different therapeutic approaches in melasma: advances and limitations. Front Pharmacol. 2024;15:1337282.
[4] Sheth VM, Pandya AG. Melasma: a comprehensive update: part I. J Am Acad Dermatol. 2011;65:689–97.
[5] Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. J Dermatol Sci. 2007;46:111–6.
[6] Freitag FM, Cestari TF, Leopoldo LR, Paludo P, Boza JC. Effect of melasma on quality of life in a sample of women living in southern Brazil. J Eur Acad Dermatol Venereol. 2008;22:655–62.
[7] Sarkar R, Arsiwala S, Dubey N, et al. Chemical peels in melasma: a review with consensus recommendations by Indian pigmentary expert group. Indian J Dermatol. 2017;62:578–84.
[8] Mahajan VK, Patil A, Blicharz L, et al. Medical therapies for melasma. J Cosmet Dermatol. 2022;21:3707–28.
[9] Nomakhosi M, Heidi A. Natural options for management of melasma, a review. J Cosmet Laser Ther. 2018;20:470–81.
[10] Wang Y, Zhao J, Jiang L, Mu Y. The application of skin care product in melasma treatment. Clin Cosmet Investig Dermatol. 2021;14:1165–71.
[11] Zhang Q, Tu Y, Gu H, et al. A cream of herbal mixture to improve melasma. J Cosmet Dermatol. 2019;18:1721–8.
[12] Zhou LL, Baibergenova A. Melasma: systematic review of the systemic treatments. Int J Dermatol. 2017;56:902–8.
[13] Wang Y, Fan X, Qu H, Gao X, Cheng Y. Strategies and techniques for multi-component drug design from medicinal herbs and traditional Chinese medicine. Curr Top Med Chem. 2012;12:1356–62.
[14] Yingli Z, Lei L, Jianjun Z, et al. Determination of Puerarin, Paeoniflorin, and Salvianolic Acid B in Lutai Danshen Baishao Granules by HPLC. World Chinese Med. 2022;17:3139–42.
[15] Xinjuan H, Meiyu L, Qing L, et al. Anti-melasma effect and mechanism of Lutai Danshen Baishao Granules based on Nrf2/Keap1 pathway. China J Tradit Chin Med Pharmacy. 2023;38:3353–7.
[16] Yi Y, Xiao-Guang Z. Study on the rationality of the number of samples selected in the health food human experimentation. J Food Safety Qual. 2018;9:3095–9.
[17] Piyavatin P, Chaichalotornkul S, Nararatwanchai T, Bumrungpert A, Saiwichai T. Synbiotics supplement is effective for Melasma improvement. J Cosmet Dermatol. 2021;20:2841–50.
[18] Bavarsad N, Mapar MA, Safaezadeh M, Latifi SM. A double-blind, placebo-controlled randomized trial of skin-lightening cream containing lycopene and wheat bran extract on melasma. J Cosmet Dermatol. 2021;20:1795–800.
[19] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210–6.
[20] Kim JH, Lee JE, Kim T, et al. 7,3',4'-Trihydroxyisoflavone, a Metabolite of the soy isoflavone daidzein, suppresses α-melanocyte-stimulating hormone-induced melanogenesis by targeting melanocortin 1 Receptor. Front Mol Biosci. 2020;7:577284.
[21] Gao D, Kim JH, Kim CT, et al. Evaluation of anti-melanogenesis activity of enriched pueraria lobata stem extracts and characterization of its phytochemical components using HPLC-PDA-ESI-MS/MS. Int J Mol Sci . 2021;22:8105.
[22] Wen SY, Wu YS, Liu H, et al. Paeoniflorin found in Paeonia lactiflora root extract inhibits melanogenesis by regulating melanin-related signal transduction in B16F10 cells. J Cosmet Dermatol. 2023;22:2824–30.
[23] Cha JY, Yang HJ, Moon HI, Cho Y-S. Branched-chain amino acids complex inhibits melanogenesis in B16F0 melanoma cells. Immunopharmacol Immunotoxicol. 2012;34:256–64.
[24] Kaiyue Z, Xiaoqian Y, Hui Z, et al. Study on Pharmacological Effects of Deer Placenta. Jilin J Chin Med. 2019;39:634–7.
[25] Nakai S, Fujita M, Kamei Y. Health promotion effects of soy isoflavones. J Nutr Sci Vitaminol (Tokyo). 2020;66:502–7.
[26] Thorp AA, Sinn N, Buckley JD, Coates AM, Howe PRC. Soya isoflavone supplementation enhances spatial working memory in men. Br J Nutr. 2009;102:1348–54.
[27] Yang TY, Wei JC, Lee MY, Chen CMB, Ueng K-C. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and tolerability of Fufang Danshen (Salvia miltiorrhiza) as add-on antihypertensive therapy in Taiwanese patients with uncontrolled hypertension. Phytother Res. 2012;26:291–8.
[28] Liu FX, Zhang DP, Ma YM, et al. Effect of Jiawei Tongqiao Huoxue decoction in basilar artery dolichoectasia mice through yes-associated protein/transcriptional co-activator with PDZ-binding motif pathway. J Ethnopharmacol. 2023;314:116599.
[29] Jiang Z, Cui X, Qu P, Shang C, Xiang M, Wang J. Roles and mechanisms of puerarin on cardiovascular disease: a review. Biomed Pharmacother. 2022;147:112655.