Eduvest – Journal of Universal Studies
Volume 6 Number 7, July, 2026
p- ISSN 2775-3735- e-ISSN 2775-3727

The Efficacy of a Combination of Oral Antioxidants (Vitamin C, Vitamin E, and Alpha-Lipoic Acid) as an Adjuvant Therapy for Vitiligo: A Systematic Review and Narrative Synthesis

Irnayati Rahman*, Antonius Wibowo, Putri Jati Utami
Universitas Islam Indonesia, Indonesia
Email: d10060irnayatirahman@gmail.com*

Keywords
vitiligo; autoimmunity; quality of life disorders.

Abstract
Vitiligo is a chronic acquired depigmentation disorder characterized by progressive melanocyte destruction, affecting approximately 0.5–2% of the global population and causing significant psychosocial impairment. The involvement of oxidative stress in melanocyte damage has encouraged the exploration of antioxidant supplementation as an adjunctive therapeutic approach. This study aimed to evaluate the efficacy of oral antioxidant combinations, particularly vitamin C, vitamin E, and alpha-lipoic acid (ALA), as adjunctive therapies for vitiligo and to assess the consistency of available clinical evidence. A systematic review and narrative synthesis were conducted following the PRISMA 2020 guidelines. Literature searches were performed in PubMed/MEDLINE, the Cochrane Library, Scopus, ScienceDirect, Google Scholar, and ClinicalTrials.gov. Eligible studies included randomized controlled trials evaluating oral antioxidant combinations combined with conventional vitiligo therapies, with outcomes including repigmentation, oxidative stress biomarkers, quality of life, and adverse effects. Two randomized controlled trials involving patients with vitiligo met the inclusion criteria. The findings demonstrated that antioxidant combinations, particularly ALA, vitamin C, and vitamin E combined with narrowband ultraviolet B (NB-UVB) therapy, showed potential benefits in improving repigmentation and reducing oxidative stress markers. However, another study reported no significant additional clinical improvement, indicating inconsistent outcomes influenced by disease subtype, lesion extent, treatment duration, and therapeutic protocols. In conclusion, oral antioxidant combinations represent a promising complementary therapy for vitiligo; however, current evidence remains insufficient to support their routine clinical application. Further large-scale randomized clinical trials with standardized protocols are required to establish their effectiveness and clinical relevance.

INTRODUCTION

Vitiligo is the most common acquired depigmentation disorder, characterized by progressive damage to functional melanocytes, resulting in milky-white macular lesions on the skin. The global prevalence of vitiligo is estimated to range from 0.5–2% of the world's population, affecting individuals across all racial and age groups without significant gender predilection (Bastonini et al., 2025). Although it is not life-threatening, vitiligo has a substantial psychosocial impact, including decreased self-confidence, social stigmatization, and

impairments in quality of life comparable to those associated with other severe dermatological conditions (Bhardwaj & Kaur, 2020).

The pathogenesis of vitiligo is multifactorial, involving complex interactions among autoimmunity, intrinsic melanocyte dysfunction, and oxidative stress. Scientific evidence suggests that the accumulation of reactive oxygen species (ROS) plays a central role in melanocyte apoptosis (Białczyk et al., 2023). In patients with vitiligo, increased epidermal hydrogen peroxide (H_2O_2) levels have been observed, accompanied by reduced endogenous antioxidant capacity, including decreased activity of catalase, superoxide dismutase, and glutathione peroxidase. This oxidant–antioxidant imbalance creates a microenvironment that damages melanocytes while simultaneously triggering adaptive immune responses that exacerbate depigmentation (Bishnoi et al., 2024).

This pro-oxidative condition provides a strong rationale for exploring antioxidant-based interventions as adjunctive therapeutic strategies (Farías et al., 2017; Nazari et al., 2024). Oral antioxidant therapy aims to reduce systemic oxidative stress, protect residual melanocytes from further damage, and potentially enhance the effectiveness of conventional vitiligo therapies, such as narrowband ultraviolet B (NB-UVB) phototherapy. Among various antioxidant agents, the synergistic combination of vitamin C (ascorbic acid), vitamin E (α-tocopherol), and alpha-lipoic acid (ALA) has attracted particular attention due to its complementary mechanisms of action across different cellular compartments (Awoleye & Adedeji, 2024; Shanaida et al., 2025). Vitamin C regenerates oxidized vitamin E, while ALA regenerates both antioxidants and increases intracellular glutathione levels, thereby forming a layered antioxidant network that may theoretically neutralize ROS more effectively than single-agent supplementation (Ferreira et al., 2025).

Vitiligo represents one of the most common acquired pigmentary disorders worldwide and has become an important dermatological and psychosocial health concern due to its chronic nature, visible manifestations, and substantial impact on patients' quality of life (Christensen & Jafferany, 2023; Cortés et al., 2022). The disease is characterized by progressive destruction or dysfunction of melanocytes, resulting in depigmented macules that may appear on various body areas. Although vitiligo is not associated with direct mortality, its consequences extend beyond physical appearance, affecting psychological well-being, social interactions, self-esteem, and emotional health. Current global health perspectives increasingly recognize vitiligo not merely as a cosmetic condition but as a complex immune-mediated disorder requiring comprehensive therapeutic approaches. Current evidence estimates that vitiligo affects approximately 0.5–2% of the global population across different ethnicities, age groups, and geographic regions, without significant gender differences (Haulrig et al., 2024).

The global burden of vitiligo is further intensified by its psychosocial consequences and the limitations of currently available therapeutic options. Previous systematic evidence has demonstrated that individuals with vitiligo frequently experience stigma, reduced self-confidence, anxiety, depression, and impaired quality of life comparable to patients with other severe dermatological diseases (Ezzedine et al., 2021). Despite advances in dermatological treatments, including phototherapy, immunomodulatory agents, corticosteroids, and emerging targeted therapies, achieving stable and long-term repigmentation remains challenging. Conventional therapies often require prolonged treatment durations and may produce variable outcomes depending on disease subtype, disease activity, lesion distribution, and individual

patient characteristics. Therefore, identifying additional therapeutic strategies that can enhance treatment responses and protect melanocytes from further damage remains an important research priority.

Recent scientific developments have revealed that oxidative stress plays a fundamental role in the pathogenesis of vitiligo. The imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms contributes significantly to melanocyte injury, apoptosis, and subsequent autoimmune activation. Studies have shown that vitiligo lesions demonstrate increased levels of hydrogen peroxide (H_2O_2) and impaired antioxidant enzyme activity, including reduced catalase, superoxide dismutase, and glutathione-related defense mechanisms (Chang & Ko, 2023; Białczyk et al., 2023). This oxidative imbalance creates an unfavorable cellular environment that promotes melanocyte dysfunction and amplifies inflammatory immune responses. Consequently, antioxidant therapy has emerged as a potential complementary strategy aimed at restoring redox balance, protecting melanocytes, and improving the effectiveness of established vitiligo treatments.

Among various antioxidant interventions, combinations containing vitamin C, vitamin E, and alpha-lipoic acid (ALA) have received increasing attention due to their complementary biological mechanisms. Vitamin C functions as a water-soluble antioxidant capable of regenerating oxidized vitamin E, while vitamin E protects lipid membranes from oxidative damage. Meanwhile, ALA acts as an amphipathic antioxidant that can regenerate other antioxidants, increase intracellular glutathione levels, and support mitochondrial function. The theoretical advantage of combining these agents lies in their ability to provide broader antioxidant protection compared with single-agent supplementation. This mechanism provides a scientific rationale for investigating oral antioxidant combinations as adjunctive therapies alongside conventional vitiligo management, particularly narrowband ultraviolet B (NB-UVB) phototherapy.

Several previous studies have investigated the clinical relevance of antioxidant supplementation in patients with vitiligo; however, their findings remain inconsistent. Dell'Anna et al. (2007) conducted a randomized, double-blind, placebo-controlled clinical trial involving patients with nonsegmental vitiligo and reported that antioxidant supplementation containing alpha-lipoic acid (ALA), vitamin C, and vitamin E combined with NB-UVB therapy improved repigmentation outcomes and oxidative stress biomarkers. Conversely, Bhardwaj and Kaur (2020) reported that oral antioxidant supplementation added to standard therapy did not significantly improve oxidative stress indices or short-term clinical outcomes among patients with unstable vitiligo. These conflicting findings indicate that the therapeutic efficacy of antioxidant combinations may depend on several factors, including disease subtype, lesion extent, disease stability, intervention duration, and concurrent therapies.

Although previous studies have provided important insights into the potential role of antioxidants in vitiligo management, several limitations remain unresolved. Existing clinical evidence is limited by the small number of controlled trials, heterogeneous antioxidant formulations, differences in treatment protocols, and variations in outcome assessments. Furthermore, previous reviews have generally discussed antioxidant therapy broadly or included multiple pigmentary disorders rather than specifically evaluating the efficacy of oral combinations containing vitamin C, vitamin E, and ALA as adjunctive therapies for vitiligo. The absence of a focused synthesis examining the consistency, clinical relevance, and

methodological quality of available evidence represents a significant research gap that limits evidence-based decision-making in clinical practice.

Addressing this research gap is essential because clinicians require stronger evidence regarding whether antioxidant combinations provide meaningful additional benefits beyond established therapies. As vitiligo management continues to evolve with the emergence of targeted therapies, such as Janus kinase (JAK) inhibitors, and advances in phototherapy approaches, complementary strategies targeting oxidative mechanisms remain clinically relevant. A systematic evaluation of antioxidant-based interventions can help determine whether these supplements should be considered supportive treatments, identify patient groups that may benefit most, and guide future clinical trials toward more standardized therapeutic approaches. Therefore, synthesizing available evidence is necessary to strengthen the scientific foundation of adjunctive antioxidant therapy in vitiligo.

The novelty of this research lies in providing a focused systematic review and narrative synthesis specifically examining the efficacy of oral antioxidant combinations containing vitamin C, vitamin E, and alpha-lipoic acid as adjunctive therapies for vitiligo. Unlike previous reviews that evaluated antioxidants more generally, this study emphasizes controlled clinical evidence, antioxidant combinations, clinical outcomes, oxidative stress parameters, and methodological limitations of existing studies. By integrating findings from available randomized controlled trials, this research provides a comprehensive interpretation of whether antioxidant combinations demonstrate clinically meaningful benefits and under which therapeutic conditions these effects may occur.

The objective of this study is to systematically evaluate the effectiveness of oral antioxidant combinations as adjunctive therapies in patients with vitiligo by assessing their effects on repigmentation outcomes, disease-related clinical scores, oxidative stress biomarkers, quality of life indicators, and safety profiles. This study also aims to identify factors influencing therapeutic responses, including vitiligo subtype, lesion distribution, treatment duration, and concurrent conventional therapies. Through systematic evaluation based on established review methodologies, this research seeks to clarify the current level of evidence and identify areas requiring further investigation.

The contribution of this research is expected to benefit dermatological science, clinical practitioners, researchers, and patients by providing evidence-based insights into the potential role of antioxidant combinations in vitiligo treatment. For clinicians, the findings may support more informed decisions regarding the selection of complementary therapies and patient counseling. For researchers, this study highlights existing limitations and proposes directions for future large-scale randomized clinical trials with standardized protocols. For patients, improved understanding of adjunctive treatment options may contribute to more effective and personalized vitiligo management strategies. Ultimately, this research contributes to the development of a more comprehensive therapeutic framework that integrates oxidative stress regulation with conventional approaches for managing vitiligo.

METHOD

Eligibility criteria

This systematic review was developed based on the PICO framework. The included population consisted of patients of all age groups with a clinical diagnosis of vitiligo, including

nonsegmental, segmental, or mixed types, without restrictions on disease severity or lesion location. The intervention assessed was a combination of oral antioxidants containing at least two of the following components: vitamin C (ascorbic acid), vitamin E (tocopherol), and/or alpha-lipoic acid (ALA), administered as adjunctive therapy alongside conventional vitiligo treatments. Comparators included conventional therapy alone, placebo, or no additional intervention. The primary outcomes included repigmentation rates and changes in Vitiligo Area Scoring Index (VASI) or Vitiligo Disease Activity (VIDA) scores, while secondary outcomes included oxidative stress biomarkers, quality of life measures such as the Dermatology Life Quality Index (DLQI), and adverse effects. Eligible study designs included randomized controlled trials (RCTs), quasi-randomized controlled trials, and controlled clinical trials (CCTs) with comparison groups.

Studies published as case reports, case series, observational studies without control groups, narrative reviews, or expert opinions were excluded. Studies evaluating single antioxidant agents, topical antioxidants without oral combinations, or supplements that did not contain vitamin C, vitamin E, or ALA were also excluded. In addition, studies involving pigmentary disorders other than vitiligo, in vitro studies, animal studies, unpublished research protocols, duplicate publications, and studies without extractable numerical data were excluded. Full-text articles that could not be obtained despite attempts to contact the authors were also excluded from the review.

Resources

A comprehensive literature search was conducted on several electronic databases, namely PubMed/MEDLINE, Cochrane Library (CENTRAL), Scopus, and ScienceDirect. To minimize publication bias, additional searches are also planned on grey literature sources, namely ClinicalTrials.gov and Google Scholar, as well as through bibliography searches of all articles that meet the inclusion criteria. There is no restriction on the year of publication until the time of the last search. Studies in English and Indonesian.

Search strategy

The search strategy is structured based on predefined PICO components, using a combination of controlled and free-text terms. Search terms for the population include vitiligo and leukoderma. Terms for the intervention included antioxidants, ascorbic acid, vitamin C, tocopherol, vitamin E, thioctic acid, alpha-lipoic acid, ALA, oral antioxidants, and antioxidant combinations. For external, the terms used include repigmentation, oxidative stress, VASI, VIDA, and adjuvant therapy. The search strategy is then adjusted to the indexing system and syntax of each database.

Selection process

All articles obtained from database search results and additional sources will be imported into the reference management tool, then duplicates are removed before the screening process. The study selection was carried out in two stages. The first stage is the screening of titles and abstracts by two independent reviewers based on the eligibility criteria that have been set. The second stage is a full-text assessment of the article that is considered potentially relevant by both reviewers.

If there is a difference of opinion at one of the stages, the settlement is carried out through discussion until a consensus is reached; If a consensus is not reached, the final decision will be determined by the third reviewer. The reasons for exclusion at the full text assessment stage

are noted in detail. The entire study selection process will be reported using the PRISMA 2020 flowchart.

Data extraction and methodological quality assessment

Data extraction was carried out independently by two reviewers of all studies that met the inclusion criteria. The extraction results are then cross-verified to ensure data accuracy and consistency. If discrepancies are found between reviewers, the differences are resolved through discussion until a consensus is reached. If consensus is not obtained, then adjudication is carried out by the third reviewer. The data extracted from each study include: (1) the characteristics of the study, namely the name of the first author, the year of publication, the country or location of the study, the design of the study, and the number of subjects in each group; (2) the characteristics of the subject, namely age, sex, type of vitiligo, disease activity, duration of the disease, and the extent, distribution, or location of the lesion when reported; (3) the characteristics of the intervention, namely the type of oral antioxidant combination used, the antioxidant components administered (vitamin C, vitamin E, and/or alpha-lipoic acid), the dose, frequency, duration of administration, time of initiation of the intervention, and conventional therapies administered simultaneously; (4) comparative characteristics, i.e. control group types, such as placebo, conventional therapy alone, or no additional interventions; and (5) research outputs, which include primary outputs in the form of degree of re-pigmentation and changes in VASI or VIDA scores, and secondary outputs in the form of biomarkers of oxidative stress, quality of life, incidence of side effects, timing of outcome assessment, and other relevant clinical variables.

Methodological quality and risk of bias assessments were conducted on all studies that met the inclusion criteria after the full text review stage. Assessments are conducted independently by two reviewers, and any disagreements are resolved through discussion or by involving a third reviewer. For studies with a randomized controlled trial (RCT) design, risk of bias assessment was conducted using Cochrane Risk of Bias 2 (RoB 2). The domains assessed included the randomization process, deviation from the intervention in question, missing output data, output measurement, and selection of reported outcomes. The risk of bias is then classified as low, there is concern, or high. For quasi-RCT or clinical controlled trial (CCT) studies that are not completely randomized, the assessment was carried out using the ROBINS-I instrument. In addition, reporting quality indicators such as randomization, blinding, completeness of external data, conflicts of interest, and protocol registration are recorded when available in the article (Diaz et al., 2025).

Statistical analysis

The analysis was carried out descriptively on all included studies by presenting the characteristics of the study, subjects, interventions, comparators, and outputs in the form of a summary table. Continuous output data is presented according to the reporting of each study, in the form of mean and standard deviation or median and range/interquartile, while dichotomous output data is presented in the form of number and proportion. The results of each study were then systematically compared based on the direction of the effect, the magnitude of the reported effects, and the consistency of the findings on clinical outcomes and biomarkers of oxidative stress.

Given that there were only two RCT studies that met the inclusion criteria, and that there was clinical and methodological heterogeneity in the therapy regimen, antioxidant

composition, duration of intervention, and outcome measurements, meta-analyses were not performed. The synthesis of results was carried out narratively according to the SWiM (Synthesis Without Meta-analysis) approach (Ezzedine et al., 2021). Formal statistical heterogeneity tests, including I^2, as well as publication bias evaluations using funnel plots or Egger regression tests were not conducted because the number of studies was so small that the results were unstable and potentially misleading. Therefore, the final interpretation was carefully carried out taking into account methodological quality, risk of bias, and consistency of results between studies.

Publication bias

If the number of included studies is sufficient (>10 studies), potential publication bias will be evaluated using funnel plots and Egger regression tests; But since it is not possible, publication bias will be discussed narratively.

RESULT AND DISCUSSION

Study selection

The process of identification, screening, eligibility assessment, and inclusion of studies in this systematic review is presented in Figure 1 according to the guidelines of PRISMA 2020. A total of 338 articles were obtained through electronic database searching. After the elimination of duplication of 55 articles, there are 283 journals left for the title and abstract screening stage. From this stage, only 2 articles were considered relevant and met the criteria for a full text review. All complete texts were successfully obtained and further assessed against the inclusion and exclusion criteria that had been set. The results of the full-text assessment showed that both articles met the eligibility criteria, so 2 randomised controlled clinical trial (RCT) studies were included in the final synthesis.

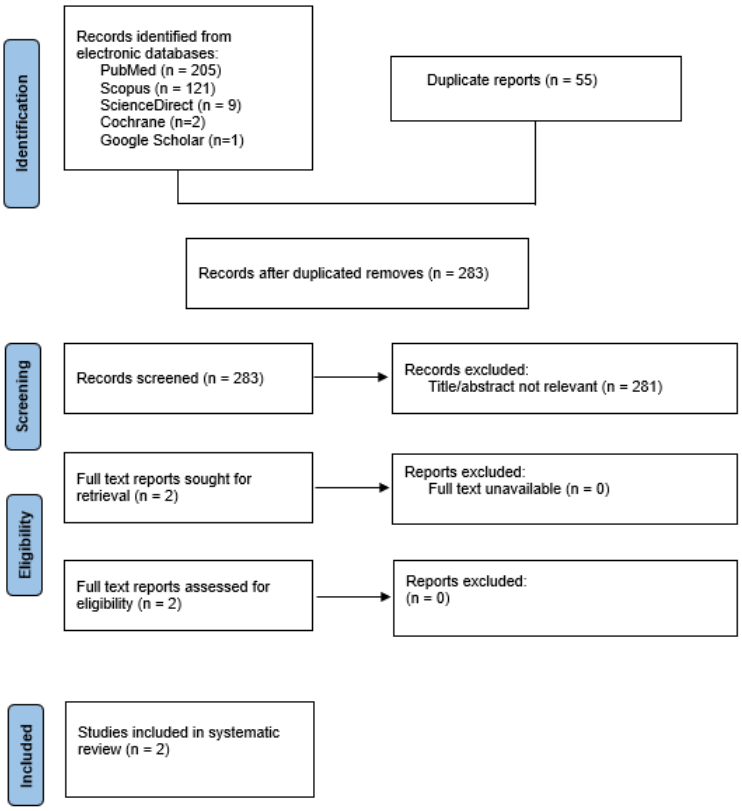


Figure 1. PRISMA flowchart for study selection

Table 1. Baseline characteristics of the included study

Yes	Author/Year	Study design	Participant Criteria	Sample size	Types of Vitiligo*	BSA (%)*	Age (Years)	Intervention		Dosage
								Oral antioxidants	Placebo	
1.	Dell'Anna et al., 2007	■ Randomized controlled clinical trials ■ Double camouflage ■ Placebo-controlled ■Multisenter	■ Adult patients with nonsegmental (generalized) Vitiligo ■ Age > 18 years old ■ Duration of the disease > 1 year ■ Lesions > 15% of the body surface area	N = 35 (Male = 14) N = 28 finished/ Analyzed	■ Vitiligo nonsegmental (generalisata) = 35	15–42% (AP) vs 15–38% (placebo)	39.9 years (24–61)	**AP:** *α-lipoic acid*, vitamin C, vitamin E, Polyunsaturated fatty acids (PUFAs), cysteine monohydrate.	NB-UVB	AP group (for AP tablet): ■ α-lipoic acid 50 mg, ■ vitamin C 50 mg, ■ vitamin E 20 mg, ■ cysteine monohydrate 50 mg, ■ PUFA 12% per tablet Dosage: 2 tablets/day Placebo Group: NB-UVB only
2.	Bhardwaj and Kh	■ Open-ended randomized clinical	■ Adult patients with unstable vitiligo vulgaris	N = 40(Male = 21)	■ Focal = 9 ■ Mucos	≤3%: 9 (Kel. A/control) vs 7 (Kel.	30.7 years	Antioksidan oral: vitamin C, vitamin E, beta-carotene,	oral prednisolone + oral 8-methoxy	Kel. B: vitamin C 300 mg, vitamin E 400 IU, beta-carotene 30 mg,

aur, 2020	trials ■ Preliminary study	■ Age ≥ 18 years, ■ Not receiving any therapy in the previous 2 months ■ Do not accept medications containing antioxidants.	al = 5 ■ Acrofacial = 1 ■ Segmental = 0 ■ Mixed = 17 ■ Generalisata = 7 ■ Universal =1	B/antioxidant) >3%: 11 (Kel. A /control) vs 13 (Kel. B /antioxidant)	zinc oxide, sodium selenate, cupric oxide, manganese sulphate	psoralen + PUVASol/Paparan sinar matahari terapeutik; tacrolimus 0.1% topical on face/neck lesions.	zinc oxide 40 mg, sodium selenate 200 µg, cupric oxide 2 mg, manganese sulphate 5 mg/day Control group (Kel. A): ■Prednisolone 1 mg/kg 2 consecutive days/week ■ 8-methoxypsoralen 0.6 mg/kgBB on 3 days an interval of the week; ■Tacrolimus 0.1% nighttime for face/neck lesions.

***Note:** The vitiligo type variable had non-uniform data availability between studies. The study of Bhardwaj and Kaur (2020) reported the distribution of vitiligo subtypes in detail, while the study of Dell'Anna *et al*. (2007) only mentions the population as nonsegmental vitiligo (generalista) with no subtype distribution.
The extent of lesion involvement was reported in different formats between studies; Dell'Anna *et al.* reported a percentage of body surface area in a range, while Bhardwaj and Kaur reported in the ≤3% and >3% categories.

Abbreviation description: AP, antioxidant pool; NB-UVB, narrowband ultraviolet B; PUFA, polyunsaturated fatty acids; PUVASol, psoralen plus ultraviolet A with sunlight exposure; kgBB, kilograms of body weight: Kel.A, group A; Kel.B, group B.

Study characteristics

The two studies that met the inclusion criteria were randomised clinical trials with different methodological and clinical characteristics (Table 1). The study by Dell'Anna et al. was a randomized, double-blind, placebo-controlled, multicenter clinical trial in 35 adult patients with nonsegmental vitiligo (generalista); The duration of vitiligo disease ranged from 2–10 years in the intervention group and 1–8 years in the placebo group; 28 patients completed the study and were analyzed. This study was conducted in Italy–the Netherlands. Criteria for patients with an average age of 40 years, the duration of vitiligo disease ranged from 2–10 years in the intervention group and 1–8 years in the placebo group, and lesion area at baseline was reported to be 15–42% in the intervention group and 15–38% in the placebo group. The intervention was a combination of antioxidants (AP) containing alpha-lipoic acid, vitamin C, vitamin E, polyunsaturated fatty acids (PUFAs), and cysteine monohydrate, administered for 2 months before and 6 months during NB-UVB therapy. This study showed an increase in clinical re-pigmentation and improvement of oxidative stress biomarkers .

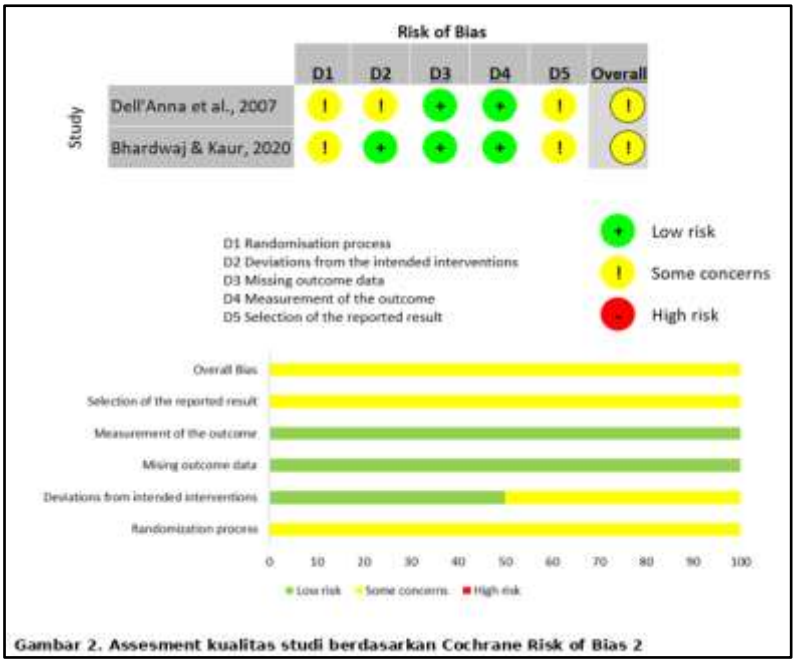
The study by Bhardwaj and Kaur was an open-label clinical trial on a pilot study in 40 adult patients with unstable vitiligo vulgaris; 21 male patients with an average age of 30.7 years. The study was conducted in India, the duration of the disease was reported to be 9.1±3.91 years in the control group and 7.4±4.74 years in the antioxidant group. The distribution of

vitiligo types at baseline includes focal, mucosal, acrofacial, mixed, generalized, and universal, with lesion area involvement reported as ≤3% and >3% of body surface area. The intervention was a combination of oral antioxidants containing vitamin C, vitamin E, beta-carotene, zinc oxide, sodium selenate, cupric oxide, and manganese sulphate, which was administered with standard therapy in the form of oral prednisolone, 8-methoxypsoralen, PUVASol, and topical tacrolimus for 1 month (Haulrig et al., 2024). In general, both studies involved patients with relatively chronic vitiligo. In contrast to the Dell'Anna et al. study, this study did not show any significant additional benefits to oxidative stress index (OSI) or short-term clinical outcomes. Overall, both studies showed that the response to the combination of oral antioxidants was likely influenced by vitiligo subtypes, lesion area, disease stability, type of basic therapy, and duration of intervention.

Methodological quality assessment of included studies

Methodological quality assessments were conducted on both randomised clinical trial studies that met the inclusion criteria using Cochrane Risk of Bias 2 (RoB 2) for five main domains, namely bias in the randomisation process, bias due to deviation from the intervention in question, bias due to missing output data, bias in output measurement, and bias in the selection of reported outcomes. In addition, reporting quality indicators such as randomization, blinding, sample size, conflict of interest statements, and protocol pre-registration were also examined to provide a more comprehensive picture of the quality of study reporting.

Based on the assessment using RoB 2 (Figure 2), none of the studies fell into the overall low-risk category of bias. The study by Dell'Anna et al. was classified as having some concerns about the risk of bias, mainly because concealment allocation was not described in detail, there was a loss of subjects during follow-up (only 28 of the 35 participants completed the study and there was a clear follow-up), and insufficient information was available regarding the pre-established analysis protocol. The study by Bhardwaj and Kaur is also considered to have a risk of bias of some concerns, especially related to the lack of clarity of randomization methods, open-label design, and potential bias in the assessment of clinical outcomes. Therefore, although both studies were RCTs, their overall methodological quality was still limited and should be carefully considered in the interpretation of the review results.



Gambar 2. Assesment kualitas studi berdasarkan Cochrane Risk of Bias 2

Synthesis of the main results of the included study

Two RCT studies included showed that the effectiveness of oral antioxidant combinations as adjunct therapy in vitiligo is still inconsistent. The study by Dell'Anna et al. involved adult patients with nonsegmental/generalized vitiligo, with lesion area at baseline of 15–42% in the intervention group and 15–38% in the placebo group, thus representing a disease with relatively broad skin involvement. In this population, the combination of alpha-lipoic acid, vitamin C, and vitamin E in addition to NB-UVB improves clinical repigmentation, improves biomarkers of oxidative stress, and accelerates response to phototherapy. In contrast, studies by Bhardwaj and Kaur were conducted on patients with unstable vitiligo vulgaris with a more heterogeneous subtype distribution, i.e. focal, mucosal, acrofacial, mixed, generalized, and universal, and lesion involvement areas reported as ≤3% and >3% of body surface area. In this study, the additional combination of oral antioxidants showed no significant additional benefit to the oxidative stress index or short-term clinical outcomes. There is no detailed explanation of changes after intervention in each of the vitiligo subtypes.

These differences in outcomes are likely influenced by variations in vitiligo type, extent of lesion involvement, disease activity, baseline therapy regimen, and duration of intervention. Clinically, the type of vitiligo and BSA affected are important factors as they can relate to the prognosis and response to therapy, especially to phototherapy. Thus, the currently available evidence tends to support the potential benefits of combining oral antioxidants in nonsegmental/generalized vitiligo with NB-UVB therapy in the medium–long term, but it is still not strong enough to draw definitive conclusions on all vitiligo subtypes.

Vitiligo is a depigmented disease with multifactorial pathogenesis that involves the interaction between melanocyte intrinsic susceptibility, oxidative stress, innate immunity, and T cell autoimmunity γ. Thus, vitiligo is no longer understood as a mere pigmentation disorder, but rather as a metabolic immune disease that requires a multimodal therapeutic approach (Ismail et al., 2025; Ju & Bae, 2024).

In the current therapeutic landscape, NB-UVB remains one of the main therapies because it is able to suppress local inflammation while stimulating the migration and proliferation of melanocytes. In addition, the era of targeted therapy has grown rapidly with the presence of JAK inhibitors, especially topical ruxolitinib, which confirms the importance of the JAK-STAT pathway in vitiligo pathogenesis (Mukhatayev & Le Poole, 2024; Page et al., 2021; Pathak et al., 2024; Seong & Oh, 2024; Seneschal et al., 2025; Speeckaert et al., 2024; Sterne et al., 2016). However, antioxidant-based adjuvant therapy remains relevant as it targets a different component of pathogenesis, i.e., redox dysfunction. The combination of alpha-lipoic acid (ALA), vitamin C, and vitamin E theoretically complement each other: vitamin C as a hydrophilic antioxidant, vitamin E as a lipid membrane protector, and ALA as an amphipathic antioxidant that also aids in the regeneration of other antioxidants and supports mitochondrial function (Kang, 2024; Xie et al., 2023).

This systematic review found only two RCTs that met the inclusion criteria, so the strength of the evidence is still limited. The study by Dell'Anna et al. showed the most supportive results, namely that the combination of oral antioxidants containing ALA, vitamin C, and vitamin E in addition to NB-UVB resulted in better clinical re-pigmentation, lowered ROS, increased catalase activity, and reduced the need for phototherapy sessions (Tavoletti et al., 2023). In contrast, studies by Bhardwaj and Kaur showed no significant additional benefit to oxidative stress index or short-term clinical outcomes (van der Veen et al., 2023). These differences are likely influenced not only by the composition of the oral antioxidant combination or the length of the intervention, but also by the basic characteristics of the disease, especially the vitiligo subtype, the stability of the disease, and the extent of lesion/BSA involvement.

The Dell'Anna et al. study involved patients with nonsegmental/generalized vitiligo with relatively broad lesion involvement (15–42% in the intervention group and 15–38% in the placebo group), while the Bhardwaj and Kaur studies included patients with unstable vitiligo vulgaris with more heterogeneous subtypes, including focal, mucosal, acrofacial, mixed, generalized, and universal, as well as reported BSAs in the ≤3% and >3% categories. Clinically, vitiligo subtypes and lesion area are important parameters as they can relate to the prognosis of re-pigmentation and response to therapy, including phototherapy.

Based on the available data, a better response tendency was seen in nonsegmental/generalized vitiligo populations treated with a combination of oral and NB-UVB antioxidants, as shown in the study of Dell'Anna et al.; However, the subtype with the best prognosis could not be definitively established, as neither study reported distrophified re-pigmentation results according to each vitiligo subtype.

Thus, the results of both studies should not be interpreted solely as a result of the presence or absence of ALA or differences in duration of therapy, but also as a reflection of the heterogeneity of the disease baseline. Overall, the findings of this review tend to support that the combination of oral antioxidants is potentially beneficial as an adjuvant therapy in vitiligo, particularly when combined with NB-UVB for an adequate duration, but the interpretation of its benefits should still take into account the subtype of the disease, lesion area, and the clinical context of the individual patient.

Interpretation

Based on two included RCTs, a combination of oral antioxidants (especially those containing alpha-lipoic acid, vitamin C, and vitamin E) showed potential as an adjuvant therapy in vitiligo, especially when combined with NB-UVB and given for a sufficient duration. However, the current strength of the evidence is still limited because the number of studies that study the therapy directly in humans is still very small, there is a heterogeneity of populations and therapy regimens, and the results between studies are not fully consistent. Thus, oral antioxidants can be considered as a promising complementary approach, but they cannot yet be recommended as a standard of therapy without the support of larger, more standardized clinical trials.

Limitations and implications

This systematic review has a major limitation in the form of very small number of studies, as there are only two RCTs that meet the inclusion criteria, accompanied by meaningful clinical and methodological heterogeneity. These differences include antioxidant composition, baseline therapy, duration of intervention, assessed outcomes, as well as disease baseline characteristics such as vitiligo subtypes, disease stability, and extent of lesion/BSA involvement, which may affect prognosis and therapy response. In addition, the methodological quality of both studies has not been completely free of risk of bias, so the power of inference is still limited. Nonetheless, these findings suggest that a combination of oral antioxidants (especially alpha-lipoic acid, vitamin C, and vitamin E) could potentially be considered as adjuvant therapy in vitiligo, particularly when combined with NB-UVB. However, this therapy cannot be routinely recommended until larger, more homogeneous RCTs are available, and use standardized clinical outcomes with a more pronounced stratification of vitiligo subtypes and lesion area.

CONCLUSION

The findings of this systematic review indicate that oral antioxidant combinations, particularly those containing alpha-lipoic acid (ALA), vitamin C, and vitamin E, demonstrate potential as adjunctive therapies for vitiligo, especially when combined with conventional treatments such as narrowband ultraviolet B (NB-UVB) phototherapy. The available evidence suggests that antioxidant supplementation may contribute to improved repigmentation outcomes, reduced oxidative stress markers, and enhanced melanocyte protection. However, the overall strength of evidence remains limited due to the small number of eligible randomized controlled trials, methodological limitations, and heterogeneity in antioxidant formulations, patient characteristics, disease subtypes, and treatment protocols. Therefore, oral antioxidant combinations cannot yet be considered standard therapy for vitiligo but may be regarded as a promising complementary approach for selected patients, particularly those with nonsegmental or generalized vitiligo undergoing phototherapy-based treatment.

Future research should focus on conducting larger, well-designed randomized controlled trials with standardized antioxidant formulations, consistent dosing regimens, longer follow-up periods, and stratification based on vitiligo subtype, disease activity, and lesion extent. Further studies should also evaluate clinically meaningful outcomes, including long-term repigmentation stability, improvements in quality of life, oxidative stress biomarkers, and potential interactions with emerging therapies such as Janus kinase (JAK) inhibitors. A more standardized research framework will help determine the specific patient populations most likely to benefit from antioxidant supplementation and provide stronger evidence for integrating antioxidant therapy into comprehensive vitiligo management strategies.

REFERENCE

Awoleye, Mercy Oluwaseun, & Adedeji, Temitope Gabriel. (2024). Revisiting the molecular mechanisms of alpha lipoic acid (ALA) actions on metabolism. *Pharmacological Research-Natural Products*, *4*, 100073.

Bhardwaj, G., & Kaur, J. (2020). Co-supplementation of oral antioxidant to PUVASol therapy has no effect on oxidative stress index in patients of unstable vitiligo: A hospital-based pilot study. *Journal of Pakistan Association of Dermatologists, 30*(1), 13–20. https://doi.org/10.66344/jpad.30.1.2020.1378

Białczyk, A., Wełniak, A., Kamińska, B., & Czajkowski, R. (2023). Oxidative stress and potential antioxidant therapies in vitiligo: A narrative review. *Molecular Diagnosis & Therapy, 27*(6), 723–739.

Bishnoi, A., Meghana, K. B., & Parsad, D. (2024). Medical treatment of vitiligo: A narrative review. *Pigment International*. https://doi.org/10.4103/pigmentinternational_48_24

Chang, Y. C., & Ko, W. C. (2023). The role of oxidative stress in vitiligo: An update on its pathogenesis and therapeutic implications. *Cells, 12*(6), 936. https://doi.org/10.3390/cells12060936

Christensen, Rachel E., & Jafferany, Mohammad. (2023). Psychiatric and psychologic aspects of chronic skin diseases. *Clinics in Dermatology*, *41*(1), 75–81.

Cortés, Hernán, Rojas-Márquez, Martín, Del Prado-Audelo, María L., Reyes-Hernández, Octavio D., González-Del Carmen, Manuel, & Leyva-Gómez, Gerardo. (2022). Alterations in mental health and quality of life in patients with skin disorders: a narrative review. *International Journal of Dermatology*, *61*(7), 783–791.

Diaz, M. J., Tran, J. T., Rose, D., Wei, A., Lakshmipathy, D., et al. (2025). Dietary interventions, supplements, and plant-derived compounds for adjunct vitiligo management: A review of the literature. *Nutrients, 17*(2), 357. https://doi.org/10.3390/nu17020357

Farías, Jorge G., Molina, Víctor M., Carrasco, Rodrigo A., Zepeda, Andrea B., Figueroa, Elías, Letelier, Pablo, & Castillo, Rodrigo L. (2017). Antioxidant therapeutic strategies for cardiovascular conditions associated with oxidative stress. *Nutrients*, *9*(9), 966.

Ferreira, C., King, B., & Torres, T. (2025). JAK inhibitors for the treatment of vitiligo: Current evidence and emerging therapeutic potential. *Drugs*. https://doi.org/10.1007/s40265-025-02246-1

Haulrig, M. B., Baskaran, S., Bergmann, M., Løvendorf, M. B., & Dyring-Andersen, B. (2024). The global epidemiology of vitiligo: A systematic review and meta-analysis of the incidence and prevalence. *JEADV Clinical Practice, 3*(5), 1199–1215. https://doi.org/10.1002/jvc2.526

Kang, C. (2024). Ruxolitinib cream 1.5%: A review in non-segmental vitiligo. *Drugs*. https://doi.org/10.1007/s40265-024-02027-2

Mukhatayev, Z., & Le Poole, I. C. (2024). Vitiligo: Advances in pathophysiology research and treatment development. *Trends in Molecular Medicine*. https://doi.org/10.1016/j.molmed.2024.04.009

Nazari, Ahmad, Osati, Parisa, Seifollahy Fakhr, Siavash, Faghihkhorasani, Ferdos, Ghanaatian, Masoud, Faghihkhorasani, Fereshteh, Rezaei-Tazangi, Fatemeh, Pazhouhesh Far,

Nazanin, Shourideh, Amir, & Ebrahimi, Nasim. (2024). New emerging therapeutic strategies based on manipulation of the redox regulation against therapy resistance in cancer. *Antioxidants & Redox Signaling*.

Shanaida, Mariia, Lysiuk, Roman, Mykhailenko, Olha, Hudz, Nataliia, Abdulsalam, Abdullateef, Gontova, Tetiana, Oleshchuk, Oleksandra, Ivankiv, Yana, Shanaida, Volodymyr, & Lytkin, Dmytro. (2025). Alpha-lipoic acid: An antioxidant with anti-aging properties for disease therapy. *Current Medicinal Chemistry*, *32*(1), 23–54.

Seong, S. H., & Oh, S. H. (2024). Up-and-coming drugs for the treatment of vitiligo. *Annals of Dermatology*. https://doi.org/10.5021/ad.24.038

Speeckaert, R., Caelenberg, E. V., Belpaire, A., et al. (2024). Vitiligo: From pathogenesis to treatment. *Journal of Clinical Medicine, 13*(17), 5225. https://doi.org/10.3390/jcm13175225

Tavoletti, G., Avallone, G., Conforti, C., et al. (2023). Topical ruxolitinib: A new treatment for vitiligo. *Journal of the European Academy of Dermatology and Venereology*. https://doi.org/10.1111/jdv.19162

van der Veen, J. P. W. R. H., Duinkerken, M., Wolkerstorfer, A., & Bekkenk, M. W. (2023). The impact of antioxidants on vitiligo and melasma: A scoping review and meta-analysis. *Antioxidants, 12*(12), 2082.

Xie, B., Zhu, Y., Shen, Y., Xu, W., & Song, X. (2023). Treatment update for vitiligo based on autoimmune inhibition and melanocyte protection. *Expert Opinion on Pharmacotherapy*. https://doi.org/10.1080/14728222.2023.2193329