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REVIEW ARTICLE

Alternative Systemic Treatments for Vitiligo: A Review

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Abstract Vitiligo is a common, acquired disorder of skin pigmentation that can significantly impact quality of life. It often represents a therapeutic challenge, which has resulted in interest in alternative treatments such as herbal and vitamin supplements. In this review, we provide an overview of the most commonly studied complementary agents, describe proposed mechanisms of action, identify potential adverse effects, and discuss the primary evidence supporting their use. Our discussion focuses on L-phenylalanine, *Polypodium leucotomos*, khellin, *Ginkgo biloba*, and vitamins and minerals, including vitamins B12, C, and E, folic acid, and zinc used as monotherapy or in combination with other treatments for the management of vitiligo.

Key Points

A number of studies describe the use of systemic alternative therapies, such as herbal and vitamin supplements, to improve treatment outcomes in vitiligo.

There is some evidence for an additive effect with phototherapy for L-phenylalanine, *Polypodium leucotomos,* antioxidant vitamins. and khellin.

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1 Introduction

Vitiligo is a skin condition characterized by the loss of melanocytes and development of depigmented patches [1]. It affects 0.5–4 % of the world's population, and its prevalence is similar between genders and races [1–3]. Vitiligo can also result in profound emotional distress and reduced quality of life [3–5]. The peak age of presentation is 10–30 years, a time when patients are especially vulnerable to the negative psychosocial impact of the disease [1, 6]. There are several types of vitiligo, including generalized and segmental. Segmental vitiligo is less common, presents at an earlier age, is unilaterally distributed, and is less prone to relapse [1, 7].

Generalized vitiligo is increasingly recognized to be an autoimmune disease [8–10], yet its initiation and the precise pathogenesis of melanocyte destruction remain to be elucidated. Among the processes implicated are immune dysregulation, neurogenic factors, catecholamine-mediated cytotoxicity, and oxidative stress [11, 12]. Treatments available to induce repigmentation include topical steroids, calcineurin inhibitors, vitamin D analogs, phototherapy, laser therapy, and surgery; however, no topical products currently carry US FDA approval to increase the rate of repigmentation in vitiligo. Furthermore, current treatment results can be slow, unsatisfactory, and limited by side effects [3, 4, 13]. Accordingly, there is interest among patients and physicians in the use of complementary treatments, such as herbal and vitamin supplements [3]. The efficacy and safety of these products is much less well-established than those of drugs that are subjected to a formal clinical, preclinical and clinical development pathway and require the approval of the FDA for marketing clearance. Given the anecdotal promise of these treatments, we performed a search of PubMed/MEDLINE databases

for systemic alternative treatments for vitiligo, specifically herbal products and vitamin supplements. All prospective and retrospective studies available in English since 1966 were included in our review, with priority given to prospective, randomized trials. No studies involving systemic alternative treatments and vitiligo were excluded. Our search terms included 'vitiligo', 'leukoderma', 'alternative treatment', and 'complementary treatment'. It should be noted that other alternative treatment techniques, including acupuncture and moxibustion, have been described in the treatment of vitiligo. Furthermore, several alternative systems of medicine, such as homeopathy, Ayurveda, Unani, and Chinese medicine, have also been used to treat vitiligo; however, as this article focuses on systemic treatments, these holistic practices are beyond the scope of this discussion.

2 Discussion

Overall, we identified 27 studies involving systemic alternative treatments and vitiligo, including prospective controlled trials (n = 15), prospective uncontrolled trials (n = 9), and retrospective studies (n = 3) (Fig. 1). Publications identified included those involving the study of L-phenylalanine (L-Phe), *Polypodium leucotomos*, khellin, *Ginkgo biloba* (GB), and vitamins such as vitamin B12, C, E, folic acid, and zinc. We critically reviewed the literature in order to present an overview of these systemic agents, describe proposed mechanisms of action, identify potential adverse effects, and discuss the primary evidence supporting their use in the management of vitiligo.

2.1 L-Phenylalanine

L-Phe is an essential amino acid and precursor to tyrosine in the melanin synthesis pathway. Oral phenylalanine has been explored in the treatment of vitiligo, primarily in combination with ultraviolet A (UVA) phototherapy (Table 1).

Siddiqui et al. examined the use of L-Phe with UVA phototherapy in 149 patients over 18 months. Patients received 50–100 mg/kg of L-Phe daily plus UVA treatment twice weekly (group 1, n = 132), 100 mg/kg of L-Phe alone (group 2, n = 6), or were followed without treatment (group 3, n = 11). In group 1, 71.2 % of patients responded to treatment, with repigmentation rates between 25 and 77 %, and 13.6 % had disease progression. No patients in groups 2 or 3 showed repigmentation, and 16.6 % and 36.6 % had progression, respectively [14]. The authors also conducted a double-blind trial involving 32 patients who were administered L-Phe or placebo and were treated with or without concurrent UVA therapy. At 6 months, 75 % of patients showed improvement with 30–60 % repigmentation. Phenylalanine alone was less effective as only one patient responded to treatment, demonstrating 25 % repigmentation. No patients receiving UVA with placebo showed improvement, and 33 % demonstrated progression [14].

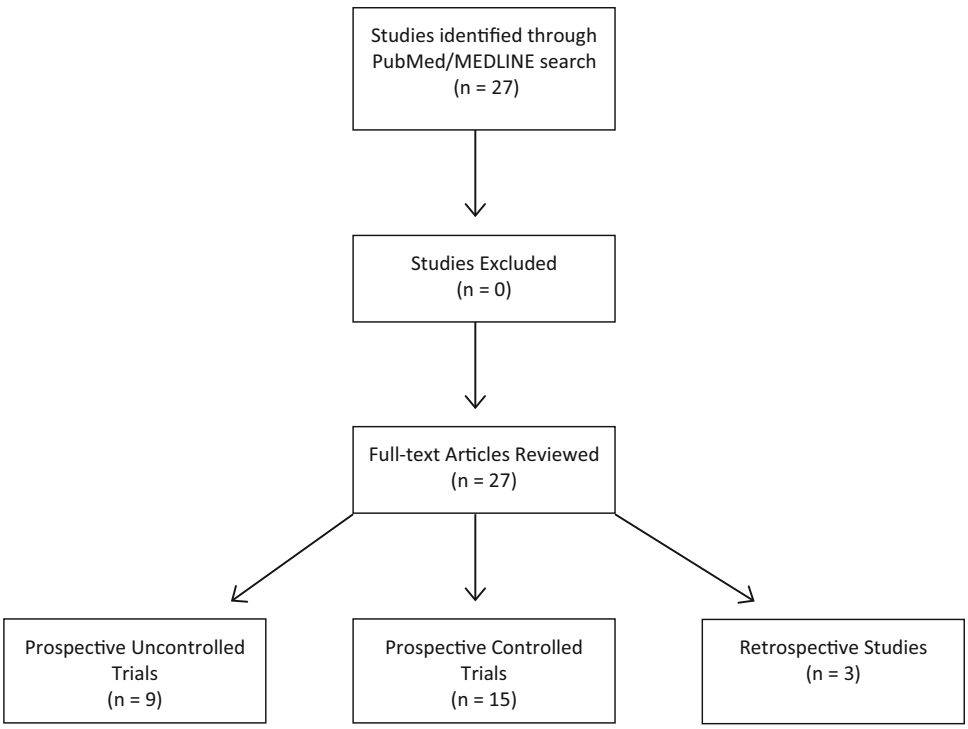

Fig. 1 Study selection process for alternative systemic vitiligo treatments

Table 1 Studies of oral L-phenylalanine in vitiligo treatment

Author	Year	Study type	Intervention	Oral dose (mg/kg)	No. of patients	Treatment period (months)	Primary outcome	Adverse effects
Antoniou et al. [15]	1989	Randomized, controlled	Oral L-Phe ± 10 % topical phenylalanine + UVA phototherapy	100	21	6	82 and 90 % of patients in the oral and oral + topical groups, respectively, showed ≥51 % repigmentation vs. 10 % of control patients	None
Camacho and Mazuecos [20]	2002	Randomized, controlled	Oral L-Phe + 10 % topical phenylalanine + UVA phototherapy/sunlight + 0.025 % clobetasol	100	70	6–24	90.9 % showed improvement. At least 75 % improvement in 68.5 % of patients was observed, with the highest rate of repigmentation on the face (87.9 %), followed by the trunk (60.4 %) and limbs (54.6 %)	NA
Cormane et al. [16]	1985	Controlled	Oral L-Phe + UVA phototherapy	50	19	6–8	Repigmentation observed in 94.7 % (26.3 % dense and 68.4 % sparse repigmentation)	None
Siddiqui et al. [14]	1994	Randomized, controlled, open	Oral L-Phe or placebo ± UVA phototherapy	50–100	149	18	L-Phe + UVA: 25–77 % repigmentation in 71.2 % of patients, 15.1 % stable, 13.6 % progression L-Phe alone: 83.3 % stable, 16.6 % progression No treatment: 63.6 % stable, 36.6 % progression	NA
Siddiqui et al. [14]	1994	Double-blinded, randomized, controlled	Oral L-Phe or placebo ± UVA phototherapy	100	32	6	L-Phe + UVA: 75 % of patients showed improvement with 30–60 % repigmentation L-Phe alone: 1 patient (20 %) showed 25 % repigmentation, 4 (60 %) showed stable disease, and 1 patient (20 %) showed progression Placebo + UVA: No improvement noted. Four patients (66.6 %) were stable, 2 patients (33.3 %) had progression	NA
Kuiters et al. [19]	1986	Uncontrolled	Oral L-Phe + sunlight	50	13	3	43.3 % of patients responded to treatment, demonstrating 81 % mean repigmentation	NA
Schulpis et al. [21]	1989	Uncontrolled	Oral L-Phe + UVA phototherapy	100	13	3–4	Six patients showed 50–90 % improvement; the remainder failed to respond	None
Thiele and Steigleder [17]	1987	Uncontrolled	Oral L-Phe + UVA phototherapy	50	20	6	85 % of patients showed repigmentation, which was, at most, 50 % of affected surface area	NA
Camacho and Mazuecos [18]	1999	Retrospective	Oral L-Phe ± 10 % topical phenylalanine + 30 min of sun exposure daily	50–100	193	6–36	56.7 % of patients had at least 75 % response. 63.2 % achieved full repigmentation on the face, and 35.7 % and 21.1 % for the trunk and limbs, respectively. No significant difference between the 50 and 100 mg/kg doses	NA
Greiner et al. [61]	1994	Retrospective	Oral L-Phe + UVA phototherapy	50–100	41	60	44 % had permanent repigmentation. 52 % were satisfied with treatment	None

L-*Phe* L-phenylalanine, *NA* not addressed in study, *UVA* ultraviolet A

Antoniou et al. randomized 21 patients to treatment with 100 mg/kg of L-Phe, followed by UVA exposure (group 1) or 100 mg/kg along with 10 % L-Phe topical cream applied 20 min before phototherapy (group 2). At 6 months, at least 75 % repigmentation was observed in five patients in the oral treatment group, while seven patients in the oral plus topical group observed at least 75 % repigmentation. Only 10 % of patients in the control group treated with UVA alone showed over 50 % improvement, compared with 82 and 90 % in treatment groups 1 and 2, respectively [15].

In two other trials investigating 50 mg/kg of L-Phe and UVA phototherapy twice weekly, response rates were between 85 and 95 % after 6–8 months [16, 17]. In one retrospective study of 193 patients treated with 50–100 mg/kg orally, 10 % Phe gel, and 30 min of sun exposure, ≥75 % improvement occurred in 56.7 % of patients. Complete repigmentation was achieved in 63.2 % of patients on the face, 35.7 % on the trunk, and 21.1 % on the limbs. No significant difference was observed between the 50 and 100 mg/kg doses ($p = 0.48$) [18].

Patients from Curacao were treated with L-Phe and were exposed to sunlight. Repigmentation occurred in 43.3 % of patients at 3-month follow-up, with an average of 81 % repigmentation [19]. Camacho and Mazuecos treated 70 patients with oral L-Phe, 10 % topical gel, 0.025 % clobetasol nightly, and sunlight or UVA lamp exposure. Patients were followed for 6–25 months. At least 75 % improvement was observed in 68.5 % of patients, with the highest rate of repigmentation observed on the face (87.9 %), then the trunk (60.4 %) and the limbs (54.6 %) [20].

Few to no side effects have been reported using phenylalanine, and it is safe to use in children. In an uncontrolled study of 13 pediatric patients, 100 mg/kg L-Phe with UVA phototherapy resulted in complete repigmentation in three patients and 50–90 % improvement in six patients. Repigmentation occurred most readily on the face and extremities [21].

The uptake of phenylalanine by melanocytes, and conversion to tyrosine by the enzyme phenylalanine hydroxylase (PAH), is essential for the formation of pigment [12]. It has been hypothesized that the metabolism and uptake of phenylalanine is impaired in vitiligo [12, 22]; however, phenylalanine appears to be beneficial in vitiligo unrelated to its role in the tyrosine pathway. It has also been proposed that L-Phe may interfere with the production of antibodies against melanocytes [15, 23]. In animal studies, one group demonstrated that phenylalanine supplementation reduced antibody production, which was thought to result from saturation of amino acid transporters, limiting the available pool of amino acids for antibody synthesis [23]. Therefore, L-Phe may act to limit further attack on melanocytes, while phototherapy induces repigmentation.

In summary, L-Phe may be considered as a supplement to treatment with UVA or sunlight as it has been shown to improve outcomes in several randomized trials.

2.2 *Polypodium leucotomos*

Polypodium leucotomos, a fern indigenous to Central America, has been available as a health supplement for 30 years [24], and *P. leucotomos* extract has been studied for the treatment of various conditions such as psoriasis, melasma, UV damage, and vitiligo [24–26] (Table 2).

Middelkamp-Hup and colleagues investigated the use of *P. leucotomos* along with narrowband ultraviolet B (NBUVB) for vitiligo. Fifty patients received 250 mg of *P. leucotomos* three times daily or placebo, along with two weekly sessions of NBUVB. After 25–26 weeks, repigmentation of the head and neck occurred in 44 % of *P. leucotomos* patients compared with 27 % of controls ($p = 0.06$). No significant difference in repigmentation of the trunk or extremities was observed. The benefit was most pronounced in patients with lighter skin types, likely reflecting *P. leucotomos*-mediated prevention of oxidative damage since lighter skin has less inherent antioxidant capacity [27].

Pacifico and colleagues enrolled 57 patients with generalized vitiligo to receive NBUVB phototherapy twice daily with or without 480 mg of *P. leucotomos* daily. At 6 months, 47.8 % of patients responded to treatment in the *P. leucotomos* and NBUVB group versus 22 % with NBUVB alone [28]. Reyes et al. examined the use of *P. leucotomos* in combination with psoralen and ultraviolet A (PUVA) and 8-methoxypsoralen. Nineteen patients were randomized to receive PUVA plus *P. leucotomos* or placebo. After 12 weeks, half of the patients in the *P. leucotomos* group demonstrated 50 % repigmentation or greater, whereas none of the patients in the placebo group achieved 50 % repigmentation. At baseline, blood samples showed patients with vitiligo had increased expression of CD25 and HLA-DR+, and decreased expression of CD8+CD45RO+ cells. In patients treated with *P. leucotomos*, but not in control patients, there was a normalization of lymphocyte ratios, suggesting an immunomodulatory effect [29]. *P. leucotomos* has been shown to modulate cellular immunity and promote an anti-inflammatory cytokine milieu [27]. In mouse models, *P. leucotomos* extract decreased levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6, both of which interfere with melanocyte functioning and promote lymphocyte chemotaxis [30]. There is also likely benefit in vitiligo from its antioxidant properties and elimination of

Table 2 Studies of oral *Polypodium leucotomos* in vitiligo treatment

Author	Year	Study type	Intervention	Oral dose	No. of patients	Treatment period (months)	Primary outcome	Adverse effects
Middelkamp-Hup et al. [27]	2007	Double-blinded, randomized controlled	Oral *Polypodium leucotomos* + NBUVB phototherapy twice weekly	250 mg tid	50	6–7	Benefit observed in repigmentation of the head and neck, as repigmentation occurred in 44 % of *Polypodium leucotomos* patients compared with 27 % of controls. No significant difference in repigmentation for the trunk or extremities	Mild itching occurred in 40 % of patients taking *Polypodium leucotomos* vs. 21 % of control patients
Pacifico et al. [28]	2009	Randomized, controlled	NBUVB phototherapy twice weekly ± oral *Polypodium leucotomos*	480 mg daily	57	6	47.8 % in the *Polypodium leucotomos* + NBUVB group vs. 22 % with NBUVB alone	NA
Reyes et al. [29]	2006	Double-blinded, randomized controlled	PUVA phototherapy three times weekly ± oral *Polypodium leucotomos*	720 mg daily	19	3	50 % of patients in the *Polypodium leucotomos* group demonstrated at least 50 % repigmentation vs. none of the placebo group	None
Mohammad [26]	1989	Uncontrolled trial	Oral *Polypodium leucotomos* + sun exposure during spring/summer months	360 mg daily	22	5	All patients had complete repigmentation	NA

NA not addressed in study, *NBUVB* narrowband ultraviolet B, *PUVA* psoralen and ultraviolet A, *tid* three times daily

reactive oxygen species (ROS), resulting in a reduction of the oxidative stress [27].

Polypodium leucotomos displays photoprotective properties and may be beneficial to patients undergoing phototherapy [24]. The photoprotective effects of *P. leucotomos* were demonstrated in a study of nine patients (Fitzpatrick skin type II–III) exposed to UV radiation with or without an oral dose of 7.5 mg/kg of *P. leucotomos*. Patients receiving *P. leucotomos* showed a significant decrease in UV-induced erythema, epidermal proliferation, and pyrimidine dimer formation [31]. The mechanism of action of this effect is unknown but may involve inhibition of ROS, support of DNA repair enzymes, and maintenance of Langerhans cells [24, 31, 32].

There is minimal toxicity associated with oral administration of *P. leucotomos* [33]. Adverse reactions are limited and include mild pruritus and gastrointestinal upset [27]. In summary, when used in combination with NBUVB or PUVA therapy, *P. leucotomos* may improve repigmentation as well as provide photoprotective properties

2.3 Khellin

Khellin is an extract from the Mediterranean fruit *Ammi visnaga*. Since khellin is structurally similar to the psoralens used in PUVA, interest developed in the use of khellin as a safer alternative to psoralens, which are known to crosslink DNA and be mutagenic [34, 35]. In contrast, khellin does not create DNA crosslinks upon UVA exposure in vitro or within mammalian cells [36].

In one study, 60 patients were treated with 100 mg of khellin or placebo, along with 15 min of natural sunlight exposure daily. After 4 months, 16.6 % of patients had 90–100 % repigmentation, 23.3 % showed 50–60 % repigmentation, and 36.6 % did not respond. No repigmentation was observed among 30 control patients [37] (Table 3).

Hofer et al. retrospectively reviewed the outcomes of 28 patients treated with UVA phototherapy and 100 mg of khellin for generalized vitiligo. Among patients receiving at least 3 months of treatment, 41 % demonstrated at least 70 % repigmentation, and nausea was experienced by 29 % of patients. Long-term follow-up was available for up to 9.2 years (mean 3.3 years) and showed no instances of actinic damage or skin cancer [34]. Ortel et al. investigated the use of UVA phototherapy three times weekly along with oral ($n = 25$) or topical ($n = 3$) khellin. After 6 months, 41 % of patients achieved 70 % repigmentation or greater. Side effects included elevations in hepatic enzymes (28 %), nausea (21 %,) and orthostasis (7 %) [35].

While the toxicity of khellin is reported to be less than that of psoralen, it has been reported to cause transaminitis,

Table 3 Studies of khellin in vitiligo treatment

Author	Year	Study type	Intervention	Oral dose (mg)	No. of patients	Treatment period (months)	Primary outcome	Adverse effects
Abdel-Fattah et al. [37]	1982	Double-blinded, controlled	Khellin or placebo + natural sunlight	100	60	4	16.6 % of patients had 90–100 % repigmentation, 23.3 % showed 50–60 % repigmentation, and 36.6 % did not respond. No repigmentation was observed among placebo controls	NA
Ortel et al. [35]	1988	Uncontrolled	Khellin (oral or topical) + UVA phototherapy	100	28	6	41 % of patients achieved at least 70 % repigmentation	Transaminitis (28 %), nausea (21 %), and orthostasis (7 %)
Hofer et al. [34]	2001	Retrospective	Khellin + UVA phototherapy	100	28	3	41 % of patients had at least 70 % repigmentation	Nausea (29 %)

NA not addressed in study, *UVA* ultraviolet A

nausea, and orthostatic hypotension [35]. Khellin has been shown to provide benefit over sunlight alone, but the use of systemic khellin may be limited by the potential side effects. Accordingly, research interest has shifted towards the topical application of khellin within liposomes in combination with phototherapy [38, 39].

2.4 *Ginkgo biloba*

GB is a traditional Chinese herb that has gained popularity in treating a variety of conditions, including cardiovascular disease, anxiety, dementia, macular degeneration, and vitiligo [3, 5, 40].

Parsad et al. conducted a double-blind study of GB in 52 patients with limited, slow-spreading vitiligo. Patients were treated with 40 mg of GB monotherapy or placebo three times daily. Arrest of active disease was seen in 80 versus 36.6 % of control patients ($p = 0.006$). At least 75 % repigmentation was observed in 40 % of patients taking GB compared with 9 % of control patients. Notably, all patients with acrofacial vitiligo had cessation of active disease [5] (Table 4).

Szczurko et al. treated 12 patients with 60 mg of GB twice daily for 12 weeks. All patients had cessation of disease progression and demonstrated an average repigmentation of 15 % based on the Vitiligo Area Scoring Index ($p = 0.021$). Overall, the greatest improvement was on the trunk and lower extremities [40].

The anti-inflammatory properties of GB are thought to relate to a reduction in cyclooxygenase activity and decreased IL-8 and vascular endothelial growth factor (VEGF) release in response to TNF-α [41]. Since oxidative stress plays a role in vitiligo, the antioxidant properties of GB may also contribute to the observed benefit [5, 40]. Moreover, GB may further inhibit the progression of vitiligo through its anxiolytic properties since psychological stress has been shown to exacerbate vitiligo [40].

The majority of patients report no adverse reactions while taking GB; however, the most common side effect is mild gastrointestinal upset [40]. While there is a potential risk of coagulopathy associated with GB [42], in the trial by Szczurko et al. no significant changes were observed in platelet concentration, partial thromboplastin time, or international normalized ratio from baseline values [40]. Moreover, GB should be used with caution in patients taking other drugs for anticoagulation.

Based on the results of two prospective trials, GB, as a monotherapy, is a promising alternative treatment that has been shown to inhibit disease progression and augment repigmentation.

2.5 Vitamin B12 and Folic Acid

Vitiligo is associated with decreased serum levels of vitamin B12 and folic acid [43, 44]. In addition, an association between vitiligo and pernicious anemia has been observed [45, 46]. Therefore, the role of B12 and folate in the management of vitiligo has been explored (Table 5).

Montes and colleagues reported that among 15 vitiligo patients, 73.3 % had folic acid deficiency, 33.3 % had B12 deficiency, and 26.6 % demonstrated decreased vitamin C levels. Upon daily vitamin supplementation, disease progression stopped in all patients, and 80–100 % repigmentation was observed in all patients within 2 years [47].

Juhlin and Olsson treated 100 patients with vitamin B12 and folate, along with sunlight or home UVB exposure. At 3–6 months, repigmentation occurred in 52 % of patients

Table 4 Studies of *Ginkgo biloba* in vitiligo treatment

Author	Year	Study type	Intervention	Oral dose	No. of patients	Treatment period (months)	Primary outcome	Adverse effects
Parsad et al. [5]	2003	Double-blinded, randomized, controlled	*Ginkgo biloba* monotherapy or placebo	40 mg three times daily	52	6	Cessation of active disease in 80 % of patients taking *Ginkgo biloba* vs. 36.6 % of placebo patients, and ≥75 % repigmentation in 40 % of patients vs. 9 %	None
Szczurko et al. [40]	2011	Prospective uncontrolled	*Ginkgo biloba* monotherapy	120 mg daily	12	3	All patients had cessation of disease progression and showed an average score improvement of 5 to 4.5 on the vitiligo area scoring index, and average repigmentation of 15 %	One case of potential gastrointestinal upset. No change in coagulation labs

and 64 % had cessation of disease progression [48]. Of note, no comparison was made to a control group receiving only light therapy, therefore the contribution of the vitamins cannot be deduced.

Another uncontrolled trial examined the use of broadband UVB two to three times weekly, along with vitamin B12, vitamin C, and folic acid. All nine patients demonstrated cessation of disease progression and at least 51 % repigmentation within 2–8 months [49].

A randomized, controlled trial by Tjioe et al. did not show additional benefit from vitamin B12 and folic acid supplementation in 27 patients treated with NBUVB. Patients were randomized to receive either NBUVB alone or NBUVB along with B12 and folate. After 1 year, 92 % of patients showed repigmentation but no significant difference was observed between groups ($p = 0.175$) [50].

Vitamin B12 and folic acid supplementation may act via decreasing homocysteine levels. Homocysteine has been noted to be elevated in vitiligo patients, which may relate to the role of B12 and folate in the conversion of homocysteine to methionine [51]. In one study, the average homocysteine level was significantly higher in patients with vitiligo than in controls, and patients with active vitiligo had significantly higher homocysteine levels than those with stable disease [51]. Similarly, Silverberg and Silverberg showed that elevated serum homocysteine was associated with vitiligo, and correlated with the extent of disease in 24 children [52]. Homocysteine is thought to directly damage melanocytes by inducing oxidative damage [44].

Since vitamin B12 and folic acid are water-soluble vitamins with no toxicity when used at typical treatment doses, supplementation is associated with minimal cost and risk. However, evidence to support the use of B12 and folic acid supplementation remains unclear as the only randomized controlled trial conducted did not reveal additional benefit compared with NBUVB alone.

2.6 Antioxidant Vitamins

Antioxidants, notably vitamin E, have an important role in the skin to scavenge ROS, prevent membrane oxidation, and reduce UVB-induced skin damage [53]. Passi and colleagues evaluated the levels of various antioxidants in the epidermis of patients and concluded that those with vitiligo had significantly lower levels of ubiquinol, vitamin E, glutathione, and catalase [54]. Similarly, Khan et al. showed reduced vitamin C and E levels in vitiligo patients compared with controls [55].

Elgoweini and colleagues randomized 24 patients to receive treatment with NBUVB with or without oral vitamin E supplementation (Table 6). Vitamin E supplementation was associated with superior clinical outcomes as 72.7 versus 55.6 % of patients, respectively, achieved ≥51 % repigmentation. The mean number of treatments until patients achieved 50 % repigmentation was fewer in the vitamin E group (16 vs. 20 treatments). In addition, patients in the NBUVB plus vitamin E group experienced less post-phototherapy erythema (70 vs. 85 %). Malondialdehyde levels were measured as a marker of lipid oxidation and were found to be significantly reduced in the vitamin E group [53].

Dell'Anna and colleagues conducted a double-blind, randomized trial of 35 patients treated with NBUVB twice weekly in combination with an 'antioxidant pool' composed of α-lipoic acid, vitamin C, vitamin E, and polyunsaturated fatty acids. Patients began taking the antioxidant supplement 2 months prior to the initiation of NBUVB therapy. After 2 months of antioxidant supplementation, the catalase activity within peripheral monocytes was 151 % of baseline value, and the production of ROS was 57 % of the value before supplementation. After 6 months of NBUVB, 47 % of patients taking the antioxidant pool showed at least 75 % repigmentation compared with only 18 % of controls [56].

Table 5 Studies of vitamin B12 or folic acid in vitiligo treatment

Author	Year	Study type	Intervention	Dose	No. of patients	Treatment period (months)	Primary outcome	Adverse effects
Tjioe et al. [50]	2002	Controlled	NBUVB phototherapy three times weekly ± vitamin B12 and folic acid	Vitamin B12: 200 mg PO daily Folic acid: 5 mg PO daily	27	12	92 % of patients showed repigmentation, but no significant difference in the rates of repigmentation between groups	None
Don et al. [49]	2006	Uncontrolled	Broadband UVB two to three times weekly + vitamin B12, vitamin C, and folic acid	Vitamin B12: 200 mg PO daily Vitamin C: 1 g PO daily Folic acid: 10 mg PO daily	9	2–8	All 9 patients had cessation of disease progression and at least 51 % repigmentation	NA
Juhlin and Olsson [48]	1997	Uncontrolled	Vitamin B12, folic acid, and sunlight or UVB lamp	Vitamin B12: 1 mg PO daily Folic acid: 4 mg PO daily	100	3–6	Repigmentation in 52 % of patients. Six patients demonstrated 100 % repigmentation. 64 % of patients had cessation of disease progression	None
Montes et al. [47]	1992	Uncontrolled	Supplementation of vitamin B12, vitamin C, and folic acid	Vitamin B12: 200 mg IM injection weekly Vitamin C: 1 g PO daily Folic acid: 4 mg PO daily	15	24	Disease progression stopped in all patients within several weeks and significant repigmentation was observed after 3 months. 80–100 % repigmentation by 2 years	None

NA not addressed in study, *NBUVB* narrowband ultraviolet B, *PO* per os (by mouth), *UVB* ultraviolet B, *IM* intramuscular

Table 6 Studies of antioxidant vitamins and zinc in vitiligo treatment

Author	Year	Study type	Intervention	Oral dose	No. of patients	Treatment period (months)	Primary outcome	Adverse effects
Antioxidant vitamins								
Akyol et al. [57]	2002	Randomized, controlled	PUVA phototherapy ± vitamin E supplementation	900 IU daily	30	6	No significant difference in clinical outcomes between groups but significantly less generation of lipoperoxides in the vitamin E group	NA
Dell'Anna et al. [56]	2007	Double-blinded, randomized, controlled	NBUVB phototherapy twice weekly ± antioxidant pool containing α-lipoic acid, vitamin C, vitamin E, and PUFA	α-Lipoic acid: 100 mg daily Vitamin C: 100 mg daily Vitamin E: 40 mg daily PUFA: 12 %	35	6–8	Antioxidant pool + NBUVB group showed a significant benefit as 47 % of patients demonstrated ≥75 % repigmentation vs. 18 % of controls. Catalase activity and ROS were 114 and 60 % of baseline, respectively, within peripheral blood monocytes	None
Elgoweini et al. [53]	2009	Randomized, controlled	NBUVB phototherapy three times weekly ± vitamin E	400 IU daily	24	6	72.7 % in vitamin E group vs. 55.6 % of control patients achieved ≥51 % repigmentation. Mean number of treatments to achieve 50 % repigmentation was significantly less in the vitamin E group (16 vs. 20 treatments)	None
Zinc								
Yaghoobi et al. [60]	2011	Randomized, controlled	Topical corticosteroids ± oral zinc sulfate	440 mg daily	25	4	Trend towards a higher response rate with corticosteroid + zinc compared with topical corticosteroids alone, with 24.7 vs. 21.43 % mean response	Gastric irritation (13.3 %)

IU International Units, *NA* not addressed in study, *NBUVB* narrowband ultraviolet B, *PUFA* polyunsaturated fatty acids, *PUVA* psoralen and ultraviolet A, *ROS* reactive oxygen species

Akyol et al. randomized 30 patients to receive PUVA alone or PUVA plus vitamin E. While there was no significant difference in clinical outcomes between groups, there was significantly less generation of lipoperoxides in the group with the Vitamin E [57].

While UV exposure is effective in inducing repigmentation, it also inhibits antioxidant function and promotes oxidative stress [53]. In the trial by Dell'Anna et al., the control group showed an almost 10 % reduction in antioxidant activity after phototherapy compared with baseline [56]. Thus, the synergy between vitamin E and other antioxidants with phototherapy may be related to augmentation of the antioxidant supply, thereby maximizing the benefit from phototherapy.

Overall, antioxidant vitamins, notably vitamin E, appear to increase efficacy when combined with phototherapy, as shown in two separate prospective randomized studies.

2.7 Zinc

Zinc plays a role in the regulation of gene expression and acts as an enzyme co-factor for superoxide dismutase, an antioxidant in the skin [58]. Furthermore, zinc may prevent apoptosis of melanocytes as decreases in intracellular zinc concentrations trigger the activation of apoptotic caspases [59].

Shameer et al. found 21.6 % of vitiligo patients had deficient zinc levels compared with no patients in the control group (p = 0.0002) [58]. Yaghoobi et al. randomized 35 patients with vitiligo to receive 0.05 % clobetasol propionate on the body and 0.1 % triamcinolone acetonide for face and flexure surfaces with or without 440 mg of oral zinc sulfate supplementation daily. Zinc status was comparable between groups at baseline. After 4 months, the mean response rate was higher in the corticosteroid plus zinc group (24.7 vs. 21.43 %; p = 0.40) (Table 6) [60].

The use of zinc in vitiligo therapy has been shown to offer a slight benefit when used in combination with topical steroids; however, this merits further study. Nonetheless, one limiting aspect of zinc supplementation is treatment-related gastrointestinal side effects [59]. In the trial by Yaghoobi et al., 13.3 % of patients taking zinc complained of gastric irritation [60].

3 Conclusions

A number of complementary treatments for vitiligo, specifically herbal products and vitamin supplements, have been studied to supplement traditional treatment modalities.

In randomized trials, L-Phe was shown to improve outcomes when added to therapy with UVA or sunlight. Furthermore, *P. leucotomos* improved outcomes when added to NBUVB or PUVA therapy, and may improve treatment safety through its photoprotective properties. Khellin provides benefit beyond treatment with sunlight alone and may be a safer alternative to PUVA; however, treatment with khellin is limited by risks of transaminitis and nausea. In two prospective trials, GB inhibited disease progression and augmented repigmentation. Evidence in support of B12 and folic acid supplementation is lacking as the only randomized trial did not show an additional benefit when added to NBUVB therapy. In two controlled trials, supplementation with vitamin E alone, or in combination with other antioxidants, was shown to improve outcomes and tolerability of phototherapy. Zinc may offer a marginal benefit compared with topical medications but its use may be limited by gastric side effects.

While a number of studies have shown benefit associated with the use of these alternative treatments, larger, well-controlled trials are warranted to firmly establish the place of these agents in the therapeutic hierarchy. Moreover, the use of these alternative treatments can be considered as a supplement to the treatment regimen of interested or treatment refractory patients as they appear to be relatively safe and may provide additional benefit in outcomes and patient satisfaction.

Compliance with Ethical Standards

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References

1. Taieb A, Picardo M. Clinical practice. Vitiligo. N Engl J Med. 2009;360(2):160–9.
2. Lotti T, Gori A, Zanieri F, Colucci R, Moretti S. Vitiligo: new and emerging treatments. Dermatol Ther. 2008;21(2):110–7.
3. Szczurko O, Boon HS. A systematic review of natural health product treatment for vitiligo. BMC Dermatol. 2008;8:2.
4. Kostopoulou P, Jouary T, Quintard B, Ezzedine K, Marques S, Boutchnei S, et al. Objective vs. subjective factors in the psychological impact of vitiligo: the experience from a French referral centre. Br J Dermatol. 2009;161(1):128–33.
5. Parsad D, Dogra S, Kanwar AJ. Quality of life in patients with vitiligo. Health Qual Life Outcomes. 2003;1:58.
6. Yaghoobi R, Omidian M, Bagherani N. Vitiligo: a review of the published work. J Dermatol. 2011;38(5):419–31.
7. Hann SK, Park YK, Chun WH. Clinical features of vitiligo. Clin Dermatol. 1997;15(6):891–7.
8. Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, Turka LA. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-gamma for autoreactive CD8(+)

T-cell accumulation in the skin. J Invest Dermatol. 2012;132(7):1869–76.
9. Spritz RA. Recent progress in the genetics of generalized vitiligo. J Genet Genomics. 2011;38(7):271–8.
10. Spritz RA. Shared genetic relationships underlying generalized vitiligo and autoimmune thyroid disease. Thyroid. 2010;20(7):745–54.
11. Egli F, Walter R. Images in clinical medicine. Vitiligo and pernicious anemia. N Engl J Med. 2004;350(26):2698.
12. Schallreuter KU, Chavan B, Rokos H, Hibberts N, Panske A, Wood JM. Decreased phenylalanine uptake and turnover in patients with vitiligo. Mol Genet Metab. 2005;86(Suppl 1):S27–33.
13. Xiao BH, Wu Y, Sun Y, Chen HD, Gao XH. Treatment of vitiligo with NB-UVB: a systematic review. J Dermatolog Treat. 2015;26(4):340–6.
14. Siddiqui AH, Stolk LM, Bhaggoe R, Hu R, Schutgens RB, Westerhof W. L-phenylalanine and UVA irradiation in the treatment of vitiligo. Dermatology. 1994;188(3):215–8.
15. Antoniou C, Schulpis H, Michas T, Katsambas A, Frajis N, Tsagaraki S, et al. Vitiligo therapy with oral and topical phenylalanine with UVA exposure. Int J Dermatol. 1989;28(8):545–7.
16. Cormane RH, Siddiqui AH, Westerhof W, Schutgens RB. Phenylalanine and UVA light for the treatment of vitiligo. Arch Dermatol Res. 1985;277(2):126–30.
17. Thiele B, Steigleder GK. Repigmentation treatment of vitiligo with L-phenylalanine and UVA irradiation [in German]. Z Hautkr. 1987;62(7):519–23.
18. Camacho F, Mazuecos J. Treatment of vitiligo with oral and topical phenylalanine: 6 years of experience. Arch Dermatol. 1999;135(2):216–7.
19. Kuiters GR, Hup JM, Siddiqui AH, Cormane RH. Oral phenylalanine loading and sunlight as source of UVA irradiation in vitiligo on the Caribbean island of Curacao NA. J Trop Med Hyg. 1986;89(3):149–55.
20. Camacho F, Mazuecos J. Oral and topical L-phenylalanine, clobetasol propionate, and UVA/sunlight–a new study for the treatment of vitiligo. J Drugs Dermatol. 2002;1(2):127–31.
21. Schulpis CH, Antoniou C, Michas T, Strarigos J. Phenylalanine plus ultraviolet light: preliminary report of a promising treatment for childhood vitiligo. Pediatr Dermatol. 1989;6(4):332–5.
22. Schallreuter KU, Zschiesche M, Moore J, Panske A, Hibberts NA, Herrmann FH, et al. In vivo evidence for compromised phenylalanine metabolism in vitiligo. Biochem Biophys Res Commun. 1998;243(2):395–9.
23. Ryan WL, Carver MJ. Inhibition of antibody synthesis by L-phenylalanine. Science. 1964;143(3605):479–80.
24. Emanuel P, Scheinfeld N. A review of DNA repair and possible DNA-repair adjuvants and selected natural anti-oxidants. Dermatol Online J. 2007;13(3):10.
25. Nestor M, Bucay V, Callender V, Cohen JL, Sadick N, Waldorf H. *Polypodium leucotomos* as an adjunct treatment of pigmentary disorders. J Clin Aesthet Dermatol. 2014;7(3):13–7.
26. Mohammad A. Vitiligo repigmentation with anapsos (*Polypodium leucotomos*). Int J Dermatol. 1989;28(7):479.
27. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral *Polypodium leucotomos* extract: a randomized double-blind placebo-controlled study. J Eur Acad Dermatol Venereol. 2007;21(7):942–50.
28. Pacifico A, Vidolin AP, Leone G, Iacovelli P. Combined treatment of narrowband ultraviolet B light (NBUVB) phototherapy and oral *Polypodium leucotomos* extract versus NB UVB phototherapy alone in the treatment of patients with vitiligo. J Am Acad Dermatol. 2009;3(Suppl 1):AB154.
29. Reyes E, Jaen P, de las Heras E, Carrion F, Alvarez-Mon M, de Eusebio E, et al. Systemic immunomodulatory effects of *Polypodium leucotomos* as an adjuvant to PUVA therapy in generalized vitiligo: a pilot study. J Dermatol Sci. 2006;41(3):213–6.
30. Brieva A, Guerrero A, Pivel JP. Immunomodulatory properties of a hydrophilic extract of *Polypodium leucotomos*. Inflammopharmacology. 2002;9(4):361–71.
31. Middelkamp-Hup MA, Pathak MA, Parrado C, Goukassian D, Rius-Diaz F, Mihm MC, et al. Oral *Polypodium leucotomos* extract decreases ultraviolet-induced damage of human skin. J Am Acad Dermatol. 2004;51(6):910–8.
32. El-Haj N, Goldstein N. Sun protection in a pill: the photoprotective properties of *Polypodium leucotomos* extract. Int J Dermatol. 2015;54(3):362–6.
33. Gonzalez S, Gilaberte Y, Philips N, Juarranz A. Current trends in photoprotection: a new generation of oral photoprotectors. Open Dermatol J. 2011;5:6–14.
34. Hofer A, Kerl H, Wolf P. Long-term results in the treatment of vitiligo with oral khellin plus UVA. Eur J Dermatol. 2001;11(3):225–9.
35. Ortel B, Tanew A, Honigsmann H. Treatment of vitiligo with khellin and ultraviolet A. J Am Acad Dermatol. 1988;18(4 Pt 1):693–701.
36. Morliere P, Honigsmann H, Averbeck D, Dardalhon M, Huppe G, Ortel B, et al. Phototherapeutic, photobiologic, and photosensitizing properties of khellin. J Invest Dermatol. 1988;90(5):720–4.
37. Abdel-Fattah A, Aboul-Enein MN, Wassel GM, El-Menshawi BS. An approach to the treatment of vitiligo by khellin. Dermatologica. 1982;165(2):136–40.
38. de Leeuw J, Assen YJ, van der Beek N, Bjerring P, Martino Neumann HA. Treatment of vitiligo with khellin liposomes, ultraviolet light and blister roof transplantation. J Eur Acad Dermatol Venereol. 2011;25(1):74–81.
39. Valkova S, Trashlieva M, Christova P. Treatment of vitiligo with local khellin and UVA: comparison with systemic PUVA. Clin Exp Dermatol. 2004;29(2):180–4.
40. Szczurko O, Shear N, Taddio A, Boon H. *Ginkgo biloba* for the treatment of vitilgo vulgaris: an open label pilot clinical trial. BMC Complement Altern Med. 2011;11:21.
41. Trompezinski S, Bonneville M, Pernet I, Denis A, Schmitt D, Viac J. *Gingko biloba* extract reduces VEGF and CXCL-8/IL-8 levels in keratinocytes with cumulative effect with epigallocatechin-3-gallate. Arch Dermatol Res. 2010;302(3):183–9.
42. Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with G*inkgo biloba*: a case report and systematic review of the literature: a case report and systematic review of the literature. J Gen Intern Med. 2005;20(7):657–61.
43. Karadag AS, Tutal E, Ertugrul DT, Akin KO, Bilgili SG. Serum holotranscobalamine, vitamin B12, folic acid and homocysteine levels in patients with vitiligo. Clin Exp Dermatol. 2012;37(1):62–4.
44. Shaker OG, El-Tahlawi SM. Is there a relationship between homocysteine and vitiligo? A pilot study. Br J Dermatol. 2008;159(3):720–4.
45. Howitz J, Schwartz M. Vitiligo, achlorhydria, and pernicious anaemia. Lancet. 1971;1(7713):1331–4.
46. Sabry HHSJ, Hashim HM. Serum levels of homocysteine, vitamin B12, and folic acid in vitiligo. Egypt J Dermatol Venereol. 2014;34:65–9.
47. Montes LF, Diaz ML, Lajous J, Garcia NJ. Folic acid and vitamin B12 in vitiligo: a nutritional approach. Cutis. 1992;50(1):39–42.
48. Juhlin L, Olsson MJ. Improvement of vitiligo after oral treatment with vitamin B12 and folic acid and the importance of sun exposure. Acta Derm Venereol. 1997;77(6):460–2.
49. Don P, Iuga A, Dacko A, Hardick K. Treatment of vitiligo with broadband ultraviolet B and vitamins. Int J Dermatol. 2006;45(1):63–5.

50. Tjioe M, Gerritsen MJ, Juhlin L, van de Kerkhof PC. Treatment of vitiligo vulgaris with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12. Acta Derm Venereol. 2002;82(5):369–72.
51. Singh S, Singh U, Pandey SS. Increased level of serum homocysteine in vitiligo. J Clin Lab Anal. 2011;25(2):110–2.
52. Silverberg JI, Silverberg NB. Serum homocysteine as a biomarker of vitiligo vulgaris severity: a pilot study. J Am Acad Dermatol. 2011;64(2):445–7.
53. Elgoweini M, Nour El Din N. Response of vitiligo to narrowband ultraviolet B and oral antioxidants. J Clin Pharmacol. 2009;49(7):852–5.
54. Passi S, Grandinetti M, Maggio F, Stancato A, De Luca C. Epidermal oxidative stress in vitiligo. Pigment Cell Res. 1998;11(2):81–5.
55. Khan R, Satyam A, Gupta S, Sharma VK, Sharma A. Circulatory levels of antioxidants and lipid peroxidation in Indian patients with generalized and localized vitiligo. Arch Dermatol Res. 2009;301(10):731–7.
56. Dell'Anna ML, Mastrofrancesco A, Sala R, Venturini M, Ottaviani M, Vidolin AP, et al. Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial. Clin Exp Dermatol. 2007;32(6):631–6.
57. Akyol M, Celik VK, Ozcelik S, Polat M, Marufihah M, Atalay A. The effects of vitamin E on the skin lipid peroxidation and the clinical improvement in vitiligo patients treated with PUVA. Eur J Dermatol. 2002;12(1):24–6.
58. Shameer P, Prasad PV, Kaviarasan PK. Serum zinc level in vitiligo: a case control study. Indian J Dermatol Venereol Leprol. 2005;71(3):206–7.
59. Bagherani N, Yaghoobi R, Omidian M. Hypothesis: zinc can be effective in treatment of vitiligo. Indian J Dermatol. 2011;56(5):480–4.
60. Yaghoobi R, Omidian M, Bagherani N. Original article title: "Comparison of therapeutic efficacy of topical corticosteroid and oral zinc sulfate-topical corticosteroid combination in the treatment of vitiligo patients: a clinical trial". BMC Dermatol. 2011;11:7.
61. Greiner D, Ochsendorf FR, Milbradt R. Vitiligo therapy with phenylalanine/UVA. Catamnestic studies after five years [in German]. Hautarzt. 1994;45(7):460–3.