

Safety and Feasibility of Compound Glycyrrhizin–Based Combination Therapy for Coexisting Facial Vitiligo and Melasma: A Real-World Retrospective Study

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Background: The coexistence of vitiligo and melasma poses a therapeutic challenge, as interventions for one condition may adversely affect the other. Compound glycyrrhizin (CG), an immunomodulatory agent widely used in vitiligo management in China, has been explored in combination treatment strategies. However, data on its use in patients concurrently affected by melasma are limited.

Methods: This retrospective analysis included 29 adults with facial non-segmental vitiligo and coexisting melasma who received oral CG for 12 months, in combination with topical tacrolimus and phototherapy using melasma shielding. Clinical parameters were evaluated using the Facial Vitiligo Area Scoring Index (F-VASI) and Melasma Area and Severity Index (MASI), along with standardized facial photography and serum chemokine profiling.

Results: Among the 29 patients who underwent combination therapy, the mean baseline F-VASI was 0.99 ± 0.65 , which decreased by $54.93\% \pm 19.99\%$ over 12 months. Initial repigmentation was observed at a mean of 4.17 ± 1.26 months. Melasma severity remained largely stable throughout the treatment period (baseline MASI 16.51 ± 7.31 vs 15.97 ± 7.02 post-treatment). In parallel, serum CXCL10 and CCL20 levels showed a downward trend over time, coinciding with clinical improvement.

Conclusion: In this retrospective real-world cohort, facial vitiligo improved during 12 months of CG-based combination therapy without apparent worsening of coexisting melasma. The regimen was well tolerated, with no severe adverse events. Controlled studies are needed to confirm efficacy and clarify the independent role of CG.

Plain Language Summary: This retrospective real-world study evaluates the efficacy and safety of oral CG in patients with coexisting facial vitiligo and melasma.

Significant repigmentation was achieved in vitiligo without worsening melasma severity, despite concurrent phototherapy.

Serum CXCL10 and CCL20 levels decreased in parallel with vitiligo improvement, supporting an anti-inflammatory mechanism.

CG was well tolerated, with no serious adverse events observed during 12-month follow-up.

Findings support the potential of CG as a safe, integrative approach for managing complex pigmentary disorders.

Keywords: vitiligo, melasma, compound glycyrrhizin, F-VASI, CXCL10, CCL20

Introduction

Vitiligo and melasma are among the most prevalent pigmentary disorders in Asian populations and are frequently encountered in dermatology clinics. Population-based analyses suggest that vitiligo may be associated with an increased likelihood of melasma, although precise estimates of coexisting disease are lacking.¹ Their coexistence—although still

insufficiently quantified—can complicate management because therapies may improve one disorder while aggravating the other. Vitiligo is characterized by well-demarcated depigmented macules due to the selective loss of functional melanocytes. Among available treatments, narrowband ultraviolet B (NB-UVB) phototherapy remains a cornerstone, promoting melanocyte regeneration and repigmentation. In contrast, melasma is an acquired hyperpigmentary disorder affecting sun-exposed facial areas, particularly in individuals with darker skin types. Its pathogenesis involves complex interactions among ultraviolet exposure, hormonal influences, and inflammatory mediators.² Although distinct in pathophysiology, both conditions exert a significant psychosocial burden. Their coexistence poses a unique therapeutic dilemma: NB-UVB, while effective for vitiligo, may aggravate melasma through UV-induced melanogenesis and inflammation, whereas depigmenting agents such as hydroquinone may provoke chemical leukoderma or worsen vitiligo.^{3,4} To date, an optimal treatment strategy for individuals with concurrent vitiligo and melasma remains undefined.

Compound glycyrrhizin (CG), a bioactive formulation derived from licorice root, possesses potent anti-inflammatory and immunomodulatory properties. It has been reported to inhibit cytotoxic T-cell activity, suppress melanocyte apoptosis, and promote melanocyte survival, suggesting potential therapeutic benefits in vitiligo.⁵ While prior studies have explored its use in vitiligo,⁶ no report to date has systematically evaluated its feasibility or safety in patients concurrently affected by vitiligo and melasma, where treatment conflicts often limit therapeutic options. In hyperpigmentation disorders, licorice-derived constituents have been reported to inhibit tyrosinase activity and reduce oxidative stress pathways involved in melanogenesis, which may provide biological plausibility for use in patients with coexisting melasma.^{7,8} In addition, CXCL10 and CCL20 are inflammation-related chemokines implicated in immune cell recruitment and disease activity in vitiligo; therefore, we measured their longitudinal trends as supportive biological correlates alongside clinical outcomes.

The present study retrospectively examined the clinical course and tolerability of oral CG in patients concurrently affected by vitiligo and melasma. Therefore, we conducted a retrospective real-world study to assess the feasibility and safety of a CG-based combination regimen and to characterize longitudinal changes in F-VASI, MASI, and serum CXCL10/CCL20 in adults with coexisting facial non-segmental vitiligo and melasma.

Methods

Study Design and Participants

This retrospective observational study was conducted in the Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China, between January 2021 and May 2025. Clinical records and serum biomarker data were reviewed for 29 consecutive adult patients with coexisting facial non-segmental vitiligo and melasma. Exclusion criteria included segmental or non-facial vitiligo, non-facial melasma, age <18 years, pregnancy or lactation, photosensitivity disorders, systemic immunomodulator use within 3 months, active infection, or incomplete clinical or follow-up documentation. The study protocol was approved by the Institutional Clinical Research Ethics Committee of Huashan Hospital (No. KY-2022-512). Written informed consent for publication of clinical images was obtained from all participants whose photographs are included in this manuscript.

Treatment and Follow-Up Protocol

Patients were treated with oral CG at a dose of 50 mg three times daily for 12 months. Topical 0.1% tacrolimus ointment was applied twice daily to vitiligo lesions only; no melasma-directed topical agents were prescribed during the study period. Sunscreen use was advised as part of routine photoprotection counseling, but it was not prescribed as a protocolized melasma intervention to minimize confounding in melasma assessment. Adjunctive phototherapy was administered using either in-clinic NB-UVB twice weekly or home-based phototherapy devices (NB-UVB or 308-nm excimer light), with treatment frequency determined by routine clinical practice, lesion characteristics, and device availability. Melasma-involved areas were physically shielded at each irradiation session using opaque materials (eg, opaque medical tape/patch or an opaque cut-out template), so that only vitiligo lesions were exposed to irradiation, thereby minimizing incidental UV exposure to hyperpigmented patches.

Patients underwent follow-up every 4 weeks during active disease and every 3 months after vitiligo stabilization. At each visit, standardized facial photographs and clinical assessments were documented.

Clinical Assessments

Vitiligo severity was evaluated using the Facial Vitiligo Area Scoring Index (F-VASI), while melasma severity was measured using the Melasma Area and Severity Index (MASI), using standard scoring methods. Time to initial repigmentation was defined as the interval from treatment initiation to the first clinically detectable perifollicular, marginal (edge-to-center), or diffuse repigmentation. Vitiligo activity signs (including trichrome sign, confetti-like depigmentation, and Koebner phenomenon) were assessed within the facial vitiligo distribution, consistent with the study population and the use of F-VASI as the primary outcome. Clinical photographs used for longitudinal comparison (including those presented in Figure 1) were obtained under Wood's lamp at baseline and follow-up, under consistent imaging settings whenever feasible. All assessments were performed retrospectively based on standardized clinical photographs obtained at each follow-up visit.

Serum Biomarker Measurement

Serum CXCL10 and CCL20 levels were measured at baseline, Month 6, and Month 12. After centrifugation, serum samples were stored at -80°C and analyzed using a commercially available magnetic-bead chemiluminescent immunoassay. All samples were tested in duplicate, and mean values were used.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD or median (IQR), as appropriate. Paired changes between two time points were assessed using the Wilcoxon signed-rank test. Variables measured at three time points (Month 0, Month 6, and Month 12) were analyzed using the Friedman test with Dunn's post hoc test. Categorical variables were summarized descriptively. A two-tailed P value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). A post-hoc power analysis based on the observed paired change in F-VASI from baseline to Month 12 was conducted using G*Power (version 3.1.9.7; Heinrich-Heine-University Düsseldorf, Germany).



Figure 1 Facial vitiligo and melasma before and after treatment under Wood's lamp ($n = 29$). Images were obtained under Wood's lamp at baseline and follow-up.

Results

A total of 29 patients with coexisting facial vitiligo and melasma were included (Table 1). The mean age was 44.21 ± 6.79 years, with a female predominance (90%). At baseline, the mean duration of vitiligo was 16.41 ± 12.28 months, and melasma was 15.79 ± 10.93 months. Among the cohort, 60.8% exhibited trichrome sign, 58.6% had confetti-like depigmentation, and 10.3% showed the Koebner phenomenon at baseline (Month 0). Facial vitiligo showed marked clinical improvement during the follow-up period. The mean baseline F-VASI score was 0.99 ± 0.65 , which decreased by $54.93\% \pm 19.99\%$ at Month 12 (Table 1). The average time to initial repigmentation was 4.17 ± 1.26 months, while stabilization from active to inactive disease occurred at a mean of 3.82 ± 1.74 months. Representative clinical photographs are shown in Figure 1. Consistently, the prevalence of trichrome, confetti-like, and Koebner signs progressively declined over time (Figure 2). Melasma severity remained largely stable throughout the treatment course. The baseline Facial MASI score was 16.51 ± 7.31 , compared to 15.97 ± 7.02 post-treatment, with no significant deterioration despite concurrent phototherapy (Table 1).

Serum chemokine analysis demonstrated significant reductions in inflammatory markers. CXCL10 decreased from 245.97 ± 73.64 at baseline (Month 0) to 211.00 ± 52.52 at Month 6 and 181.44 ± 32.92 at Month 12, and CCL20 decreased from 22.48 ± 5.37 at baseline to 19.05 ± 3.77 at Month 6 and 16.75 ± 2.00 at Month 12, paralleling clinical improvement in vitiligo activity (Figure 3).

Discussion

In this retrospective study, oral compound glycyrrhizin (CG) was administered as part of a combination regimen in patients with coexisting facial vitiligo and melasma. Over the course of treatment, a majority of patients exhibited improvement in vitiligo activity, without clinical exacerbation of melasma. In general, repigmentation is most commonly perifollicular, and may also present as marginal (edge-to-center) or diffuse repigmentation. These findings are clinically relevant, especially in Asian populations where both pigmentary disorders are prevalent and often coexist. Notably, no severe adverse events were observed during the follow-up period, suggesting that CG may serve as a well-tolerated component within a multimodal treatment approach.

The rationale for using CG in vitiligo stems from its reported immunomodulatory and anti-inflammatory properties. Vitiligo pathogenesis is largely driven by autoimmune mechanisms, including cytotoxic T-cell-mediated melanocyte destruction and elevated proinflammatory cytokines such as interferon- γ and TNF- α .⁹ CG has been proposed to modulate these pathways by suppressing NF- κ B signaling, enhancing regulatory T-cell (Treg) function, and mimicking glucocorticoid receptor activity with fewer systemic side effects.^{10,11} Prior research has similarly reported beneficial outcomes

Table 1 Baseline Characteristics and Outcomes (n=29)

	Mean/n	SD/%
Age	44.21	6.79
Gender		
Female	26	90%
Male	3	10%
Vitiligo		
Disease duration of vitiligo (month)	16.41	12.28
Baseline facial VASI	0.99	0.65
Facial VASI improvement (%)	54.93	19.99
Treatment duration from active to stable (month)	3.82	1.74
Time to initial repigmentation (month)	4.17	1.26
Melasma		
Disease duration of melasma (month)	15.79	10.93
Baseline facial MASI	16.51	7.31
Post-treatment facial MASI	15.97	7.02
Topical-tacrolimus	29	100%

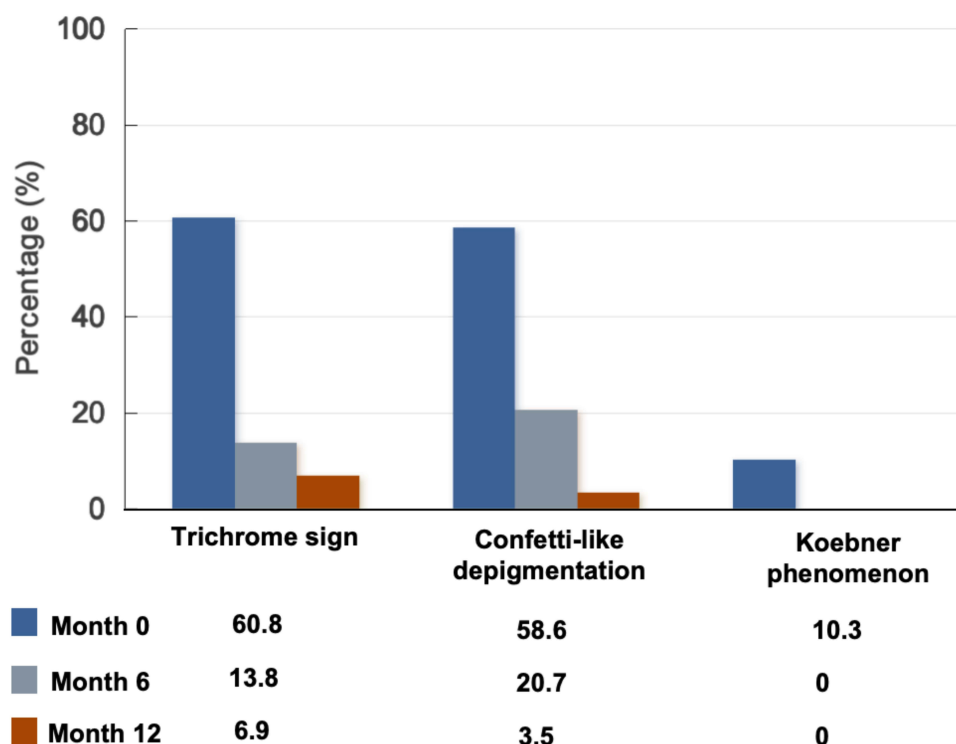


Figure 2 Longitudinal changes in clinical activity signs of facial vitiligo during follow-up (n = 29). The prevalence of trichrome sign, confetti-like depigmentation, and Koebner phenomenon declined from Month 0 to Month 6 and Month 12.

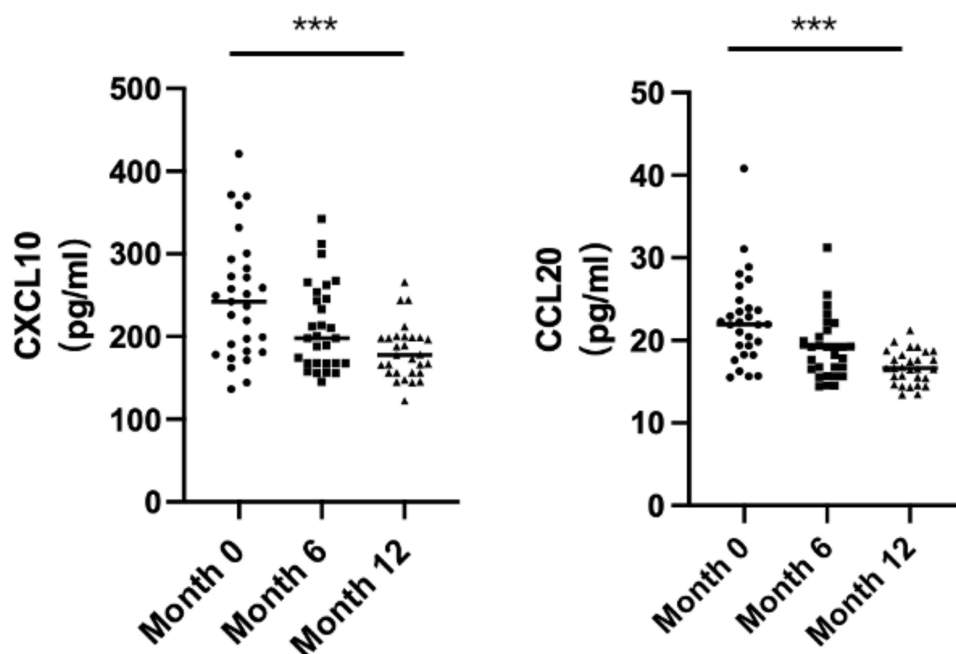


Figure 3 Longitudinal trends of serum CXCL10 and CCL20 (n = 29). Serum levels were measured at baseline (Month 0), Month 6, and Month 12 and are presented as mean $\pm$ SD. *** indicates $P < 0.001$ for overall differences across time points.

with CG in vitiligo management.⁶ Although these mechanisms provide a plausible theoretical basis, the precise contribution of CG to clinical improvement in our cohort cannot be definitively determined due to the retrospective design and concurrent use of other therapies.

Importantly, no cases of melasma worsening were documented during the treatment period, even in patients undergoing adjunctive phototherapy. Although licorice-derived compounds have been reported to have anti-inflammatory and pigment-modulating effects, clinically meaningful melasma lightening often requires sustained melasma-directed interventions (eg, strict photoprotection and topical depigmenting regimens), which were not protocolized in our study to minimize confounding and potential irritation in patients with concomitant vitiligo. Given the retrospective design and absence of a control group, melasma outcomes should be interpreted cautiously, and “no worsening” may still be clinically meaningful in patients receiving phototherapy primarily for vitiligo.

Consistent with previous reports on phototherapy-based management of facial vitiligo, repigmentation in this study was typically noted within approximately four months of treatment initiation.¹² More than half of the patients achieved moderate to marked improvement in facial VASI scores over 12 months. Melasma severity was largely stable overall; any small numerical changes in MASI were not the primary focus of this retrospective cohort and should not be over-interpreted without formal statistical confirmation. The treatment regimen was generally well tolerated, with only occasional mild gastrointestinal discomfort or fatigue reported. These findings support the potential value of CG as part of an integrated treatment strategy for complex pigmentary disorders.

Several clinical insights can be drawn from this cohort. First, the coexistence of melasma may reflect areas of relatively preserved melanocyte activity, which could serve as a favorable substrate for repigmentation in vitiligo.¹³ Second, CG-based regimens, especially when combined with topical tacrolimus and photoprotection, may offer a practical and safer alternative for patients who are either intolerant to or reluctant to pursue phototherapy. This may be particularly relevant in resource-limited settings or among individuals with darker skin types at risk of post-inflammatory hyperpigmentation.¹⁴

Nonetheless, this study has several limitations. The sex distribution was imbalanced (female predominance), which may reflect the melasma-overlap population and real-world referral patterns, and limits generalizability. Its retrospective nature, limited sample size, and lack of a control group preclude causal inference. The absence of objective tools for pigment quantification and reliance on photographic assessments may introduce subjective bias. Furthermore, the independent effect of CG cannot be isolated due to concurrent use of tacrolimus and phototherapy in most cases, and phototherapy delivery was heterogeneous (in-clinic NB-UVB versus home-based devices), which may confound outcome interpretation. Future prospective, randomized controlled studies with standardized pigment evaluation tools and longer follow-up durations are warranted to validate these preliminary observations and clarify the specific role of CG in modulating pigmentary balance.

Conclusions

In conclusion, CG-based combination therapy appeared feasible and well tolerated in patients with coexisting facial vitiligo and melasma, with improvement in vitiligo and no apparent worsening of melasma. Larger controlled studies are needed to confirm efficacy and clarify the independent contribution of CG.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Clinical Research Ethics Committee of Huashan Hospital (Approval No. KY-2022-512). Written informed consent was obtained from all participants prior to enrollment.

Consent

Written informed consent was obtained from all participants after the purpose and procedures of the study were explained.

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Author Contributions

Zhengzhou Shi and Yijian Zhu designed the study, conducted clinical assessments, collected and analyzed the data, and drafted the manuscript. Qianqian Wang and Li Zhang contributed to laboratory testing, data verification, statistical analysis, and manuscript revision. Suqing Liu and Min Jiang assisted with patient management, follow-up, and clinical supervision. Leihong Xiang oversaw the study design, provided critical guidance throughout the project, and approved the final manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest.

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