Review Article

Topical Integrative Approaches to Vitiligo: A Systematic Review

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Relevance

Vitiligo is a common skin depigmentation disorder caused by the autoimmune destruction of melanocytes, resulting in non-scaly, white macules and patches. Vitiligo does not pose a significant health threat, although it can greatly impair one's self-esteem, social life, and quality of life. First-line treatment options include topical steroids, topical calcineurin inhibitors, and phototherapy. With the emergence of the first FDA approved topical, ruxolitinib, the role of emerging topicals has been more prominent in the integrative space. As a result, numerous topical integrative and herbal approaches are available for the management of vitiligo, although the efficacy of many formulations has largely been anecdotal.

Objective

The purpose of this review is to systematically review literature assessing the efficacy of topical integrative approaches for the treatment of vitiligo.

Methods

A PubMed and Embase search for clinical studies were performed using the following keywords: ("Integrative" OR "alternative" OR "complementary" OR "natural" OR "herbs" OR "cosmeceuticals" OR "botanicals" OR "Ayurveda" OR "calcipotriol" OR "vitamin D" OR "antioxidant" OR "Janus Kinase") AND "Vitiligo" AND "Topical." Steroids, topical calcineurin inhibitors, and topicals applied simultaneously to oral treatment were excluded; vitamin D analysis was limited to topical monotherapy.

Results

Forty-eight clinical trials and case reports were included in the systematic review. Studies have assessed the efficacy and/or safety of topical *Shvitrahara lepa*, *cucumis melo*, curcumin, herbal extracts, vitamin D3 analogues, psoralen, *Psoralea corylifolia*, khellin, topical antioxidants, and janus kinase (JAK) inhibitors.

Conclusion

The results demonstrate the clinical utility of many integrative topical formulations, either in isolation or in combination with phototherapy. Numerous integrative topical formulations are available for the treatment of vitiligo including *Shyitrahara lepa*, *Cucumis melo*, curcumin, herbal extracts, vitamin D3 analogues, psoralen, *Psoralea corylifolia*, khellin, topical antioxidants, and JAK inhibitors. Topical treatments yielded different responses and may be associated with local skin reactions. Relatively few topical treatments were assessed in isolation, and synergistic effects are depicted by many studies. Of all the topicals that were reviewed, ruxolitinib (JAK inhibitor) has the most robust clinical evidence and is FDA-approved.

INTRODUCTION

Vitiligo is a relatively common skin depigmentation disorder with a global prevalence of 0.5-2%.[1] Caused by autoimmune destruction of melanocytes, it is characterized by distinct, non-scaly, white macules and patches with equal distribution across genders and ethnic groups.[2] Despite equal prevalence, the emotional impact of vitiligo can be greater among certain racial groups, as depigmented lesions are most visible among those with darker skin tones. Presentations vary, although it commonly presents sym-

metrically with high incidence on periorificial skin in addition to other sites such as elbows, wrists, inguinal folds, knees, and ankles.[3] Vitiligo can be categorized as generalized, segmental, or acrofacial, with further subtypes including inflammatory and ponctué. Generalized vitiligo, also known as bilateral or nonsegmental vitiligo, is more common and characterized by progressive destruction of skin and mucosal melanocytes bilaterally, potentially involving the eyes and ears. Localized vitiligo can be further subdivided into segmental and focal, with segmental vitiligo characterized by a dermatomal distribution that typically does not cross the midline.[4] Acrofacial vitiligo is confined to the head and distal extremities, with too many lesions to be categorized as focal.[3] Inflammatory vitiligo is a rare subtype of vitiligo in which depigmented patches are surrounded by raised erythema and inflammation,[5] and vitiligo ponctué refers to vitiliginous lesions presenting as multiple 1-to-5 mm depigmented macules, mimicking confetti.[6] A prospective observational study from 2005-2007 including 114 children with vitiligo found nonsegmental vitiligo to be associated with a greater number of lesions and greater body surface area involvement.[7] Furthermore, a more frequent progression of disease and a higher incidence of Koebner phenomenon were observed in children with nonsegmental vitiligo. In contrast, progression of segmental vitiligo often occurs in the first year, with depigmentation ceasing after 1.5-2 years in most patients.[8]

CD8+ cytotoxic T cells, regulatory T cells, and inappropriately activated cutaneous memory T cells are implicated in melanocyte destruction,[9] although a variety of other factors are implicated in pathogenesis for some individuals. For example, specific human leukocyte antigen- (HLA-) A alleles are associated with vitiligo. A 2016 systematic review including 3,042 patients and 5,614 controls found 33 HLA-A alleles reported, three of which were significantly associated with increased vitiligo risk (HLA-A*02, A*33, and Aw*31), two of which were significantly associated with decreased risk (HLA-A*09 and Aw*19), with the remaining 28 unassociated.[10] Yet, vitiligo is a polygenic, multifactorial disorder, and genome-wide associated studies have described approximately 50 genetic loci associated with increased vitiligo risk.[11] Proteins encoded by such genes include those involved in immune regulation, cellular apoptosis, and melanocyte regulation. In addition, vitiligo can arise following medication use, such as immunotherapy for melanoma and nonmelanoma metastatic cancers.[12,13] The diagnosis of vitiligo is often made clinically. In addition, vitiligo can be diagnosed with a Wood's lamp or skin biopsy. A Wood's lamp provides long-wave ultraviolet light to detect skin fluorescence.[14] Under normal conditions, the light will appear violet, and the skin will not fluoresce. However, changes in skin pigmentation can promote color change under a Wood's lamp. Wood's lamp use for the diagnosis of vitiligo is especially useful for patients with lighter skin types in which depigmentation may be more difficult to observe with the naked eye. However, other skin conditions may elicit fluorescence variation with a Wood's lamp.[15] In addition, skin biopsies can be obtained which will exemplify absent melanocytes, in contrast to malfunctioning melanocytes characteristic of other skin conditions. Common differential diagnoses for vitiligo include tuberous sclerosis complex, tinea versicolor, *Pityrosporum* folliculitis, tinea capitis, erythrasma, porphyria cutanea tarda, pityriasis alba nevus depigmentosus, nevus anemicus, idiopathic guttate hypomelanosis, piebaldism, progressive maculra hypomelanosis, melasma, corneal abrasions, and solar lentigines.[15]

Comorbidities may include various autoimmune disorders, thyroid disease, pernicious anemia, and Addison's disease. A 2015 cross-sectional study found almost 20% of vitiligo patients to have at least one comorbid autoimmune disease.[16] In comparison to the general population, patients with vitiligo exhibited a higher prevalence of thyroid disease, alopecia areata, inflammatory bowel disease, pernicious anemia, lupus, Guillain-Barre syndrome, discoid lupus, linear morphea, myasthenia gravis, and Sjogren syndrome.[16] Complications of vitiligo can involve sunburns, iritis of the eye, and loss of cochlear melanocytes with subsequent hearing loss.[17]

Furthermore, vitiligo can greatly impair one's self-esteem, social life, and quality of life,[18] increasing the importance of effective treatment. A study involving one hundred patients with vitiligo found a greater proportion of patients with involvement of exposed areas to complain of unpleasant emotions than those with involvement of unexposed areas (88% vs. 27%).[19] There is no cure for vitiligo, although first-line options for management typically include steroids, topical calcineurin inhibitors, and phototherapy. The emergence of ruxolitinib offers the first FDA-approved topical agent for vitiligo. Integrative therapies involve the use of multiple topicals that may include pharmaceutical, herbal extract, and phytochemical ingredients. Integrative therapies appear to be more effective than single therapies, although they are associated with more adverse effects.[20] Treatment modalities are often selected based on individual patient characteristics such as disease severity and disease activity. Patients with rapidly progressive vitiligo may consider systemic glucocorticoids or immunosuppressants, along with an increased risk for potential side effects. Phototherapy can inhibit disease progression via induction of T-cell apoptosis, downregulation of inflammatory cytokines, upregulation of interleukin-10, and stimulation of melanocyte migration and proliferation.[21] Although different wavelengths are available, narrowband ultraviolet-B (NB-UVB) is considered the most effective and safest phototherapy option. Localized vitiligo can be managed via topical corticosteroids, topical calcineurin inhibitors, and targeted phototherapy.

Beyond these conventional treatment options, integrative approaches for the management of vitiligo are used globally by both patients and clinicians. In 2007, a questionnaire study found that 65% of responding patients at a Nigerian dermatology clinic had applied some form of herbal remedy before presenting to the clinic, including patients with vitiligo.[22] Similarly, a questionnaire study conducted in Saudi Arabia found that 40% of 1,901 respondents were complementary and alternative medicine users.[23] The study did not specify the number of vitiligo

patients among the respondents; however, among complementary and alternative medicine users, vitiligo was predominantly treated with black seeds, honey, and Zamzam water (holy water from Makkah). In addition, a 2021 review found that Persian medicine scholars used 50 different medicinal plants to treat vitiligo, many of which have been shown to have immune-regulating properties.[24] Lastly, a review on traditional Siddha medicines discussed Cassia senna leaves, *Ixora arborea* Roxb root and bark, *Lannea coromandelica* bark, and *Rhinacanthus nasutus* leaves in the context of vitiligo treatment. However, literature documentation of such use often failed to include controlled, clinical evidence, and thus efficacy is largely anecdotal.[25]

In addition to the ample anecdotal evidence of successful integrative approaches for vitiligo, researchers have assessed the efficacy of various interventions. A prior systematic review assessed the efficacy of nutrition, supplement, and herbal-based oral interventions for the treatment of vitiligo.[26] Oral phenylalanine with UVA therapy, oral *Ginkgo biloba* monotherapy, and oral *Polypodium leucotomos* with phototherapy or photochemotherapy demonstrated the greatest efficacy. A wide variety of herbal and traditional topical formulas have similarly been utilized in the treatment of vitiligo; studies have specifically assessed the efficacy of topical *Shvitrahara lepa*, *Cucumis melo*, curcumin, herbal extracts, vitamin D3 analogues, psoralen, *Psoralea corylifolia*, khellin, honey bee, *Allium cepa*, *Avena sativa*, and topical antioxidants. In the pharmaceutical space, topical janus kinase (JAK) inhibitors and bimatoprost have emerged for the management of vitiligo. Many topical treatments are administered in conjunction with phototherapy, and some topical treatments depict a synergistic effect with oral or systemic approaches. This review aims to review and summarize the topical therapies for vitiligo in the integrative space. We have elected to focus the pharmaceutical discussion on bimatoprost and ruxolitinib given the prevalence of steroid phobia. In particular, ruxolitinib represents the only FDA-approved non-steroidal approved for the topical treatment of vitiligo. The calcineurin inhibitors and topical steroids have been discussed extensively elsewhere and are not discussed here.[27]

METHODS

A PubMed and Embase search (**Figure 1**) for articles with the following keywords was performed: ("Integrative" OR "alternative" OR "complementary" OR "natural" OR "herbs" OR "cosmeceuticals" OR "botanicals" OR "Ayurveda" OR "calcipotriol" OR "vitamin D" OR "antioxidant" OR "Janus Kinase") AND "Vitiligo" AND "Topical." Results were filtered to only include clinical trials with human subjects. Fifty-two (52) PubMed and two-hundred eighty-one (281) Embase articles resulted. Article titles and abstracts were reviewed by three reviewers; those with relevant subject matter were retrieved for full-text review. In addition, their associated references were scanned for relevant reports (13). Steroidal topical treatments and calcineurin inhibitors were excluded, in addition to integrative topical therapies that were administered simultaneously to oral treatment. Vitamin D analysis was limited to topical monotherapy. Forty-eight (48) clinical studies and case reports were included in the efficacy analysis and are listed in **Table 1**.

RESULTS

SHVITRAHARA LEPA

Ayurveda is an alternative medicine system heavily practiced in India and Nepal. The doshas, which represent the three physiological energy descriptors, are the primary determinants of health and disease in Ayurveda.[28] Ayurvedic medicine encompasses a variety of holistic practices and treatments, many of which are botanically based, and is widely used in the treatment of vitiligo.

Shvitrahara lepa is an Ayurvedic topical ointment that has been utilized in conjunction with an oral decoction known as *Shvitrahara kashaya* for the treatment of vitiligo. A decoction is an extract prepared via boiling herbal material. The ointment contains Haratala, an arsenic containing compound with immunomodulatory properties, which has been proposed to prevent the self-destruction of melanocytes in patients with vitiligo.[29] In 2011, Dhanik et al conducted a randomized, controlled clinical trial to assess the role of *Shvitrahara kashaya* and *Shvitrahara lepa* on lesion characteristics in patients with either segmental or generalized vitiligo.[29] Three treatment groups were included in the analysis: Group I (n = 25) received both the decoction and ointment, Group II (n = 15) received just the ointment, and Group III (n = 10) received oral psoralens and UVA therapy (PUVA) to serve as a conventional medical standard. Those receiving only topical *Shvitrahara lepa* (Group II) experienced a mean reduction in vitiliginous lesion body surface area of 0.41 ± 0.28 cm^2 ($p < 0.001$). Although this result is statistically significant, the mean reduction in area of vitiliginous lesions in both Group I and Group III were significantly greater than that in Group II. Similarly, although Group II experienced an average decrease in lesion number of 3.27 ± 0.96 ($p < 0.001$), the mean change in lesion number was significantly greater in both Group I and Group III. There was no significant difference in the reduction in the number of lesions between Group I and III, although Group III subjects experienced a significantly greater reduction of total surface area than both Group I and II.

Eight out of 10 Group III subjects developed sunburn, severe itching, and gastric upset upon taking oral psoralen. The mild improvement in lesion surface area and number among subjects receiving solely topical *Shvitrahara lepa* suggests that the topical ointment has synergistic effects on lesion characteristics in patients with vitiligo when combined with oral *Shvitrahara kashaya*. One of the concerns that was not addressed by the authors is the potential for arsenic exposure and toxicity with long-term use, as long-term arsenic exposure is associated with several medical issues such as the development of cutaneous malignancies.

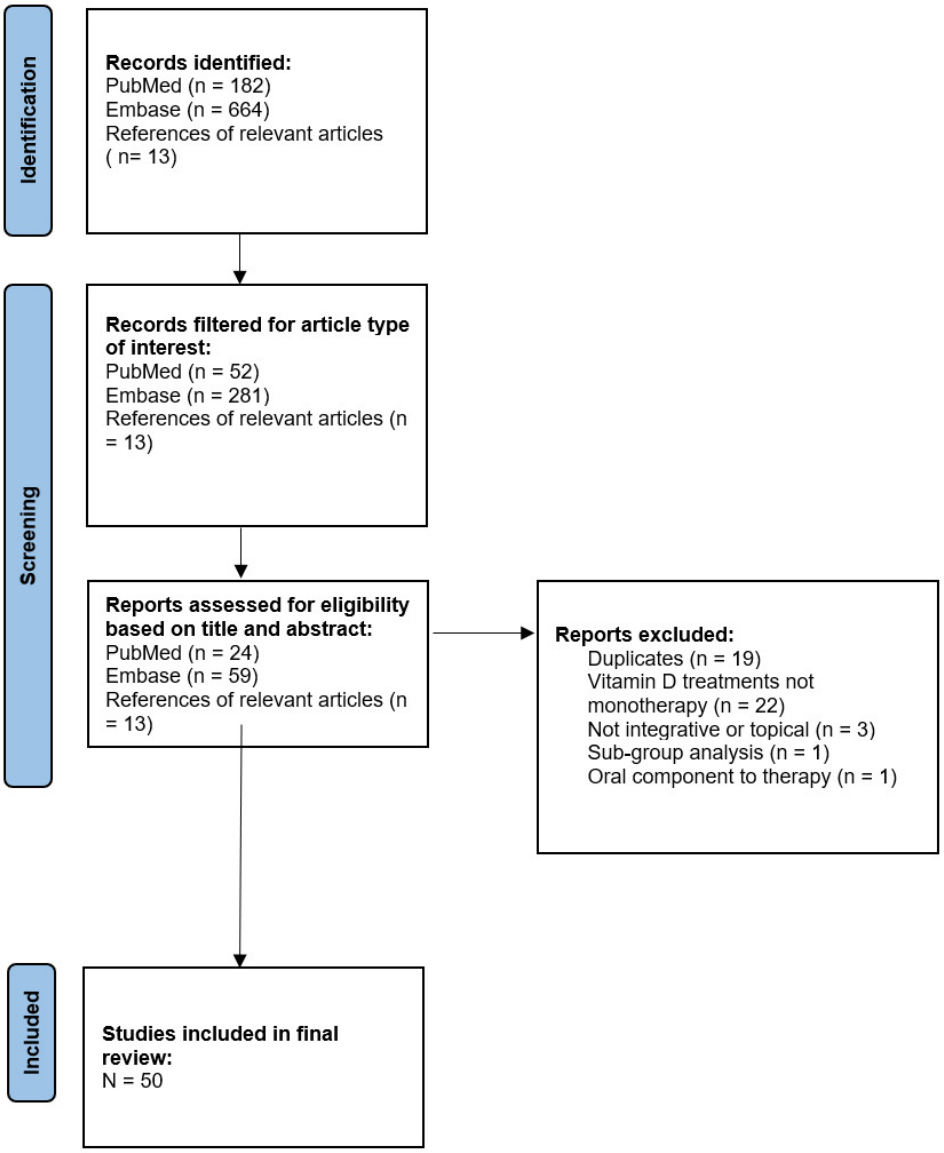

Figure 1. PRISMA flow-diagram of the literature search strategy.

The search strategy conducted with PubMed and Embase yielded 182 and 664 records, respectively. Filtering for clinical studies with human subjects resulted in 52 reports from PubMed and 281 reports from Embase. Title and abstract review resulted in 24 PubMed reports and 58 Embase reports. 19 duplicates were removed, and 27 reports were excluded based on various criteria. In addition, the references of relevant articles were scanned for additional reports, of which 13 were included in the final review. Fifty (50) clinical studies and case reports were included in the systematic review.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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CUCUMIS MELO

Cucumis melo, also known as muskmelon, is a plant species of the Cucurbitaceae family. Extracts are rich in antioxidants and contain high superoxide dismutase (SOD) activity which help counteract the oxidative stress implicated in melanocyte deconstruction.[30] Two studies have assessed the efficacy of a topical gel containing *Cucumis melo*, SOD, and catalase in the treatment of vitiligo.

Yuksel et al evaluated the change in surface area of vitiligo patients receiving either NB-UVB (n = 15) or NV-UVB with topical *Cucumis melo* superoxide dismutase and catalase gel (n = 15). However, they found no significant difference in healing percentages of measured areas between each group.[31] Similarly, a 2012 study assessed the efficacy of the gel alone against a placebo gel and found no significant changes in lesion area and perifollicular pigmentation in both groups.[32] Both pilot studies suggest that the combination gel containing *Cucumis melo*, superoxide dismutase, and catalase is not beneficial or effective in the topical treatment of vitiligo.

A distinct topical formulation containing *Cucumis melo* extract, acetylcysteine, and phenylalanine was assessed in an open observational study.[33] The study included four treatment groups: Group A was treated with the gel alone, twice daily; Group B was treated with UVB phototherapy alone, once weekly; Group C was treated with twice-daily topical gel and once weekly UVB phototherapy; Group D was treated with clobetasol propionate 0.05% ointment, a class 1 topical corticosteroid, twice daily. Greater than 75%

Table 1. Summary of Integrative Topical Treatments for Vitiligo.

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
Shivitrahara lepa (Group II)	6 months	RCT	-Shivitrahara lepa and oral Shvitrahara Kashaya (Group I) -PUVA (Group III)	n = 25 (Group I) n = 15 (Group II) n = 10 (Group III)	-VSA Reduction -Lesion Number	-Group II experienced a mean reduction in VSA of 0.41 ± 0.28 cm^2 ($p < 0.001$) -Group II experienced a mean reduction in lesion number of 3.27 ± 0.96 ($p < 0001$) -Mean reduction in VSA and in lesion number in Group I/III were significantly greater than II -8/10 Group III subjects developed adverse reactions	-Frequency of topical application not specified	Dhanik et al (2011)
Gel containing Cucumis melo, SOD, catalase with NB-UVB	6 months	Comparative study	NB-UVB monotherapy	n = 15 in each treatment group	-VSA Reduction	-No significant difference in VSA reduction between each group	-Frequency of NB-UVB not specified	Yuksel et al (2009)
Gel containing Cucumis melo, SOD, catalase and sun exposure	Twice daily for 6 months	RCT, R/L controlled	Placebo gel	n = 23	-VSA Reduction -Perifollicular pigmentation	-No significant changes in lesion area and perifollicular pigmentation in both groups		Naini et al (2012)
Formulation containing Cucumis melo extract, acetylcysteine, phenylalanine (Group A)	All topicals administered twice daily for 12 weeks	Open-label study	-Once Weekly UVB (Group B) -Topical gel and once weekly UVB (Group C) -Clobetasol propionate 0.05% ointment (Group D)	n = 149	% Repigmentation	- >75% repigmentation: 38.4% Group A, 61.1% Group B, 73.5% Group C, 56.2% Group D -Less than 10% of subjects in each group depicted <25% repigmentation		Buggiani et al (2012)
Tetrahydrocurcuminoid cream and NB-UVB (Group A)	-Twice daily for 12 weeks; NB-UVB twice weekly	RCT, preliminary	NB-UVB monotherapy (Group B)	n = 10	% Repigmentation, converted into scores	-Both treatment groups depicted significantly improved repigmentation -Significant inverse association between repigmentation and duration of disease in both groups -From week 8 onwards, repigmentation scores in Group A were better than Group B ($p = 0.078$)		Asawanonda and Klahan (2010)
Vitilinex (herbal bio-actives) (Group A)	12-weeks	RCT	-Vitilinex with UVB combination treatment (Group B) -NB-UVB phototherapy alone (Group C)	n = 62 randomized equally to each treatment group	% Repigmentation	- >75% repigmentation: 39% Group A, 69.5% Group B, 37.5% Group C -50-75% repigmentation: 26% Group A, 17.5% Group B, 25% Group C - 5-50% repigmentation: 22% Group A, 8.7% Group B, 18.75% Group C - <25% repigmentation: 13% Group A, 4.3% Group B, 18.75%	-Frequency of topical application not specified	Van et al (2019)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						Group C - >50% repigmentation: 65% Group A, 87% Group B, 62.5% Group C		
Nigella sativa seed oil	Twice daily for 6 months	Open-label study		n = 33	% Repigmentation	-10/23 (43.5%) with facial involvement achieved repigmentation ≥ 50%; significant pre- and post-treatment difference in these 10 (p = 0.001) -7/16 (43.8%) with hand involvement achieved repigmentation ≥ 50%; significant pre- and post-treatment difference in these 7 (p = 0.005) -7/8 with genital involvement achieved repigmentation ≥ 50%; significant pre- and post-treatment difference in these 7 (p = 0.004)		Sarac et al (2019)
Calcipotriol 50 µg/g	-Twice daily topical monotherapy -Combination treatment included PUVA 3x weekly - 3-9 months therapy, mean = 6 months	Open study	Combination with oral or topical PUVA	n = 22 (topical monotherapy) n = 4 (combination)	VSA Reduction	-3/4 (75%) of combination therapy showed good response -5/22 (23%) of monotherapy showed >90% improvement -7/22 (32%) showed 50-90% improvement -5/22 (23%) showed 30-50% improvement -5/22 (23%) showed <30% improvement	-Duration of therapy was not controlled -Only four subjects received combination	Ameen et al (2001)
Calcipotriol	-Daily topical application -3-6 months, mean = 3.9 months	Prospective, R/L comparative, open study	Untreated control lesion	n = 24	% Repigmentation	-No significant difference between treated and control -21/24 (87.5%) had no repigmentation -3/24 (12.5%) had partial repigmentation Of improved: -1/3 had repigmentation on the treated lesion and no repigmentation on the untreated control -2/3 had repigmentation (20% and 30%) on treated but spontaneous repigmentation of (20% and 10%) of untreated control	-% Calcipotriol not specified -Duration of therapy was not controlled	Chiavérini et al (2002)
Calcipotriol 50 µg/g (Cal)	Twice daily for 4 months	Open, comparative clinical trial	Clobetasol 0.05% (Clo)	n = 22 Cal n = 20 Clo	% Repigmentation	-Significantly greater repigmentation with Clobetasol than Calcipotriol		Köse et al (2002)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						-0-25%: 10/22 Cal, 3/20 Clo -25-50%: 8/22 Cal, 4/20 Clo -50-75%: 4/22 Cal, 5/20 Clo -75-100% 0/22 Cal, 4/20 Clo -100% 0/22 Cal, 4/20 Clo -4/22 Cal: transient irritation and erythema -7/20 Clo: transient erythema, acneiform papules, telangiectasia of skin		
Calcipotriol	3 months, frequency not specified	Open, comparative clinical trial	-Topical betamethasone -Topical PUVA -NB-UVB	n = 34	Repigmentation	-Calcipotriol repigmentation in 1/10 cases (10%) -Betamethasone repigmentation in 3/11 cases (27%) -No repigmentation in topical PUVA (0%) -NB-UVB repigmentation in 7/13 cases (53%)	-Abstract	Uksal et al (2002)
Calcipotriol 50 µg/g cream or ointment	Twice daily for 6 months	Prospective, observation study		n = 14, aged 3-12 -9/14 received cream -5/14 received ointment	VSA Reduction	-10/14 showed improvement -4/14 showed no response -Better results with ointment than cream Among responders: -3 showed complete resolution -4 showed 50-80% improvement -3 showed 30-50% improvement		Gargoom et al (2004)
Calcipotriol 0.005% (Group II)	-Twice-daily for 3 months -Group III: betamethasone in the morning, calcipotriene in the evening	RCT	-Betamethasone 0.05% (Group I) -Combination Therapy (Group III)	n = 15 in each treatment group	% Repigmentation	-No patients achieved >75% -50-75%: 2/15 GI, 1/15 GII, 4/15 GIII -25-50%: 7/15 GI, 5/15 GII, 7/15 GIII -Combined therapy had significantly faster repigmentation onset, better stability, less side effects -Side effects (atrophy, lesional burning) were more common in Group I than II/III ($p < 0.05$)		Kumaran et al (2006)
Calcipotriol	-Twice-daily for 6 months -Combination treatment included PUVA 3x weekly	RCT	Combination with PUVA	n = 30 in each treatment group	% Repigmentation	Group I: 1/6 (16.7%) responded, all with <50% repigmentation Group II: all patients responded. 70% showed >75% repigmentation	% Calcipotriol not specified	Shehzad et al (2007)
Calcipotriol 0.005% (R side)	5 months	Case report, R/L comparative	Pimecrolimus cream 1% (L side)	n = 1	Clinical improvement of vitiliginous lesions	-Significant improvement with the two agents, especially pimecrolimus -Pimecrolimus was more effective -Re-pigmentation started second	-Measurements of surface area reduction not included -Frequency of topical	Bilaç et al (2009)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						month	application not specified	
Calcipotriene 0.005% (Group C)	-Twice-daily for 5 months -Group A: betamethasone in the morning, calcipotriene in the evening	RCT	-Betamethasone dipropionate 0.05% (Group A) -Combination Therapy (Group B)	n = 20 in each treatment group	VSA Reduction	-Final follow-up depicted 80%, 75%, 65% vitiliginous lesion reduction in groups A, B, C, respectively -Significant difference in lesion reduction among the groups, ANOVA ($p < 0.05$)		Alam et al (2014)
Calcipotriol 0.005% (Group A)	Twice daily for 3 months treatment duration, final follow-up at 4 months	RCT	-Betamethasone dipropionate 0.05% (Group B) -Combination Therapy (Group C)	n = 53 in each treatment group	VASI	-Mean change of VASI: 38.77% Group C, 26.23% Group B, 18.30% Group A -Mean change in VASI was statistically greater in group C ($p = 0.008$) -Side effects included erythema, burning, atrophy, acneiform eruption, with no significant differences between groups		Zahoor et al (2017)
Tacalcitol 0.0002%	Once daily for 1 month	Case report	Tacalcitol 0.0002% and 30 minutes of sunlight exposure	n = 1	Clinical improvement of vitiliginous lesions	The region treated with combination therapy healed completely, while the region treated with ointment alone did not improve		Amano et al (2008)
Tacalcitol 20 μg/g	Once daily for 9 months	Case report		n = 1	Clinical observation of repigmentation	Promoted moderate repigmentation of patient's vitiligo lesions but also hyperpigmentation of freckles	-Measurement of degree of repigmentation not included	Oiso and Kawada (2012)
Topical psoralen and UVA	4 months	Open-label study	UVB radiation	n = 281	% Repigmentation	-46% treated with topical PUVA showed repigmentation after 4 months -52% in the UVB group showed repigmentation after 4 months -In the second group -Fewer side effects with UVB compared to topical PUVA	-Frequency of treatment not specified	Westerhof and Nieuweboer-Krobotova (1997)
Ointment containing Psoralea corylifolia seed powder	Once daily for 12 weeks	Open-label, self-controlled study	No treatment, control	n = 20	VSA Reduction, documented with 20-megapixel camera	-Pre- and post-treatment pigmentation differences were statistically significant for small, circular vitiligous lesions ($p \leq 0.05$)		Hussain et al (2016)
Psoralea corylifolia and sunlight	Once daily for 6 months	Open, randomized pilot trial	-Indicated homeopathic treatment -Combination treatment	n = 20 in each treatment group	-VASI -VitilQoL -DLQI	-Intra-group changes were significant in all 3 outcomes ($p < 0.001$) -All treatment regimens were equally effective and safe	-5 patients dropped out	Mir et al (2022)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						-Significant differences in groups for VitiQoL total scores, favoring Psoralea corylifolia and combination treatment		
Khellin gel (water, 2-propanol, propylene glycol, khellin)	Applied 30 minutes before UVA exposure for 6 months	Open-label, self-controlled study	Water, 2-propanol, propylene glycol)	n = 36	% Repigmentation	-Repigmentation >10% occurred in 86.1% of khellin-treated sides, in contrast to 66.6% in placebo-treated sides ($p < 0.01$) -Better results in younger patients with shorter disease duration	-Frequency of UVA exposure not specified	Orecchia et al (1998)
Topical khellin with UVA (KUVA)	3-5 weekly treatments	Pilot study	Systemic PUVA	n = 33	% Repigmentation	-Local KUVA required longer duration and higher UVA doses -Better KUVA results with younger patients -No adverse effects with KUVA -PUVA adverse effects included erythema, itching, GI disturbances	-Treatment duration not consistent -Some subjects had to interrupt therapy course for some time (1-3 months)	Valkova et al (2004)
Khellin 4% with monochromatic excimer light 308 nm and vitamin E (Group II)	Once weekly phototherapy for 12 weeks	Open-label, controlled study	-Weekly light therapy and oral vitamin E (Group I) -Oral vitamin E (Group III)	n = 16 in each treatment group	% Repigmentation	-Excellent repigmentation: 25% Group I, 56.25% Group II, 0% Group III		Saraceno et al (2009)
Khellin with monochromatic excimer light 308 nm	Two treatments weekly for 1 year	Open-label		n = 20	% Repigmentation	- >75% repigmentation in 9/20 -50-75% repigmentation in 5/20 -25-50% repigmentation in 3/20 - <20% repigmentation in 3/20 -No recurrences observed 6 months after treatment	-Subjects with resistant vitiligo	Fenniche et al (2018)
Antioxidant and mitochondrial stimulating formula (Group 5)	5 months	RCT	-Oral antioxidants, phenylalanine, and topical formulation (Group 1) -Oral antioxidants, phenylalanine, placebo cream (Group 2) -Oral antioxidants and phenylalanine (Group 3) --Placebo cream (Group 4)	n = 100	Clinical and histological response	-Best results depicted by Group 1 ($p < 0.001$) -Clinical and histological responses of Groups 1 and 5 were significantly greater than any other group	-Frequency of topical application not specified	Rojas-Urdaneta and Poleo-Romero (2007)
NB-UVB-activated Pseudocatalase PC-KUS	Twice daily for 8-12 months	Retrospective study	NB-UVB monotherapy	n = 71 (Psuedocatalase) n = 10 (NB-UVB monotherapy)	% Repigmentation	-Cessation achieved in 70/71 (99%) patients receiving pseudocatalase; the remaining patient showed partial progression of the disease on the hands -Cessation achieved in 3/10 (30%) patients receiving NB-UVB	-Duration of therapy was not controlled	Schallreuter et al (2008)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						monotherapy		
Antioxidant hydrogel with 308 nm excimer laser	Twice daily except for laser therapy days with two laser sessions weekly; cream application began 15 days before starting laser treatment	Pilot study, self-controlled, single-blinded	Vehicle placebo	n = 10	Repigmentation scores -0: no repigmentation -1: Up to 25% repigmentation -2: 26-50% repigmentation -3: 51-75% repigmentation -4: 76-100% repigmentation	-At month 3, lesions treated with active cream exhibited a repigmentation grade of 3.30 ± 0.67, and lesions treated with placebo cream exhibited a grade of 2.60 ± 0.7 ($p < 0.01$) -The first signs of repigmentation were observed after a mean of 21.9 ± 13 days in active-group lesions and 27.0 ± 14.9 days in placebo-group lesions ($p < 0.05$)		Leone and Vidolin (2015)
Hydrogel consisting of SOD, copper, zinc, vitamin B12, calcium pantothenate and excimer light (Group A)	Twice weekly for a maximum of 24 sessions	Open-label, self-controlled study	Excimer light monotherapy (Group B)	n = 30	% Repigmentation	-Significantly greater % repigmentation in Group A lesions than Group B ($p < 0.001$)		Soliman et al (2016)
Epigallocatechin-3-gallate 3%	Twice daily for 6 months	Prospective, self-controlled, comparative, open study	Pimecrolimus 1% cream	n = 46	VASI	-VASI reduction of 1.19 ± 0.42 to 0.63 ± 0.38 in EGCG-treated lesions -VASI reduction of 1.18 ± 0.43 to 0.61 ± 0.36 in pimecrolimus-treated lesions -No significant difference in VASI score reductions ($p = 0.755$) -No serious side effects		Hu et al (2021)
Coffea sp and Helianthus annuus	Once daily	Case report		n = 1	Clinical observation of repigmentation	-Repigmentation began to appear in month 3	-Total treatment duration not specified	Leite et al (2021)
Turmeric topical cream	Twice daily for 4 months	RCT	Placebo control cream	n = 24	-Lesion size -VASI -VNS -PGA	-Turmeric cream reduced the size of the lesions and improved lesion's appearance significantly compared to placebo ($p < 0.001$) -Patient's satisfaction score was higher following turmeric application compared to placebo ($p < 0.05$)		Jalalmanesh et al (2022)
Ruxolitinib 1.5%	Twice daily for 20 weeks	Open-label, proof of concept		n = 9	% VASI Improvement	-Four patients with significant facial involvement: 76% improvement in facial VASI (95% CI 53-99%; $p = 0.001$) -23% improvement in overall VASI in all pts (95% CI 4-43%, $p = 0.02$) -Adverse events included erythema, hyperpigmentation,		Rothstein et al (2017)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						transient acne		
Ruxolitinib	-Topical ruxolitinib 1.5% applied twice daily (pt 1)	Case series		n = 2, although one received oral tofacitinib	Repigmentation	-Pt 1 observed significant repigmentation of face, except for his forehead, which was regularly protected from the sun by a cap -Upon removing the cap, he noted repigmentation in his forehead as well		Joshipura et al (2018)
Ruxolitinib 1.5% with optional NB-UVB	Twice daily for 32 weeks	Open-label study, extension		n = 8	VASI	-Significant mean improvement in overall VASI of 37.6% ± 31.2% (p = 0.011) at 52 weeks; effect was most pronounced for facial vitiligo -5/8 had a treatment response -5/8 completed the trial and were followed up at 6 months, all of which maintained response -3/8 had erythema, 2/8 had transient acne	-32-week extension of study conducted by Rothstein et al (2017)	Joshipura et al (2018)
Ruxolitinib cream (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD)	Once or twice daily, depending on treatment group for 24 weeks	RCT	Control cohort	n = 130	-fVASI -Protein expression (1,104 proteins)	-Number of proteins significantly modulated: 204 in 1.5% BID, 162 in 1.5% QD, 71 in 0.5% QD, 29 in 0.15% QD, 56 in vehicle cohort -Chemokine C-X-C Motif Chemokine Ligand 10 (CSCL10) was significantly down-regulated in 1.5% QD and BID groups		Owens et al (2019)
Ruxolitinib (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD)	Twice-daily 1.5% for 1 year -Once-daily 1.5% -Once-daily 0.5% -Once-daily 0.15	RCT	Control cohort	n = 157	-VASI50 -VASI75 -fVASI50	-Week 24 fVASI50: 45% (1.5% BID), 50% (1.5% QD), 26% (0.5% QD), 32% (0.15% QD) -Week 52: 58% (1.5% BID) reached fVASI50, which was the highest response -Dose-dependent manner for VASI50 at week 52		Rosmarin et al (2020)
Ruxolitinib	-Twice-daily 1.5% for 1 year -Once-daily 1.5% -Once-daily 0.5% -Once-daily 0.15%	Sub-analysis from RCT	Comparison groups included different % formulations and treatment frequencies	n = 157, randomized equally to each treatment group	T-VASI50 and T-VASI75	-Ruxolitinib 1.5% BID produced highest response in most body areas -At 1 year, 1.5% BID T-VASI50 and T-VASI75: -All body regions: 45.0% and 15.0%, respectively -Head/neck: 60.0% and 55.0%, respectively -Trunk: 29.4% and 11.8%, respectively -Upper extremities: 52.9% and 23.5%, respectively	-Abstract -Subgroup analysis from NCT03099304	Grimes et al (2020)

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
						-Lower extremities: 52.6% and 26.3%, respectively -Hands: 15.0% and 5.0%, respectively -Feet: 29.4% and 17.6%, respectively		
Ruxolitinib cream (1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD)	Twice-daily 1.5% for 1 year -Once-daily 1.5% -Once-daily 0.5% -Once-daily 0.15%	Sub-analysis from RCT	Control cohort	n = 157	-VASI50 -VASI75 -fVASI50	-The 1.5% BID dose, VASI50: 60.0% head/neck region, 52.9% upper extremities, 52.6% lower extremities, 15% hands, 29.4% feet -Of those receiving 1.5% BID, a larger proportion of fVASI50 responders at 24 weeks were ≤ 50 years compared with > 50 years	-Subgroup analysis from NCT03099304	Hamzavi et al (2022)
Tofacitinib	Treatment regimen not specified	Retrospective Case Series		n = 10	Repigmentation	-5 patients achieved some repigmentation at sites of sunlight exposure or NB-UVB		Liu et al (2017)
Tofacitinib 2%	Twice daily; the average follow-up time was 153 days (range 63-367)	Nonrandomized cohort study		n = 16	% Repigmentaiton	-13/16 experienced repigmentation -4/16 experienced ≥90% repigmentation -5/16 expereienced 25-75% repigmentation -4/16 experienced 5-15% repigmentation -2/16 experienced no change -1/16 experienced slow progression of depigmentation -Facial lesions improved more than nonfacial lesions (p = 0.022) -Patients with Fitzpatrick skin type IV-VI improved more than individuals with lighter skin (p = 0.034)	-Refractory vitiligo -Concomitant treatment with topical steroids, topical calcineurin inhibitors, supplements, and phototherapy was allowed -Treatment duration was not consistent	Mobasher et al (2019)
Tofacitinib 2% and NBUVB	Twice daily for 3 months with 3x weekly NBUVB	Case series		n = 5	-fVASI	-Mean fVASI at baseline 0.62; mean fVASI at 3 months 0.22 (66% improvement) -No reported side effects		McKesey and Pandya (2020)
Tofacitinib 2% and NBUVB	Twice daily for 7 months	Case report		n = 1	Clinical observation of repigmentation	-Freckling was observed within 4 weeks -Only three depigmented linear macules remain after 3 months -Complete repigmentation at 6 months -No adverse effects		Olamiju and Craiglow (2020)
Tofacitinib 2% + vehicle	Twice-daily for 9 months	Case report		n = 1	Clinical	-Significant repigmentation	-Measurement of	Ferreira et al

Intervention	Duration	Study Design	Comparison	Subjects	Outcome Measure	Major Results	Notes or Limitations	Author
ointment with NB-UVB	and NB-UVB phototherapy 3x weekly				observation of repigmentation	observed -Minor adverse effects included erythema and transient acne	degree of repigmentation not included	(2021)
Delgocitinib	Twice daily for 8-12 weeks	Case series		n = 2	Clinical observation of repigmentation	-Case 1 achieved significant repigmentation at week 8 -Case 2 did not achieve pigmentation at week 12 -No adverse events in either case	-Treatment duration was not consistent	Yagi et al (2021)
Bimatoprost 0.01%	Twice daily for 12 weeks	Prospective, self-controlled, comparative, open study	Tacrolimus 0.1%	n = 10	-VSA Reduction -VIDA	-VSA significantly decreased among both groups compared to baseline ($p < 0.05$) -No significant difference between groups -Week 12, >50% repigmentation: 20% bimatoprost group, 10% tacrolimus		Kanokrungsee et al (2021)
Bimatoprost 0.03%	20 weeks	RCT, proof of concept	-Bimatoprost monotherapy -Bimatoprost plus mometasone -Mometasone plus placebo	n = 32	-Global response at week 20 based on an 8-point scale (0 = worse; 7 = cleared) -Response by anatomic site -Change from baseline lesion severity -Safety	-46% of the bimatoprost plus mometasone group responded overall; 18% in the bimatoprost monotherapy group responded; 0% in the mometasone plus placebo group responded -No differences in signs and symptoms of irritation among groups	-Facial lesions were not assessed	Grimes (2016)
Bimatoprost 0.01%, NB-UVB, and fractional carbon dioxide	Twice-daily application for 12 weeks	Prospective, self-controlled, comparative, open study	-Application of either bimatoprost 0.01% solution or placebo plus once-monthly fractional CO_2 laser and twice-weekly NB-UVB therapy	n = 15	-VSA -Melanin concentration	-At week 12, % change in melanin concentration from baseline was greater on the side receiving bimatoprost 0.1% (27.17 ± 13.62% vs. 22.82 ± 10.10% ($p = 0.028$) -A non-significant greater change in VSA was observed on the side receiving bimatoprost		Kanokrungsee (2021)
Honeybee, allium cepa, avena sativa with sunlight exposure	-Daily application, 20 days followed by 4 days of, for 11 months	Case report		n = 1	% Repigmentation	-Complete repigmentation of white vitiliginous lesions -No adverse effects		Djerrou (2015)

Cal: Calcipotriol Clo: Clobetasol; DLQI: Dermatological Life Quality Index; fVASI: Facial VASI; KUVA: Khellin + Ultraviolet A; L: Left; NB-UVB : Narrow-band UVA; PGA: Physician Global Assessment; PUVA: Psoralen + Ultraviolet A; R: Right; RCT: Randomized controlled trial; VASI: Vitiligo Area Scoring Index; T-VASI50: > 50% Improvement VASI; T-VASI75: > 75% Improvement VASI VIDA; Vitiligo Disease Activity Score; VitiQoL: Vitiligo Quality of Life; VNS: Vitiligo Noticeability Scale; VSA: Vitiligo Surface Area

repigmentation was observed in 38.4% of Group A subjects, 61.1% of Group B subjects, 73.5% of Group C subjects, and 56.2% of Group D subjects. Less than 10% of subjects in each group depicted less than 25% repigmentation. The results depict the moderate efficacy of topical *Cucumis melo* extract, acetylcysteine, and phenylalanine formulation. Furthermore, the results of Groups A-C depict the potential for the formulation to have a synergistic effect when combined with phototherapy. It was noted that calcineurin inhibitors were not included in the comparison. Furthermore, it is interesting that phototherapy was delivered only once a week when typical regimens are set at two or three times a week. In addition, it is important to note that phenylalanine is a precursor in melanogenesis; phenylalanine hydroxylation produces tyrosine, which further derives melanin. As such, it is difficult to conclude the efficacy of *Cucumis melo* extract alone based on the gel's incorporation of phenylalanine but only in combination with phenylalanine and acetylcysteine.

CURCUMIN

Curcumin, a polyphenol derived from the golden spice turmeric (*Curcuma longa*), has been used for the treatment of various diseases due to its antioxidant, anti-proliferative, anti-inflammatory, antiviral, antibacterial, and antifungal properties.[30] In 2010, Asawanonda and Klahan assessed the efficacy of a topical tetrahydrocurcuminoid cream in combination with NB-UVB phototherapy (Group A) versus NB-UVB phototherapy alone (Group B) in the treatment of vitiligo.[34] Scored according to a nine-point scale, both treatment groups exhibited statistically significant degrees of repigmentation from baseline; at 12 weeks, Group A experienced a score increase of 1.9 ± 1.37 ($p = 0.001$) and Group B experienced a score increase of 1.7 ± 0.1 ($p = 0.006$). Although the group receiving tetrahydrocurcuminoid cream exhibited slightly better repigmentation, the difference between the groups was not statistically significant. However, this pilot study only included ten subjects, and further analysis with a larger study population is necessary to assess the efficacy of topical tetrahydrocurcuminoid cream in the treatment of vitiligo.

HERBAL EXTRACTS

A randomized clinical trial assessed the efficacy of Vitilinex, a topical formulation containing herbal bio-actives, on the repigmentation among 62 patients with vitiligo.[35] Vitilinex was composed of two products. The first was a Skin Prep lotion (containing *Centipeda cunninghamii*, *Aloe vera*, terpinol-4-ol and dihydro avenanthramide D) and an emollient (containing black cumin seed oil, black pepper coleus forskohlii, *Psoralea coryfolia*, thyme oil, myrrh, and neroli extracts). The other two treatment groups received Vitilinex with UVB and NB-UVB monotherapy. After 12 weeks of topical treatment, greater than 50% repigmentation was observed in 65% receiving the topical formulation, 62% receiving NB-UVB monotherapy, and 87% receiving combination treatment, suggesting synergistic effects of the topical formulation and phototherapy. Interestingly, *Psoralea coryfolia* typically contained psoralens which may be synergistic with phototherapy.

In 2019, Sarac et al conducted an open-label study to analyze the efficacy of *Nigella sativa* seed oil on repigmentation of the face, hands, and genital regions.[36] They found significant pre- and post-treatment differences in 10/23 patients with facial involvement ($p = 0.001$), 7/16 patients with hand involvement ($p = 0.005$), and 7/8 patients with genital involvement ($p = 0.004$).[36] Overall, clinical studies show early evidence for the relative efficacy of herbal extract formulations in the treatment of vitiligo.

TOPICAL VITAMIN D3 ANALOGUES

Due to its ability to prevent the accumulation of reactive oxygen species, vitamin D has similarly been studied for vitiligo management. Tang et al found that vitamin D protects human melanocytes against oxidative damage via the Wnt/β-catenin signaling activation.[37] A meta-analysis including 31 studies assessing serum vitamin D levels found a significantly decreased vitamin D level among vitiligo patients compared to healthy controls (standard mean difference: -1.03; $p < 0.0001$).[38] Furthermore, topical vitamin D3 has been shown to increase serum vitamin D levels.[39] Therefore, researchers examined the efficacy of calcipotriol, a vitamin D3 analogue, in the treatment of vitiligo.

A systematic review on the efficacy of topical calcipotriol in combination with phototherapy (either UVA, NB-UVB, or excimer laser based phototherapy) for the treatment of vitiligo uncovered that phototherapy and topical calcipotriol have synergistic effects.[40] In 2001, Ameen et al found 5/22 subjects undergoing calcipotriol 50 µg/g twice daily monotherapy to exhibit greater than 90% vitiliginous surface area reduction, although 5 subjects exhibited less than a 30% response.[41] Furthermore, Chivarérini et al found no significant difference between daily topical application of calcipotriol compared to an untreated control lesion, although calcipotriol was only applied once daily.[42] The efficacy of calcipotriol may be dose-dependent, as a study with twice-daily application found 10/14 subjects to depict improvement, although a control group was omitted.[43]

Studies have depicted the synergistic effect of calcipotriene on other treatment regimens. For example, three studies found calcipotriol or calcipotriene treatment with betamethasone treatment to be more efficacious than calcipotriol or calcipotriene treatment alone.[44-46] Similarly, one study found combination treatment with PUVA to be more effective than calcipotriol monotherapy.[47] Additional studies assessing the efficacy of calcipotriol and tacalcitol, another vitamin D analogue, are reported in **Table 1**.[48-51] Interestingly, however, one case report details hyperpigmentation of freckles upon topical tacalcitol application.[52] The results suggest that vitamin D topical monotherapy is unreliable in the treatment of vitiligo, and better results may be expected with combination therapy.

PSORALEN

Psoralen is a naturally occurring bioactive organic compound found in the dried fruit seed of many plants,[53] including *Angelica archangelica*, *Heracleum lanatum*, *Pastinaca saliva*, and *Psoralea bituminosa*.[54] Psoralen is widely utilized in conjunction with phototherapy due to its ability to increase the skin's sensitivity to light. In addition to its many sources, it is contained within *Fructus Psoraleae*, a plant in the family Hydrangeaceae, which has been utilized in Ayurvedic and Traditional Chinese Medicine for the treatment of osteoporosis, psoriasis, and vitiligo.[55] Anecdotal evidence for the pigment-stimulating properties of psoralen date back to the historical period, 2000 BC to 1930 AD,[56] and the combination of oral or topical psoralen with UVA therapy is commonly referred to as PUVA. However, its utility is limited by its associated side effects which may include pruritus, phototoxic reactions, erythema, itching, scaling, giddiness, nausea, and depigmented macules.[57]

Oral PUVA treatment has been more frequently studied than topical PUVA. In 1997, Westerhof and Nieuweboer-Krobotova conducted an open-label study with 281 subjects to determine if topical PUVA is as efficacious as UVB radiation in the treatment of vitiligo.[58] However, they found no significant difference between treatment groups, and topical PUVA was associated with more side effects. Although prior work has demonstrated moderate efficacy with oral PUVA,[59] this study found UVB radiation to be a superior treatment option.

PSORALEA CORYLIFOLIA

In 2016, a study assessed the clinical outcomes of an ointment containing *Psoralea corylifolia* (PC) seed powder, a source of psoralen, on repigmentation in twenty patients with vitiligo.[60] PC possesses antioxidant, antifungal, anti-inflammatory, antibacterial, anti-tumor, and immunomodulatory properties, and has therefore been used in several traditional medicines. Furthermore, it is thought to dilate capillary plexuses, increase plasma delivery at specific sites, and stimulate pigment-producing melanoblasts, which may allow for repigmentation of vitiligo-associated white lesions. Pre- and post-treatment differences in levels of pigmentation were statistically significant for small, circular white lesions of vitiligo. However, upon patch testing, mild irritation (scale-1 level) was reported in 15 subjects, and moderate irritation (scale-2 level) was reported in 5 subjects, for which betamethasone was topically applied as a counter-irritant.

A 2021 pilot study further assessed the efficacy of *Psoralea corylifolia*, both as a monotherapy and in combination with indicated homeopathic (IH) treatment.[61] Three treatment groups existed: IH treatment only, PC treatment only, and combination treatment (IHPC). However, the IH treatment was not standardized and was instead selected on each occasion based on presenting symptoms, clinical history details, and constitutional features. Three qualified homeopaths conducted final selection of medicine for each patient, and examples of IH treatments were not provided. PC dosing regimens were based on the individual requirements of each case. All three groups exhibited a significant decrease in the Vitiligo Area Scoring Index (VASI) from baseline to month 3 and month 6, with no significant differences between groups. The PC and IHPC groups exhibited a significantly greater Vitiligo Quality of Life (VitiQoL) score than the IH group at months 3 and 6, with no significant difference between PC and IHPC. The authors concluded that all treatment regimens are equally effective and safe. Further research with larger sample sizes and the use of a true placebo or vehicle group are required to assess the efficacy of *Psoralea corylifolia*, although these pilot studies depict promising results for repigmentation, especially for small lesions.

KHELLIN

Khellin has been studied as an adjunct to phototherapy in the treatment of vitiligo. Khellin is a naturally occurring furanochromone derived from the plant *Amni visnaga* that can be administered both orally and topically to stimulate melanocytes.[30] In 1998, Orecchia et al evaluated the efficacy of a khellin gel formulation in combination with topical phototherapy for the treatment of vitiligo.[62] Thirty-six subjects with vitiligo were enrolled in the study, receiving a gel formulation consisting of water, 2-propanol, propylene glycol (WPG), and khellin on one side of the body and water, 2-propanol, propylene glycol in the absence of khellin on the other side. They found repigmentation of greater than 10% occurred in 86.1% of the khellin-WPG-treated sides, in contrast to 66.6% of the placebo-treated sides ($p < 0.01$). Young patients with shorter disease duration showed a better response.

In 2009, a controlled study assessed the efficacy of topical khellin 4% in combination with a monochromatic excimer light 308 nm.[63] Three treatment groups were included: Group I (n = 16) subjects were treated with weekly monochromatic light therapy and oral vitamin E; Group II (n = 16) subjects were treated with weekly monochromatic light therapy combined with khellin 4% ointment and oral vitamin E; and Group III (n = 16) subjects were treated solely with oral vitamin E (control). Excellent repigmentation was observed in 25% of the Group I subjects and 56.25% of the Group II subjects, and none of the Group III subjects.

In 2018, an open-label study assessed the efficacy of topical khellin in combination with a 308 nm excimer lamp among twenty patients with resistant vitiligo.[64] They observed excellent repigmentation (greater than 75%) in 9/20 subjects, good repigmentation (50-75%) in 5/20 subjects, moderate repigmentation (25-50%) in 3/20 subjects, and poor repigmentation (less than 25%) in 3/20 subjects. Furthermore, no recurrences were observed six months after treatment. Although this open-label study omitted a control group, the authors concluded that the combination of 308 nm excimer lamp treatment with topical khellin is a safe and effective treatment for vitiligo; however, larger trials are required to confirm these results.

A 2004 study sought to directly compare local khellin and UVA (KUVA) with systemic PUVA treatment.[65] The pilot study included 33 patients, and the results indicated that

local KUVA treatment required longer duration and higher UVA doses, and better KUVA results were achieved with younger patients. Yet, no patient treated with KUVA experienced any adverse effects. In contrast, some patients treated with PUVA developed erythema, itching, and gastro-intestinal disturbances. These results demonstrate that local KUVA treatment may be better tolerated than systemic PUVA treatment, although patients may require greater treatment duration to achieve the same degree of repigmentation as with PUVA. Additional studies have similarly depicted the efficacy of KUVA phototherapy,[66] highlighting its equitable efficacy compared to psoralens. Future research with a greater sample size is required to confirm such findings. Yet, these small studies show promising results.

TOPICAL ANTIOXIDANTS

In 2007, a randomized study including 100 subjects with vitiligo was conducted to assess the efficacy of an antioxidant and mitochondrial stimulating topical formula for use in hypopigmented areas for five months.[67] Five treatment groups were included in the analysis: Group 1 received oral antioxidants and phenylalanine in addition to the topical formulation; Group 2 received oral antioxidants and phenylalanine in addition to a placebo cream; Group 3 received oral antioxidants and phenylalanine only; Group 4 received a placebo cream only; and Group 5 received the topical antioxidant formulation only. Oral antioxidants included vitamin C, vitamin E, zinc, selenium, magnesium, and coenzyme Q10. Average clinical pigmentation was scored according to an 11-point scale, with 0 points indicating the absence of pigment and 11 points indicating pigment in more than 11 mm. Group 1 (oral antioxidants and phenylalanine in addition to the topical formulation) subjects exhibited the greatest repigmentation (average score of 10.4, $p < 0.001$), followed by Group 5 (receiving just the topical formulation) subjects, (average score of 9.77, $p < 0.001$). Groups 2 and 3 scores were 1.23 and 1.16, respectively, which were significantly higher than group 4, the placebo group (score of 0.08). The clinical and histological responses of both Groups 1 and 5 were significantly greater than any other group. Thus, the topical antioxidant formulation demonstrated efficacious results, further potentiated by oral administration of antioxidants and phenylalanine.

In 2016, Soliman et al assessed the efficacy of a topical antioxidant hydrogel with excimer light therapy in comparison to excimer light monotherapy.[68] The hydrogel consisted of SOD, copper, zinc, vitamin B12, and calcium pantothenate. Thirty subjects were included in the study, and 2-4 stable vitiliginous lesions of each subject were selected and divided into two groups. On each patient, group A lesions received the combination therapy, group B lesions received excimer light monotherapy only, and one lesion was left untreated as a control. Lesions were treated twice a week, up to 24 sessions. Group A lesions, receiving the topical antioxidant hydrogel along with excimer monotherapy showed greater repigmentation than Group B ($p < 0.001$). Of the lesions in Group A, 20% achieved excellent repigmentation, 26.7% achieved good repigmentation, 22.2% achieved moderate repigmentation, and 22.2% achieved poor repigmentation. In contrast, no Group B lesions achieved excellent or good repigmentation, with 48.9% exhibiting moderate repigmentation and 42.4% exhibiting poor repigmentation.

An additional pilot study evaluated the effect of an antioxidant cream versus placebo in combination with a 308 nm excimer laser. The antioxidant cream contained folic acid, phenylalanine, sitosterol, hyaluronic acid, Mexican bamboo extract, Chilean boldo tree boldine, aminoguanidine HCl, and decarboxy carnosine HCl. Ten vitiligo patients with symmetrical vitiliginous lesions were included in the study. Lesions treated with topical antioxidant hydrogel demonstrated greater and faster repigmentation than lesions treated with the vehicle control, further supporting the adjunct effect of topical antioxidants with systemic treatments or phototherpy.[69] Repigmentation was recorded according to a five-point scale (0 = no repigmentation, 1 = up to 25% repigmentation, 2 = 26-50% repigmentation, 3 = 51-75% repigmentation, and 4 = 76-100% repigmentation). At month 3, lesions treated with the antioxidant hydrogel exhibited a repigmentation grade of 3.30 ± 0.67, compared to a repigmentation grade of 2.60 ± 0.7 in lesions treated with the placebo cream ($p < 0.01$). Four additional topical formulations with antioxidant properties are listed in **Table 1**.[70-73]

HONEYBEE ALLIUM CEPA AND AVENA SATIVA

In 2015, Djerrou published a case report detailing the successful treatment of vitiligo using a formulation including honeybee *Allium cepa* and *Avena sativa*, coupled with sunlight exposure.[74] The patient achieved complete repigmentation of white vitiliginous lesions with no adverse effects. However, because phototherapy is efficacious for vitiligo, it is not clear if the formulation would have worked in the absence of sun exposure since they were used together.

JANUS KINASE INHIBITORS

Janus kinase (JAK) inhibitors are a novel class of anti-inflammatory molecules that represent the first topical medication that has been specifically FDA-approved for use in vitiligo. There is interest within the integrative dermatology space to use topical JAK inhibitors as a non-steroidal alternative.

The JAK signal transducer and activator of transcription (STAT) pathway foster cytokine-mediated signal transduction of inflammatory mediators. Together with IFN-γ (a type-II interferon), the JAK/STAT signaling pathway is implicated in the pathogenesis of vitiligo[75]; mouse vitiligo studies have suggested that the positive IFN-γ-chemokine axis feedback loop may allow the initiation and progression of vitiligo.[75] IFN-γ activates the JAK/STAT1 pathway, resulting in STAT1 phosphorylation and gene transcription. However, IFN-γ can be blocked by the inhibition of JAK1 or JAK2, suggesting that this pathway may have great pharmacologic potential in the management of vitiligo.

Oral tofacitinib is a JAK inhibitor that has been used off-label for the treatment of vitiligo with reported suc-

cess.[76,77] Recent studies have similarly assessed the efficacy of topical formulations. In 2019, Owens et al conducted a study to assess the effect of ruxolitinib cream on inflammatory profiles in patients with vitiligo, providing molecular support for its use in the treatment of vitiligo.[78] Of 1,104 proteins assessed, 204 proteins exhibited significantly modulated expression ($p < 0.05$) in the 1.5% twice-daily treatment group; 162 proteins in the 1.5% once-daily group, 71 proteins in the 0.5% once-daily group, 29 proteins in the 0.15% once-daily group, and 56 proteins in the vehicle control group exhibited significant expression modulation. Furthermore, chemokine C-X-C Motif Chemokine Ligand 10 (CXCL10), implicated in vitiligo pathogenesis by T cell recruitment to the site of inflammation, was significantly downregulated in both 1.5% twice-daily and once-daily treatment groups. This study provided evidence for the dose-dependent nature of ruxolitinib-associated inflammatory mediation.

Research has further depicted clinical efficacy. Rothstein et al evaluated twice-daily topical ruxolitinib 1.5% among 12 patients in an open-label proof-of-concept trial.[79] Nine subjects completed the study for the 20-week duration. Overall, Vitiligo Area Scoring Index scores improved 23% in enrolled patients at week 20 (95% confidence interval: 4-43%; $p = 0.02$). Furthermore, four patients who had significant facial vitiliginous involvement experienced 76% improvement in facial Vitiligo Area Scoring Index scores at week 20 (95% confidence interval: 53-99%; $p = 0.001$).

The site-specificity of response is demonstrated by a subgroup analysis from a phase 2, randomized, double-blind trial.[80] 157 subjects were included in the initial study, although the subgroup analysis included 33 patients with vitiligo affecting less than or equal to 20% of total body surface area (T-BSA), as ruxolitinib application was limited to ⩽ 20% T-BSA for practicality and safety.[81] 60% of head and neck lesions experienced greater than 50% improvement in total Vitiligo Area Scoring Index (T-VASI50). 52.9% of upper extremity lesions, 52.6% of lower extremity lesions, 29.4% of foot lesions, and 15.0% of hand lesions experienced greater than 50% response. Whereas the initial trial showed the relative efficacy of topical ruxolitinib cream in the treatment of facial and total body vitiligo,[81] the subgroup analysis found site-specific differential responses.

In addition to topical ruxolitinib, topical tofacitinib has also been studied among vitiligo patients. In 2020, Mobasher et al conducted an open-label pilot study to evaluate the clinical efficacy of topical 2% tofacitinib cream among 16 patients with vitiligo, 11 of which had generalized vitiligo.[82] Four patients experienced greater or equal to 90% repigmentation, five patients experienced 25-75% repigmentation, four patients experienced 5-15% repigmentation, and three patients did not experience repigmentation. Like ruxolitinib, the topical tofacitinib cream was significantly more effective on facial lesions than non-facial lesions ($p = 0.022$). Furthermore, greater improvement was observed on patients with Fitzpatrick skin types IV-VI ($p = 0.034$).

McKesey and Pandya similarly reported a pilot study involving 11 patients who received 2% tofacitinib cream twice daily in combination with NB-UVB for treatment of facial vitiligo.[83] The authors noted good to excellent repigmentation in all 11 patients. It is likely that this study observed more efficacious results than that reported by Mobasher et al as studied lesions were confined to the face.[82] McKensey and Pandya concluded that topical tofacitinib and phototherapy synergistically can lead to improvement of vitiligo. This observation aligns with two case reports published by Joshipura et al supporting the importance of light in the treatment of vitiligo with JAK inhibitors.[84] Interestingly, however, Mobasher et al state that their case series failed to depict a clear pattern regarding concomitant phototherapy.[82] Larger, controlled trials are necessary to determine the efficacy of topical tofacitinib monotherapy compared to combination with phototherapy.

Although topical ruxolitinib and tofacitinib are the most frequently studied topical JAK inhibitors for the treatment of vitiligo, Yagi et al reported two cases of vitiligo treated with delgocitinib, albeit with mixed results.[85] Although no adverse effects were observed in either case, only one case demonstrated significant repigmentation upon topical application. However, the successful case involved treatment of the neck, whereas the unsuccessful case involved treatment of the elbow. As previously described, site-specific differences in response have been observed with topical JAK inhibitors, which may have contributed to the differing results presented by Yagi et al. Additional studies assessing the efficacy of topical JAK inhibitors are listed in Table 1.[86-89]

BIMATOPROST

An open-label study compared the efficacy of Bimatoprost 0.01% twice daily application to Tacrolimus 0.1% twice daily for twenty weeks ($n = 10$ subjects with two or more vitiliginous lesions).[90] They found the total vitiliginous lesion surface area to decrease from baseline ($p < 0.05$), although with no significant difference compared to Tacrolimus 0.1%. The bimatoprost 0.01% and the tacrolimus 0.1% groups achieved greater than 50% repigmentation at 12 weeks in 20% and 10% of subjects, respectively. Itching and burning were similarly reported with both bimatoprost 0.01% and Tacrolimus 0.1%.

In contrast, a 2016 study utilized a greater concentration of bimatoprost. Bimatoprost 0.03% was assessed for its efficacy in vitiligo response, both as a monotherapy and in combination with mometasone.[91] Mometasone plus placebo was utilized as a control group. Thirty-two patients were randomized into one of the groups and a response was defined as 25%-50% global improvement. 46% of patients receiving bimatoprost plus mometasone were found to have a response, compared to 18% of patients receiving bimatoprost monotherapy and 0% receiving mometasone plus placebo. The results indicate a synergistic effect of bimatoprost 0.03% and mometasone administration, although few lesions exhibited repigmentation greater than 50%. There were no differences in signs and symptoms of irritation among groups.

Lastly, a 2021 study evaluated the efficacy of either bimatoprost 0.01% solution or placebo solution plus once-

monthly fractional carbon dioxide laser with twice-weekly NB-UVB therapy.[92] Fifteen subjects were included in the analysis, each with paired vitiliginous lesions that could be randomized to each treatment group. At week 12, the percent change in melanin concentration from baseline was greater on lesions receiving bimatoprost 0.1% (27.17 ± 13.62% vs. 22.82 ± 10.10% p = 0.028). A greater change in vitiligo surface area was observed among lesions receiving bimatoprost 0.01% than placebo, but the changes were not statistically significant.

These studies demonstrate the moderate efficacy of bimatoprost in the treatment of vitiligo, while highlighting potential synergistic effects of combination therapies. Additional studies with greater sample sizes are required to determine if bimatoprost 0.01% can effectively be used as a monotherapy, or if laser and/or NB-UVB supplemental therapy is required. Furthermore, additional studies are required to determine if efficacious results may similarly be observed for vitiliginous lesions of the face.

DISCUSSION AND CONCLUSION

This review highlights several studies that could potentially expand the possible topical therapies for vitiligo. The emergence of an FDA-approved topical has shifted the landscape of vitiligo into one that recognizes the medical impact of vitiligo rather than relegating it to cosmetic. Studies evaluating the topical JAK inhibitors found topical treatment to be most efficacious on lesions of the face. It is possible other topical treatments similarly exhibit site-dependent efficacy. An important note is that many topical treatments were evaluated in combination with systemic therapies or phototherapy and relatively few topical treatments were studied in isolation. Synergistic effects are depicted by many studies, which aligns with the observation that combination therapies are often more effective than single therapies.[9] Combination therapy based approaches are in agreement with clinical practice where patients will frequently be placed on multiple therapies at once.

Despite demonstrated efficacy, the clinical utility of some topical integrative therapies may be limited by their associated side effects. A systematic review of the safety of medicinal plants used in vitiligo treatment discussed adverse effects associated with *Psoralea corylifolia*, psoralen, and khellin.[57] *Psoralea corylifolia* treatment was associated with reports of blistering and erythema. Psoralen use was associated with erythema, phototoxic reactions, mild raise in liver transaminases, gastrointestinal disturbances, burns, itching, scaling, depigmented macules, pruritus, and giddiness, although some effects may have been reported with oral psoralen, rather than topical. Saraceno et al reported erythema, burning sensation, and perilesional hyperpigmentation with 4% topical khellin,[63] although other studies reported no khellin-associated side effects.[62,65] Hepatotoxicity and the impact on liver transaminases remains a concern with oral khellin,[57] although these concerns are not noted with topical application.

There are important limitations of this review. Many topical approaches were evaluated via pilot studies with small sample sizes, thereby limiting the generalizability of results. In addition, some of the studies were case series or did not include a control group. Nevertheless, the studies showed promising efficacy in agreement with other studies where control groups were used. Furthermore, many studies did not specify the location of vitiliginous lesions or if study subjects had generalized or localized vitiligo, which may impact efficacy results.

The results of this review demonstrate the efficacy of a variety of integrative approaches for the treatment of vitiligo. Additional herbs and topicals are utilized worldwide due to anecdotal evidence, although studies have assessed many traditional formulations. Promising topical integrative treatments are available for the treatment of vitiligo, many of which can be administered as an adjunct to systemic treatments and narrowband UVB or excimer phototherapy. We hope that our review will foster further studies on topical approaches to vitiligo and likely future studies will incorporate multiple promising ingredients together for a combination-based approach.

DISCLOSURES

RKS serves as a scientific advisor for LearnHealth, Codex Labs Corp, and Arbonne and as a consultant to Burt's Bees, Novozymes, Nutrafol, Incyte, Fotona, Element Apothec, Abbvie, Leo, UCB, Sun, Sanofi, Regeneron Pharmaceuticals. JM serves as a consultant for Codex Labs Corp. The other authors report no conflicts.

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ABBREVIATIONS

EH: *Ecliptae herba*
JAK: Janus kinase
JAK/STAT: Janus kinase/ signal transducer and activator of transcription
KUVA: Khellin-UVA
NB-UVB: Narrowband UVB
PMRP: *Polygoni multiflora radix praeparata*
PUVA: Psoralens-UVA
RRP: *Rehmanniae radix praeparata*
T-VASI50: >50% Improvement in total Vitiligo Area Scoring Index
T-VASI75: >75% Improvement in total Vitiligo Area Scoring Index
SOD: Superoxide dismutase

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REFERENCES

1. Bergqvist C, Ezzedine K. Vitiligo: A Review. *Dermatology*. 2020;236(6):571-592. doi:10.1159/000506103

2. Sawant NS, Vanjari NA, Khopkar U. Gender Differences in Depression, Coping, Stigma, and Quality of Life in Patients of Vitiligo. *Dermatol Res Pract*. 2019;2019(6879412):1-10. doi:10.1155/2019/6879412

3. Goh BK, Pandya AG. Presentations, Signs of Activity, and Differential Diagnosis of Vitiligo. *Dermatol Clin*. 2017;35(2):135-144. doi:10.1016/j.det.2016.11.004

4. Jalali M, Jafari B, Isfahani M, Nilforoushzadeh M. Treatment of segmental vitiligo with normal-hair follicle autograft. *Medical journal of the Islamic Republic of Iran*. 2013;27:210-214.

5. Gunasekera N, Murphy GF, Sheth VM. Repigmentation of extensive inflammatory vitiligo with raised borders using early and aggressive treatment. *Dermatology*. 2015;230(1):11-15. doi:10.1159/000366197

6. Abdel-Malek ZA, Jordan C, Ho T, Upadhyay PR, Fleischer A, Hamzavi I. The enigma and challenges of vitiligo pathophysiology and treatment. *Pigment Cell Melanoma Res*. 2020;33(6):778-787. doi:10.1111/pcmr.12878

7. Mazereeuw-Hautier J, Bezio S, Mahé E, et al. Segmental and nonsegmental childhood vitiligo has distinct clinical characteristics: a prospective observational study. *Journal of the American Academy of Dermatology*. 2010;62(6):945-949. doi:10.1016/j.jaad.2009.06.081

8. Speeckaert R, Lambert J, Bulat V, Belpaire A, Speeckaert M, van Geel N. Autoimmunity in Segmental Vitiligo. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.568447

9. Chang WL, Lee WR, Kuo YC, Huang YH. Vitiligo: An Autoimmune Skin Disease and its Immunomodulatory Therapeutic Intervention. *Front Cell Dev Biol*. 2021;9. doi:10.3389/fcell.2021.797026

10. Li Z, Ren J, Niu X, et al. Meta-Analysis of the Association between Vitiligo and Human Leukocyte Antigen-A. *BioMed Res Int*. 2016;2016(5412806):1-13. doi:10.1155/2016/5412806

11. Spritz RA, Andersen GHL. Genetics of Vitiligo. *Dermatol Clin*. 2017;35(2):245-255. doi:10.1016/j.det.2016.11.013

12. Guida M, Strippoli S, Maule M, et al. Immune checkpoint inhibitor associated vitiligo and its impact on survival in patients with metastatic melanoma: an Italian Melanoma Intergroup study. *ESMO Open*. 2021;6(2):100064. doi:10.1016/j.esmoop.2021.100064

13. Liu RC, Consuegra G, Chou S, Fernandez Peñas P. Vitiligo-like depigmentation in oncology patients treated with immunotherapies for nonmelanoma metastatic cancers. *Clin Exp Dermatol*. 2019;44(6):643-646. doi:10.1111/ced.13867

14. Al Aboud DM, Gossman W. Wood's Light. In: *StatPearls*. StatPearls Publishing; 2022. Accessed February 21, 2023. http://www.ncbi.nlm.nih.gov/books/NBK537193/

15. Delgado P, Crumpton K. A practical guide to vitiligo differential diagnoses in primary care. *Nurse Pract*. 2021;46(11):29-36. doi:10.1097/01.npr.0000794516.47158.e1

16. Gill L, Zarbo A, Isedeh P, Jacobsen G, Lim HW, Hamzavi I. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. *J Am Acad Dermatol*. 2016;74(2):295-302. doi:10.1016/j.jaad.2015.08.063

17. Ahmed jan N, Masood S. Vitiligo. *StatPearls*. Published online 2022.

18. Ongenae K, Beelaert L, Geel N, Naeyaert JM. Psychosocial effects of vitiligo. *J Eur Acad Dermatol Venerol*. 2006;20(1):1-8. doi:10.1111/j.1468-3083.2005.01369.x

19. Nogueira LSC, Zancanaro PCQ, Azambuja RD. [Vitiligo and emotions]. *An Bras Dermatol*. 2009;84(1):41-45. doi:10.1590/s0365-05962009000100006

20. Ezzedine K, Whitton M, Pinart M. Interventions for Vitiligo. *JAMA*. 2016;316(16):1708-1709. doi:10.1001/jama.2016.12399

21. Bouceiro Mendes R, Alpalhão M, Filipe P. UVB phototherapy in the treatment of vitiligo: State of the art and clinical perspectives. *Photoderm Photoimm Photomed*. 2022;38(3):215-223. doi:10.1111/phpp.12740

22. Ajose FOA. Some Nigerian plants of dermatologic importance. *Int J Dermatol*. 2007;46(s1):48-55. doi:10.1111/j.1365-4632.2007.03466.x

23. Alghamdi KM, Khurrum H, Al-Natour SH, et al. Use of Complementary and Alternative Medicine Among Dermatology Outpatients: Results From a National Survey. *J Cutan Med Surg*. 2015;19(6):570-579. doi:10.1177/1203475415584867

24. Ebrahimabadi MH, Lamardi SNS, Shirbeigi L. Immunomodulatory Effects of Medicinal Plants used for Vitiligo in Traditional Persian Medicine. *Curr Drug Discov Technol*. 2021;18(2):160-178. doi:10.2174/1570163817666200517115438

25. Sundarrajan S, Arumugam M. Documentation of traditional Siddha medicines for skin diseases from Katpadi taluk, Vellore District, Tamil Nadu, India. *European Journal of Integrative Medicine*. 2017;9:52-62. doi:10.1016/j.eujim.2016.08.163

26. Shakhbazova A, Wu H, Chambers CJ, Sivamani RK. A Systematic Review of Nutrition, Supplement, and Herbal-Based Adjunctive Therapies for Vitiligo. *J Altern Complement Med*. 2021;27(4):294-311. doi:10.1089/acm.2020.0292

27. Chang HC, Hsu YP, Huang YC. The effectiveness of topical calcineurin inhibitors compared with topical corticosteroids in the treatment of vitiligo: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2020;82(1):243-245. doi:10.1016/j.jaad.2019.07.108

28. Chopra A, Doiphode VV. Ayurvedic medicine: core concept, therapeutic principles, and current relevance. *Med Clin North Am*. 2002;86(1):75-89. doi:10.1016/s0025-7125(03)00073-7

29. Dhanik A, Sujatha N, Rai NP. Clinical evaluation of the efficacy of Shvitrahara kashaya and lepa in vitiligo. *Ayu*. 2011;32(1):66-69. doi:10.4103/0974-8520.85731

30. Gianfaldoni S, Wollina U, Tirant M, et al. Herbal Compounds for the Treatment of Vitiligo: A Review. *Open Access Maced J Med Sci*. 2018;6(1):203-207. doi:10.3889/oamjms.2018.048

31. Yuksel EP, Aydin F, Senturk N, Canturk T, Turanli AY. Comparison of the efficacy of narrow band ultraviolet B and narrow band ultraviolet B plus topical catalase-superoxide dismutase treatment in vitiligo patients. *Eur J Dermatol*. 2009;19(4):341-344. doi:10.1684/ejd.2009.0699

32. Naini FF, Shooshtari AV, Ebrahimi B, Molaei R. The effect of pseudocatalase/superoxide dismutase in the treatment of vitiligo: A pilot study. *J Res Pharm Pract*. 2012;1(2):77-80. doi:10.4103/2279-042x.108375

33. Buggiani G, Tsampau D, Hercogovà J, Rossi R, Brazzini B, Lotti T. Clinical efficacy of a novel topical formulation for vitiligo: compared evaluation of different treatment modalities in 149 patients. *Dermatol Ther*. 2012;25(5):472-476. doi:10.1111/j.1529-8019.2012.01484.x

34. Asawanonda P, Klahan SO. Tetrahydrocurcuminoid cream plus targeted narrowband UVB phototherapy for vitiligo: a preliminary randomized controlled study. *Photomed Laser Surg*. 2010;28(5):679-684. doi:10.1089/pho.2009.2637

35. Trinh Minh T, Le Huu D, Nguyen Van T, et al. Successful Treatment of Vitiligo Vietnamese Patients with Vitilinex® Herbal Bio-Actives in Combination with Phototherapy. *Open Access Maced J Med Sci*. 2019;7(2):283-286. doi:10.3889/oamjms.2019.095

36. Sarac G, Kapicioglu Y, Sener S, et al. Effectiveness of topical Nigella sativa for vitiligo treatment. *Dermatol Ther*. 2019;32(4):e12949. doi:10.1111/dth.12949

37. Tang L, Fang W, Lin J, Li J, Wu W, Xu J. Vitamin D protects human melanocytes against oxidative damage by activation of Wnt/β-catenin signaling. *Laboratory Investigation*. 2018;98(12):1527-1537. doi:10.1038/s41374-018-0126-4

38. Varikasuvu SR, Aloori S, Varshney S, Bhongir AV. Decreased circulatory levels of Vitamin D in Vitiligo: a meta-analysis. *An Bras Dermatol*. 2021;96(3):284-294. doi:10.1016/j.abd.2020.10.002

39. Bubshait DA, Al-Dakheel DA, Alanii FM. Topical vitamin D3: A randomized controlled trial (RCT). *Clinical Nutrition ESPEN*. 2018;27:16-19. doi:10.1016/j.clnesp.2018.05.009

40. Hu M, Liao K, Lei W, Zhang R, Tu C. The addition of topical calcipotriol to phototherapy enhance the efficacy of treatment in patients with vitiligo: A systematic review and meta-analysis. *Int Immunopharmacol*. 2021;98:107910. doi:10.1016/j.intimp.2021.107910

41. Ameen M, Exarchou V, Chu AC. Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo. *Br J Dermatol*. 2001;145(3):476-479. doi:10.1046/j.1365-2133.2001.04381.x

42. Chiavérini C, Passeron T, Ortonne JP. Treatment of vitiligo by topical calcipotriol. *J Eur Acad Dermatol Venerol*. 2002;16(2):137-138. doi:10.1046/j.1468-3083.2002.00407.x

43. Gargoom AM, Doweb GA, Elzorghany AH, Benghazil M, Bugrein OO. Calcipotriol in the treatment of childhood vitiligo. *Int J Clin Pharmacol Res*. 2004;24(1):11-14.

44. Kumaran MS, Kaur I, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venerol*. 2006;20(3):269-273. doi:10.1111/j.1468-3083.2006.01420.x

45. Alam MN, Wahab MA, Khondker L, Khan MSI. Comparative efficacy and safety of the combination of betamethasone dipropionate and calcipotriene with topical betamethasone dipropionate and calcipotriene alone in the treatment of localized vitiligo. *J Pak Assoc Dermatol*. 2014;24(2):143-149.

46. Zahoor M, Shaukat S, Khan MS, Ahmad TJ. Comparison of efficacy and safety of 0.005% calcipotriol ointment versus 0.05% betamethasone dipropionate ointment versus calcipotriol plus betamethasone ointment for the treatment of vitiligo. *J Pak Assoc Dermatol*. 2017;27(1):30-36.

47. Shehzad A, Khurshid K, Pal SS, Haroon TS. Topical calcipotriol versus oral psoralen-UVA (PUVA) and topical calcipotriol in the treatment of vitiligo in type IV skin. *J Pak Assoc Dermatol*. 2007;17(2):89-94.

48. Köse O, Gür AR, Kurumlu Z, Erol E. Calcipotriol ointment versus clobetasol ointment in localized vitiligo: An open, comparative clinical trial. *Int J Dermatol*. 2002;41(9):616-618. doi:10.1046/j.1365-4362.2002.01486_3.x

49. Bilaç DB, Ermertcan AT, Şahin MT, Öztürkcan S. Two therapeutic challenges: Facial vitiligo successfully treated with 1% pimecrolimus cream and 0.005% calcipotriol cream. *J Eur Acad Dermatol Venereol*. 2009;23(1):72-73. doi:10.1111/j.1468-3083.2008.02668.x

50. Amano H, Abe M, Ishikawa O. First case report of topical tacalcitol for vitiligo repigmentation. *Pediatr Dermatol*. 2008;25(2):262-264. doi:10.1111/j.1525-1470.2008.00648.x

51. Uksal U, Borlu M, Atasavun C, Ferahbas A. Comparison of four treatment regimens for vitiligo in children. *Eur J Pediatr Dermatol*. 2002;12(4):231-234.

52. Oiso N, Kawada A. Freckling promoted by topical tacalcitol in a Japanese boy with left eyelid vitiligo. *Pediatr Dermatol*. 2012;29(5):671-672. doi:10.1111/j.1525-1470.2011.01559.x

53. Ren Y, Song X, Tan L, et al. A Review of the Pharmacological Properties of Psoralen. *Front Pharmacol*. 2020;11:571535. doi:10.3389/fphar.2020.571535

54. Zobel AM, Brown SA. Psoralens on the surface of seeds of Rutaceae and fruits of Umbelliferae and Leguminosae. *Can J Bot*. 1991;69(3):485-488. doi:10.1139/b91-065

55. Yang J, Yang J, Du J, et al. General survey of Fructus Psoraleae from the different origins and chemical identification of the roasted from raw Fructus Psoraleae. *Journal of Food and Drug Analysis*. 2018;26(2):807-814. doi:10.1016/j.jfda.2017.10.009

56. Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *J Photochem Photobiol B*. 1992;14(1-2):3-22. doi:10.1016/1011-1344(92)85080-e

57. Hussain I. The Safety of Medicinal Plants Used in the Treatment of Vitiligo and Hypermelanosis: A Systematic Review of Use and Reports of Harm. *Clinical, Cosmetic and Investigational Dermatology*. 2021;14:261-284. doi:10.2147/ccid.s298342

58. Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Arch Dermatol*. 1997;133(12):1525-1528. doi:10.1001/archderm.1997.03890480045006

59. Bae JM, Jung HM, Hong BY, et al. Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2017;153(7):666-674. doi:10.1001/jamadermatol.2017.0002

60. Hussain I, Hussain N, Manan A, Rashid A, Khan B, Bukhsh S. Fabrication of anti-vitiligo ointment containing Psoralea corylifolia: in vitro and in vivo characterization. *Drug Design, Development and Therapy*. 2016;10:3805-3816. doi:10.2147/dddt.s114328

61. Mir AA, Wani GN, Prajapati R, et al. Add-on Psoralea corylifolia mother tincture external application to individualized homeopathic medicines in treatment of vitiligo: Open, randomized, pragmatic, pilot trial. *Advances in Integrative Medicine*. 2022;9(1):53-62. doi:10.1016/j.aimed.2021.03.003

62. Orecchia G, Sangalli M, Gazzaniga A, Giordano F. Topical photochemotherapy of vitiligo with a new khellin formulation. *Journal of Dermatological Treatment*. 1998;9(2):65-69. doi:10.3109/09546639809161375

63. Saraceno R, Nisticò SP, Capriotti E, Chimenti S. Monochromatic excimer light 308 nm in monotherapy and combined with topical khellin 4% in the treatment of vitiligo: a controlled study. *Dermatol Ther*. 2009;22(4):391-394. doi:10.1111/j.1529-8019.2009.01252.x

64. Fenniche S, Zaouak A, Tanfous AB, Jrad M, Hammami H. Successful Treatment of Refractory Vitiligo with a Combination of Khellin and 308-nm Excimer Lamp: An Open-Label, 1-Year Prospective Study. *Dermatol Ther (Heidelb)*. 2018;8(1):127-135. doi:10.1007/s13555-017-0218-x

65. Valkova S, Trashlieva M, Christova P. Treatment of vitiligo with local khellin and UVA: comparison with systemic PUVA. *Clin Exp Dermatol*. 2004;29(2):180-184. doi:10.1111/j.1365-2230.2004.01462.x

66. Ortel B, Tanew A, Hönigsmann H. Treatment of vitiligo with khellin and ultraviolet A. *J Am Acad Dermatol*. 1988;18(4 Pt 1):693-701. doi:10.1016/s0190-9622(88)70092-4

67. Rojas-Urdaneta JE, Poleo-Romero AG. [Evaluation of an antioxidant and mitochondria-stimulating cream formula on the skin of patients with stable common vitiligo]. *Invest Clin*. 2007;48(1):21-31.

68. Soliman M, Samy NA, Abo Eittah M, Hegazy M. Comparative study between excimer light and topical antioxidant versus excimer light alone for treatment of vitiligo. *J Cosmet Laser Ther*. 2016;18(1):7-11. doi:10.3109/14764172.2015.1052510

69. Leone G, Paro Vidolin A. Effect of an antioxydant cream versus placebo in patients with vitiligo in association with excimer laser. A pilot randomized, investigator-blinded, and half-side comparison trial. *G Ital Dermatol Venereol*. 2015;150(4):461-466.

70. Schallreuter KU, Krüger C, Würfel BA, Panske A, Wood JM. From basic research to the bedside: Efficacy of topical treatment with pseudocatalase PC-KUS in 71 children with vitiligo. *Int J Dermatol*. 2008;47(7):743-753. doi:10.1111/j.1365-4632.2008.03660.x

71. Hu W, Zhang L, Lin F, Lei J, Zhou M, Xu A. Topical epigallocatechin-3-gallate in the treatment of vitiligo. *Australas J Dermatol*. 2021;62(3):e404-e407. doi:10.1111/ajd.13612

72. Leite PM, Alves SDO, Castilho RO. The rationality involved in the popular use of coffee (Coffea sp) and sunflower seed (Helianthus annuus) for the treatment of vitiligo: a case report. *EXPLORE*. 2022;18(5):587-590. doi:10.1016/j.explore.2021.05.004

73. Jalalmanesh S, Mansouri P, Rajabi M, Monji F. Therapeutic effects of turmeric topical cream in vitiligo: A randomized, double-blind, placebo-controlled pilot study. *J Cosmet Dermatol*. 2022;21(10):4454-4461. doi:10.1111/jocd.14814

74. Djerrou Z. Successful treatment of facial vitiligo with honey bee, allium cepa and avena sativa combined to sun light exposure: A case clinical trial. *Intl J Pharm Clin Res*. 2015;7(1):9-14.

75. Qi F, Liu F, Gao L. Janus Kinase Inhibitors in the Treatment of Vitiligo: A Review. *Front Immunol*. 2021;12:790125. doi:10.3389/fimmu.2021.790125

76. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol*. 2017;77(4):675-682.e1. doi:10.1016/j.jaad.2017.05.043

77. Komnitski M, Komnitski A, Komnitski Junior A, Silva de Castro CC. Partial repigmentation of vitiligo with tofacitinib, without exposure to ultraviolet radiation. *An Bras Dermatol*. 2020;95(4):473-476. doi:10.1016/j.abd.2019.08.032

78. Owens S, Rumberger BE, Hu Y, et al. 157 Ruxolitinib Cream significantly modulates inflammatory profiles of Patients with Vitiligo. *Journal of Investigative Dermatology*. 2019;139(9, Supplement):S241. doi:10.1016/j.jid.2019.07.161

79. Rothstein B, Joshipura D, Saraiya A, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;76(6):1054-1060.e1. doi:10.1016/j.jaad.2017.02.049

80. Hamzavi I, Rosmarin D, Harris JE, et al. Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: Descriptive subgroup analyses from a phase 2, randomized, double-blind trial. *J Am Acad Dermatol*. 2022;86(6):1398-1401. doi:10.1016/j.jaad.2021.05.047

81. Rosmarin D, Pandya AG, Lebwohl M, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. *Lancet*. 2020;396(10244):110-120. doi:10.1016/s0140-6736(20)30609-7

82. Mobasher P, Guerra R, Li SJ, Frangos J, Ganesan AK, Huang V. Open-label pilot study of tofacitinib 2% for the treatment of refractory vitiligo. *Br J Dermatol*. 2020;182(4):1047-1049. doi:10.1111/bjd.18606

83. McKesey J, Pandya AG. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. *J Am Acad Dermatol*. 2019;81(2):646-648. doi:10.1016/j.jaad.2019.04.032

84. Joshipura D, Plotnikova N, Goldminz A, et al. Importance of light in the treatment of vitiligo with JAK-inhibitors. *J Dermatol Treat*. 2018;29(1):98-99. doi:10.1080/09546634.2017.1339013

85. Yagi K, Ishida Y, Otsuka A, Kabashima K. Two cases of vitiligo vulgaris treated with topical Janus kinase inhibitor delgocitinib. *Australas J Dermatol*. 2021;62(3):433-434. doi:10.1111/ajd.13572

86. Joshipura D, Alomran A, Zancanaro P, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: A 32-week open-label extension study with optional narrow-band ultraviolet B. *J Am Acad Dermatol*. 2018;78(6):1205-1207.e1. doi:10.1016/j.jaad.2018.02.023

87. Grimes P, Rosmarin D, Hamzavi I, et al. 17752 Effects of ruxolitinib cream on affected body areas in patients with vitiligo: Subgroup analysis from a 52-week, randomized, double-blind trial. *J Am Acad Dermatol*. 2020;83(6):AB198. doi:10.1016/j.jaad.2020.06.879

88. Berbert Ferreira S, Berbert Ferreira R, Neves Neto AC, Assef SMC, Scheinberg M. Topical Tofacitinib: A Janus Kinase Inhibitor for the Treatment of Vitiligo in an Adolescent Patient. *Case Rep Dermatol*. 2021;13(1):190-194. doi:10.1159/000513938

89. Olamiju B, Craiglow BG. Tofacitinib cream plus narrowband ultraviolet B phototherapy for segmental vitiligo in a child. *Pediatr Dermatol*. 2020;37(4):754-755. doi:10.1111/pde.14159

90. Kanokrungsee S, Pruettivorawongse D, Rajatanavin N. Clinical outcomes of topical bimatoprost for nonsegmental facial vitiligo: A preliminary study. *J Cosmet Dermatol*. 2021;20(3):812-818. doi:10.1111/jocd.13648

91. Grimes PE. Bimatoprost 0.03% Solution for the Treatment of Nonfacial Vitiligo. *J Drugs Dermatol*. 2016;15(6):703-710.

92. Kanokrungsee S, Khunkhet S, Rojhirunsakool S, Thadvibun K, Sahaspot T. Triple combination therapy of narrowband ultraviolet B, fractional carbon dioxide laser and topical bimatoprost 0.01% for non-segmental vitiligo on non-facial areas: A randomized half-body, double-blind, placebo-controlled, comparative study. *Dermatol Ther*. 2022;35(1):e15198. doi:10.1111/dth.15198

SUPPLEMENTARY MATERIALS

figure 1

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