



A Comprehensive Systematic Review of Investigating the Antioxidant Effect of Vitamin E in Depression

¹ Oktaberika Putri Indah Yasinta, ² Eka Pramudian Rismayanti

^{1,2} Faculty of Medicine, University of Muhammadiyah Surakarta, Central Java,
Indonesia

Corresponding Email : opiy49@gmail.com

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ABSTRACT

Introduction: Depression is a prevalent global mental health disorder with a complex, multifactorial pathophysiology. Emerging evidence suggests a significant role of oxidative stress and impaired antioxidant defense in its development and progression. Vitamin E, a potent lipid-soluble antioxidant, has been investigated for its potential therapeutic role in mitigating oxidative damage and alleviating depressive symptoms (Lee et al., 2022; Barbosa et al., 2020).

Methods: This comprehensive systematic review synthesized evidence from 14 sources, including randomized controlled trials (RCTs), meta-analyses, and observational studies. Studies were screened and selected based on predefined criteria involving human participants with depression, vitamin E intervention (as monotherapy or co-intervention), measurement of antioxidant biomarkers and depression outcomes, and specific study designs that allowed for the isolation of vitamin E effects.

Results: The pooled meta-analysis indicated a moderate beneficial effect of vitamin E supplementation on depression scores (SMD = -0.88, 95% CI: -1.54 to -0.21) (Lee et al., 2022). Observational data showed an inverse association between dietary vitamin E intake and depression risk (RR = 0.84) (Ding & Zhang, 2022). Significant improvements in antioxidant biomarkers, such as increased total antioxidant capacity (TAC) and reduced malondialdehyde (MDA), were consistently reported with vitamin E supplementation, particularly at doses of 400 IU or higher (Farshbaf-Khalili et al., 2022; Darabi et al., 2023). However, effects were more pronounced in populations with elevated oxidative stress (e.g., PCOS, occupational exposure) and when vitamin E was combined with other antioxidants or omega-3 fatty acids.

Discussion: The antidepressant effects of vitamin E appear to be mediated through its ability to reduce oxidative stress and lipid peroxidation, modulate inflammatory pathways, and possibly influence gene expression related to neuroprotection (Lee et al., 2022; Almulla et al., 2023). Significant heterogeneity in study outcomes can be attributed to factors such as dosage, formulation, population characteristics, and the common use of vitamin E as a co-intervention.

Conclusion: Vitamin E supplementation, particularly at higher doses and in populations with evident oxidative stress burden, may offer a safe and modest adjunctive benefit in the management of depression. Future research should prioritize large-scale, well-designed RCTs of vitamin E monotherapy, with stratified analyses based on baseline antioxidant status, to clarify its independent therapeutic role.

Keywords: Vitamin E, tocopherol, depression, oxidative stress, antioxidant, lipid peroxidation, systematic review, meta-analysis.

INTRODUCTION

Background

Depression is a leading cause of disability worldwide, characterized by persistent low mood, anhedonia, and a suite of cognitive and physiological symptoms. While its etiology is multifactorial, involving genetic, environmental, and neurobiological components, a growing body of research implicates oxidative stress as a key pathological mechanism (Barbosa et al., 2020). Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense systems, leading to cellular damage, particularly in lipid-rich neural tissues. This state of oxidative damage is consistently observed in individuals with major depressive disorder (MDD) and bipolar disorder (BD), manifested by elevated levels of lipid peroxidation products like malondialdehyde (MDA) and compromised antioxidant enzyme activities (Almulla et al., 2023; Adeyanju et al., 2018). Vitamin E (α -tocopherol), as the primary lipid-soluble chain-breaking antioxidant in human plasma, plays a crucial role in protecting cell membranes from peroxidative damage. Its potential to modulate this oxidative pathway presents a compelling rationale for investigating its therapeutic utility in depression (Lee et al., 2022).

Research Gap

Despite established links between oxidative stress and depression, and the known biological function of vitamin E, the clinical evidence for its specific antidepressant efficacy remains fragmented and inconclusive. Many existing studies administer vitamin E as part of a multi-nutrient supplement (e.g., with omega-3 or vitamin C), making it difficult to isolate its independent effect (Jamilian et al., 2018; Krawczyk & Rybakowski, 2012). Furthermore, there is a lack of clarity regarding optimal dosing, treatment duration, and which patient subgroups (e.g., defined by baseline oxidative stress or inflammatory markers) are most likely to benefit. While systematic reviews on antioxidants in depression exist, few have focused exclusively on vitamin E while also integrating analyses of its mechanistic impact on antioxidant biomarkers.

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Novelty

This review aims to fill this gap by providing a comprehensive and focused synthesis of evidence specifically addressing the antioxidant role of vitamin E in depression. It uniquely integrates clinical outcome data (depression scores) with biomarker data (oxidative stress and antioxidant status) to evaluate not just *if* vitamin E works, but *how* it might work. By applying strict inclusion criteria to isolate vitamin E effects where possible and analyzing factors like dose, formulation, and population characteristics, this review offers a nuanced analysis beyond a simple efficacy assessment.

Research Objective

The primary objective of this systematic review is to critically evaluate and synthesize the available evidence from interventional and observational studies on the effects of vitamin E supplementation on depressive symptoms. A secondary objective is to examine the concurrent changes in oxidative stress and antioxidant biomarkers to elucidate potential biological mechanisms.

Research Hypothesis

It is hypothesized that vitamin E supplementation will lead to a significant reduction in depressive symptom severity and that this clinical improvement will be correlated with measurable enhancements in systemic antioxidant capacity and reductions in specific markers of oxidative stress and lipid peroxidation.

Research Benefits

The findings of this review have significant implications. Firstly, they can inform clinical practice regarding the potential role of vitamin E as a safe, accessible, and cost-effective adjunctive nutraceutical in depression management, especially for individuals with biomarkers indicating high oxidative stress. Secondly, they can guide future research priorities by identifying key knowledge

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gaps, such as the need for monotherapy trials and biomarker-stratified studies. Finally, understanding the antioxidant mechanism strengthens the broader biological model of depression, potentially leading to novel diagnostic and therapeutic approaches targeting redox imbalance.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate investigating the antioxidant effect of vitamin E in depression.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Depression Population:** Does the study include participants with clinically diagnosed depression or elevated depressive symptoms measured by validated scales?
- **Vitamin E Intervention:** Does the study involve vitamin E supplementation (any form of tocopherol or tocotrienol) as primary or adjunctive treatment?
- **Antioxidant Biomarkers:** Does the study measure at least one antioxidant biomarker (e.g., oxidative stress markers, antioxidant enzyme activity, lipid peroxidation)?
- **Depression Outcomes:** Does the study include depression outcome measures using validated instruments (e.g., Hamilton Depression Rating Scale, Beck Depression Inventory, PHQ-9)?

- **Study Design:** Is the study design a randomized controlled trial, controlled clinical trial, cohort study, case-control study, systematic review, or meta-analysis?
- **Vitamin E Isolation:** Can the effects of vitamin E be isolated in this study (i.e., is it NOT a multivitamin supplement where vitamin E effects cannot be separated)?
- **Human Studies:** Is this study conducted in humans (i.e., NOT exclusively in vitro or in animal models)?
- **Study Type Quality:** Is this study NOT a case report, case series, editorial, or opinion piece?
- **Primary Depression Focus:** Do participants NOT have primary diagnoses of bipolar disorder, schizophrenia, or other major psychiatric conditions where depression is secondary?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Individuals with depression	Vitamin E supplementation	Placebo / No supplementation	Depression scores (e.g., HDRS, BDI)
Keyword 2	Patients with depressive disorders	Tocopherol intake	Standard treatment / Control group	Antioxidant biomarkers (e.g., MDA, TAC)
Keyword 3	Depressed	Alpha-tocopherol	Other antioxidants /	Oxidative

	adults	administration	Active comparator	stress reduction
Keyword 4	Major depressive disorder (MDD) patients	Vitamin E levels (serum/dietary)	Baseline / Pre-treatment status	Clinical improvement / Response rates

The Boolean MeSH keywords inputted on databases for this research are: (*"Individuals with depression" OR "Patients with depressive disorders" OR "Depressed adults" OR "Major depressive disorder (MDD) patients"*) AND (*"Vitamin E supplementation" OR "Tocopherol intake" OR "Alpha-tocopherol administration" OR "Vitamin E levels"*) AND (*"Placebo" OR "No supplementation" OR "Standard treatment" OR "Control group" OR "Other antioxidants" OR "Baseline"*) AND (*"Depression scores" OR "Antioxidant biomarkers" OR "Oxidative stress reduction" OR "Clinical improvement"*)

Data extraction

- **Study Design:**

Extract the study design type including:

- Study type (RCT, cohort, cross-sectional, case-control, systematic review, etc.)
- Duration of follow-up or intervention period
- Control/comparison group details
- Sample size and power calculation if provided

- **Population Characteristics:**

Extract participant details including:

- Sample size (intervention and control groups)
- Age range and mean age
- Sex distribution
- Depression diagnosis or criteria (e.g., DSM-5, ICD-10, screening tools)
- Baseline depression severity scores
- Comorbidities (particularly diabetes, cardiovascular disease, other psychiatric conditions)
- Medication use (antidepressants, other psychiatric medications)
- Exclusion criteria related to antioxidant use

- **Vitamin E Intervention:**

Extract all details about vitamin E exposure including:

- Form of vitamin E (alpha-tocopherol, mixed tocopherols, specific isomers)
- Dosage (IU or mg per day)
- Duration of supplementation or assessment period
- Route of administration (oral supplements, dietary intake assessment)
- Co-interventions (other vitamins, antioxidants, omega-3s administered simultaneously)
- Compliance/adherence measures
- For observational studies: method of assessing vitamin E intake or levels

- **Depression Outcomes:**

Extract depression measurement details including:

- Primary depression assessment tool (HDRS, Beck Depression Inventory, DASS-21, DSM criteria, etc.)
- Baseline depression scores

- Post-intervention depression scores
- Change from baseline (mean difference, effect size, percentage improvement)
- Response rates (if defined, include definition)
- Remission rates (if defined, include definition)
- Time points assessed
- Secondary mood outcomes (anxiety, stress if measured)

- **Antioxidant Biomarkers:**

Extract all antioxidant and oxidative stress measurements including:

- Specific biomarkers measured (e.g., vitamin E levels, tocopherol concentrations, MDA, 8-OHdG, SOD, CAT, GPx, lipid peroxides, etc.)
- Baseline biomarker values
- Post-intervention biomarker values
- Change from baseline in biomarker levels
- Sample type (plasma, serum, urine, tissue)
- Measurement methodology
- Normal reference ranges if provided

- **Primary Results:**

Extract the main findings including:

- Primary outcome results (effect size, confidence intervals, p-values)
- Statistical significance of vitamin E effects on depression
- Statistical significance of vitamin E effects on antioxidant markers
- Correlation between antioxidant changes and depression changes (if assessed)
- Dose-response relationships (if evaluated)
- Subgroup analyses results

- Number needed to treat (if calculable)

- **Mechanisms Explored:**

Extract any mechanistic information including:

- Proposed biological pathways discussed
- Oxidative stress hypothesis testing
- Inflammation markers assessed (if any)
- Neurochemical pathways mentioned
- Gene expression or genetic factors
- Brain imaging or neurological assessments
- Author interpretations of how vitamin E might work in depression

- **Safety Outcomes:**

Extract safety and adverse event data including:

- Adverse events reported
- Dropout rates and reasons
- Side effects attributed to vitamin E
- Laboratory safety parameters (liver enzymes, lipid profiles, etc.)
- Drug interactions noted
- Contraindications identified
- Serious adverse events

- **Study Limitations:**

Extract author-reported limitations and methodological concerns including:

- Sample size limitations
- Confounding factors acknowledged

- Measurement limitations
- Generalizability concerns
- Selection bias issues
- Missing data problems
- Study design limitations acknowledged by authors
- Conflicts of interest declared

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Individuals with depression" OR "Patients with depressive disorders" OR "Depressed adults" OR "Major depressive disorder (MDD) patients" AND "Vitamin E supplementation" OR "Tocopherol intake" OR "Alpha-tocopherol administration" OR "Vitamin E levels" AND "Placebo" OR "No supplementation" OR "Standard treatment" OR "Control group" OR "Other antioxidants" OR "Baseline" AND "Depression scores" OR "Antioxidant biomarkers" OR "Oxidative stress reduction" OR "Clinical improvement")	1,658
Semantic Scholar	("Individuals with depression" OR "Patients with depressive disorders" OR "Depressed adults" OR "Major depressive disorder (MDD) patients") AND ("Vitamin E supplementation" OR "Tocopherol intake" OR "Alpha-tocopherol administration" OR "Vitamin E levels") AND ("Placebo" OR "No supplementation" OR "Standard treatment" OR "Control group" OR "Other antioxidants" OR "Baseline") AND ("Depression scores" OR "Antioxidant biomarkers" OR "Oxidative stress reduction" OR "Clinical improvement")	250
Springer	("Individuals with depression" OR "Patients with depressive disorders" OR "Depressed adults" OR "Major depressive disorder (MDD) patients") AND ("Vitamin E supplementation" OR "Tocopherol intake" OR "Alpha-tocopherol administration" OR "Vitamin E levels") AND ("Placebo" OR "No supplementation" OR "Standard treatment" OR "Control group" OR "Other antioxidants" OR "Baseline") AND ("Depression scores" OR "Antioxidant biomarkers" OR "Oxidative stress reduction" OR "Clinical improvement")	3
Google Scholar	("Individuals with depression" OR "Patients with depressive disorders" OR "Depressed adults" OR "Major depressive disorder (MDD) patients") AND ("Vitamin E supplementation" OR "Tocopherol intake" OR "Alpha-tocopherol administration" OR "Vitamin E levels") AND ("Placebo" OR "No supplementation" OR "Standard treatment" OR "Control group" OR "Other antioxidants" OR "Baseline") AND ("Depression scores" OR "Antioxidant biomarkers" OR "Oxidative stress reduction" OR "Clinical improvement")	79
Wiley Online Library	("Individuals with depression" OR "Patients with depressive disorders" OR "Depressed adults" OR "Major depressive disorder (MDD) patients") AND ("Vitamin E supplementation" OR "Tocopherol intake" OR "Alpha-tocopherol administration" OR "Vitamin E levels") AND ("Placebo" OR "No supplementation" OR "Standard treatment" OR "Control group" OR "Other antioxidants" OR "Baseline") AND ("Depression scores" OR "Antioxidant biomarkers" OR "Oxidative stress reduction" OR "Clinical improvement")	68

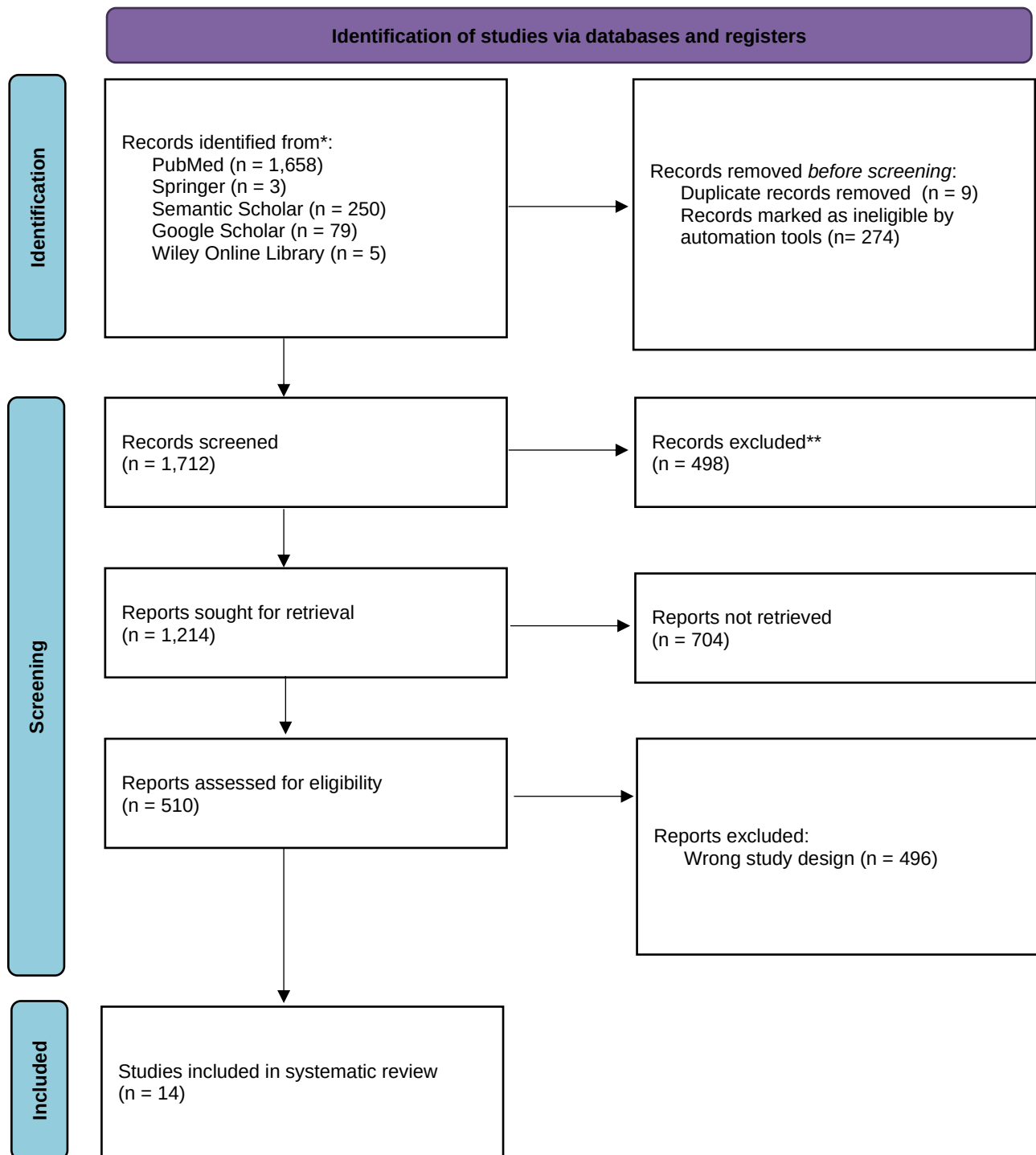


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
A. Lee et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Mazloom et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Ding et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Jamilian et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Farshbaf-Khalili et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Faezeh Darabi et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Mocking et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Krawczyk et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sahar Foshati et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Adeyanju et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Maiza Lacerda Barbosa et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Enhanced Antipsychotic Treatment, 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Almulla et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2023									
B. Meyer et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This review synthesizes evidence from 14 sources examining the relationship between vitamin E and depression, encompassing systematic reviews, meta-analyses, and primary intervention studies. The sources vary considerably in their primary focus, with some directly investigating vitamin E supplementation effects on depression, while others examine broader antioxidant mechanisms or include vitamin E as a co-intervention.

Study	Primary Focus	Population	Sample Size
A. Lee et al., 2022	Vitamin E effects on depression and anxiety	Adults with depression/anxiety or at-risk conditions	354 (depression); 306 (anxiety)
Z. Mazloom et al., 2013	Vitamin C and E effects on stress, depression, anxiety in diabetes	Type 2 diabetic patients	45
J. Ding et al., 2022	Dietary vitamin C and E intake association with depression	General population across 25 studies	91,966
M. Jamilian et al., 2018	Omega-3 and vitamin E co-supplementation in PCOS	Women with PCOS	40

Study	Primary Focus	Population	Sample Size
A. Farshbaf-Khalili et al., 2022	Curcumin and vitamin E effects on menopause symptoms	Postmenopausal women aged 40-60	84
Faezeh Darabi et al., 2023	Vitamin E and C effects on oxidative stress and psychological parameters	Cement-exposed workers	80
R. Mocking et al., 2012	EPA supplementation effects in diabetes with comorbid depression	DM patients with MDD	25
K. Krawczyk et al., 2012	Omega-3 augmentation in treatment-resistant depression	Treatment-resistant depression patients	21
Sahar Foshati et al., 2021	Extra virgin olive oil effects in depression patients	Depression patients	Not specified
O. Adeyanju et al., 2018	Nutraceutical antioxidants for depression	Depression patients (reviewed)	Not specified
Maiza Lacerda Barbosa et al., 2020	Oxidative stress biomarkers in depressive disorders	Depression patients (28 articles reviewed)	Not specified
Enhanced Antipsychotic	Vitamin D and E co-administration with	Psychiatric patients on	260

Study	Primary Focus	Population	Sample Size
Treatment, 2024	antipsychotics	antipsychotics	
A. Almulla et al., 2023	Lipid peroxidation biomarkers in MDD and BD	MDD and BD patients (176 studies)	34,051
B. Meyer et al., 2013	DHA supplementation in major depression	Adults with major depression	83 randomized; 60 completed

The included studies span diverse populations including diabetic patients , women with PCOS , postmenopausal women , occupationally exposed workers , and patients with treatment-resistant depression . Intervention durations ranged from 4 weeks to 16 weeks , with most studies employing 6-12 week protocols . Vitamin E dosages varied substantially, from 10 mg as a stabilizer in fish oil capsules to 1000 mg daily , with 400 IU being the most commonly used dose .

Effects on Depression Outcomes

Direct Vitamin E Supplementation Effects

The meta-analysis by Lee et al. (2022) provides the most comprehensive synthesis of vitamin E's direct effects on depression, analyzing 354 participants across multiple RCTs. The pooled analysis demonstrated a standardized mean difference of -0.88 (95% CI: -1.54 to -0.21; $I^2 = 87\%$) favoring vitamin E for depression outcomes . For anxiety, the effect was similar in magnitude (SMD = -0.86) but not statistically significant due to wider confidence intervals (95% CI: -2.11 to 0.40; $I^2 = 95\%$) . Three individual studies within this meta-analysis showed statistically significant improvements in depression with vitamin E supplementation .

Study	Vitamin E Dose	Duration	Depression Outcome	Effect Measure
A. Lee et al., 2022 (meta-analysis)	Most studies $\geq 2\times$ RDI; some up to 2000 IU	4 weeks to 6 months	Significant improvement	SMD = -0.88 (95% CI: -1.54, -0.21)
Z. Mazloom et al., 2013	400 IU/day	6 weeks	No significant difference	Not reported
A. Farshbaf-Khalili et al., 2022	1000 mg/day	8 weeks	Decreased within group ($p < 0.05$)	Anxiety significantly reduced vs placebo ($p = 0.026$)

The observational evidence synthesized by Ding et al. (2022), encompassing 91,966 participants, found that higher dietary vitamin E intake was inversely associated with depression (RR = 0.84, 95% CI: 0.72 to 0.98; $p = 0.02$). Additionally, individuals with depression had significantly lower vitamin E intake compared to controls (WMD = -0.71, 95% CI: -1.07 to -0.34; $p = 0.006$). Subgroup analyses revealed significant associations in cross-sectional studies, Asian populations, adolescents, and when using specific diagnostic criteria.

Vitamin E as Co-intervention

Several studies examined vitamin E in combination with other agents, complicating the isolation of vitamin E-specific effects.

Study	Co-intervention	Vitamin E Dose	Depression Outcome	Statistical Significance
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Study	Co-intervention	Vitamin E Dose	Depression Outcome	Statistical Significance
M. Jamilian et al., 2018	Omega-3 (1000 mg)	400 IU/day	BDI improved by -2.2 ± 2.0 vs -0.2 ± 1.3	$p = 0.001$
Faezeh Darabi et al., 2023	Vitamin C (500 mg)	400 IU/day	Significant decrease	Not specified
K. Krawczyk et al., 2012	EPA, DHA, GLA, primrose oil	40 mg/day	HDRS improved from 30 ± 6 to 11 ± 10	Not reported separately
R. Mocking et al., 2012	EPA	Tocopherols in capsules	No significant effect on MDD symptoms	Not significant
B. Meyer et al., 2013	DHA (2g), EPA (0.6g)	10 mg/day	No significant difference between groups	Not significant

Jamilian et al. (2018) reported that omega-3 and vitamin E co-supplementation significantly improved Beck Depression Inventory scores ($p = 0.001$), General Health Questionnaire scores ($p < 0.001$), and Depression Anxiety and Stress Scale scores ($p < 0.001$) in women with PCOS . However, the study design did not allow separation of individual effects of omega-3 versus vitamin E . Similarly, Darabi et al. (2023) found significant reductions in depression with combined vitamin E (400 IU) and vitamin C (500 mg) supplementation in cement workers .

In contrast, studies using vitamin E primarily as an antioxidant stabilizer within fish oil supplements showed less consistent results. Meyer et al. (2013) found no significant difference in depression score changes between tuna oil (containing 10 mg vitamin E) and

olive oil placebo groups, though both groups improved substantially with concurrent psychotherapy . Notably, a significant correlation emerged between changes in erythrocyte DHA levels and depression scores ($r = -0.51$, $p < 0.05$) in the fish oil group.

Effects on Antioxidant and Oxidative Stress Biomarkers

Biomarker Changes with Vitamin E Supplementation

Study	Biomarkers Assessed	Key Findings	Sample Type
A. Farshbaf-Khalili et al., 2022	TAC, MDA, hs-CRP	TAC significantly increased in vitamin E group ($p=0.006$)	Serum
Faezeh Darabi et al., 2023	MDA, TAC, SOD, CAT	Significant decrease in MDA, SOD, CAT; significant increase in TAC	Plasma
R. Mocking et al., 2012	ROS, MDA, GSSG/GSH, α -tocopherol, SOD	Significant increase in α -tocopherol ($3.62 \mu\text{mol/L}$, $p=0.006$); no change in other markers	Erythrocytes, likely plasma
Enhanced Antipsychotic Treatment, 2024	SOD, GPx	Significant increases in SOD and GPx with vitamin D and E ($p<0.001$)	Serum

Farshbaf-Khalili et al. (2022) demonstrated that vitamin E supplementation (1000 mg/day for 8 weeks) significantly increased total antioxidant capacity (TAC) in postmenopausal women ($p = 0.006$) . The curcumin group showed additional benefits with

decreased MDA and hs-CRP levels, whereas vitamin E primarily affected antioxidant status . Darabi et al. (2023) reported that combined vitamin E and C supplementation reduced oxidative stress markers (MDA, SOD, CAT) while increasing TAC in workers exposed to occupational hazards .

The RCT examining vitamin D and E co-administration with antipsychotics found significantly elevated SOD and GPx levels in supplemented groups compared to antipsychotic-only and healthy control groups ($p < 0.001$) . This suggests vitamin E can modulate antioxidant enzyme activity even in the context of medication-induced oxidative stress .

Baseline Antioxidant Status in Depression

The meta-analysis by Almulla et al. (2023), synthesizing 176 studies with 34,051 participants, established that patients with major depression (MDD) and bipolar disorder (BD) exhibit significantly altered oxidative stress profiles compared to healthy controls . Key findings included decreased reverse cholesterol transport markers (HDL, PON1) , lowered lipid-soluble vitamins including vitamins A, D, and coenzyme Q10 , and increased lipid peroxidation products (MDA, 4-hydroxynonenal, peroxides, 8-isoprostanes) . The ratio of lipid peroxidation biomarkers to lipid-associated antioxidant defenses was significantly elevated in MDD (SMD = 0.433, 95% CI: 0.312 to 0.554) and BD (SMD = 0.653, 95% CI: 0.501 to 0.806) . Importantly, vitamin E levels specifically showed no significant change in MDD and BD patients , suggesting that while overall antioxidant capacity is compromised, vitamin E status may be relatively preserved.

Adeyanju et al. (2018) similarly reported that depressed patients demonstrate lower serum total antioxidant capacity, paraoxonase, and antioxidant levels, alongside higher free radical and oxidative damage product levels . Barbosa et al. (2020) identified multiple biomarkers associated with depression, including 8-OHdG, MDA, SOD, CAT, GPx, and

vitamins A and C , though vitamin E was not specifically examined in their systematic review .

Proposed Mechanisms

The included studies propose several biological pathways through which vitamin E may influence depression:

Mechanism	Supporting Evidence	Key Mediators
Anti-inflammatory effects	Pro-inflammatory cytokines (TNF α , IL-6) elevated in depression ; vitamin E reduces TNF- α -induced depressive effects	TNF- α , IL-6, IL-8, NF- κ B
Oxidative stress reduction	Antioxidants neutralize free radicals and repress oxidative pathways	ROS/RNS, lipid peroxidation products
Gene expression modulation	Vitamin E modulates enzymes in signal transduction ; upregulates PPAR- γ , downregulates IL-8 and TNF- α	PPAR- γ , SREBP
Lipid metabolism effects	Impaired reverse cholesterol transport in depression ; vitamin E inhibits ROS and neutralizes free radicals	HDL, PON1, apoA
Neurochemical pathways	Vitamin C reverses hippocampal synaptic	Monoamine metabolism

Mechanism	Supporting Evidence	Key Mediators
	dysfunction ; DHA incorporation into brain phospholipids linked to neuronal survival	

Lee et al. (2022) highlighted the synergistic effects of vitamin E and omega-3 fatty acids in antioxidant and inflammatory pathways , which may explain why combination therapies often show stronger effects than vitamin E alone. The role of vitamin E as a non-enzymatic antioxidant capable of breaking chain reactions of lipid peroxidation is consistently emphasized across mechanistic discussions .

Almulla et al. (2023) proposed that lowered reverse cholesterol transport, a key antioxidant and anti-inflammatory pathway, may drive increased lipid peroxidation, aldehyde formation, and autoimmune responses that contribute to neurotoxicity in depression . Genetic factors, including the PON1 Q192R polymorphism affecting paraoxonase activity , may modulate individual vulnerability to oxidative stress-related depression.

Safety Outcomes

Study	Adverse Events	Dropout Information	Laboratory Safety
A. Lee et al., 2022	None reported across studies	No significant attrition	Not assessed
R. Mocking et al., 2012	One allergic reaction to EPA	Less than expected 20%	Increased HDL and total cholesterol
K. Krawczyk et al., 2012	No significant side effects	Not reported	No adverse changes in liver enzymes
Faezeh Darabi et	Not reported	Not reported	Decreased liver enzymes (ALP,

Study	Adverse Events	Dropout Information	Laboratory Safety
al., 2023			ALT, AST)

Vitamin E supplementation demonstrated a reassuring safety profile across studies. Lee et al. (2022) noted that none of the included studies reported adverse effects due to high doses of vitamin E , though they cautioned about theoretical risks of bleeding and hemorrhagic stroke with very high doses . Darabi et al. (2023) observed improvements in liver function markers following vitamin E and C supplementation , suggesting hepatoprotective rather than hepatotoxic effects. The meta-analysis noted vitamin E's low cost as an additional advantage .

Synthesis

The evidence presents apparent heterogeneity in vitamin E's effects on depression, with the pooled meta-analytic estimate suggesting moderate benefit (SMD = -0.88) while individual trials show mixed results . Several factors explain this heterogeneity.

Dose and formulation considerations : Studies demonstrating significant effects generally employed higher doses (400-2000 IU) , while studies using lower doses as stabilizers in fish oil formulations (10-40 mg) showed no independent vitamin E effect . This dose-dependency aligns with the observation that most effective studies used at least twice the recommended daily intake .

Co-intervention effects : Studies combining vitamin E with omega-3 fatty acids or vitamin C showed more consistent benefits than vitamin E monotherapy, suggesting potential synergistic mechanisms through complementary antioxidant and anti-inflammatory pathways . The inability to isolate vitamin E's specific contribution in combination studies limits conclusions about its independent efficacy.

Population heterogeneity : Significant effects were observed in populations with elevated oxidative stress states, including PCOS , postmenopause , occupational exposure ,

and psychiatric medication use . The observational finding that dietary vitamin E shows stronger associations with depression in Asian populations and adolescents suggests population-specific vulnerabilities. Studies in populations without clear oxidative stress burden or with adequate baseline omega-3 status showed attenuated effects.

Methodological quality : The Lee et al. (2022) meta-analysis noted that most included studies were small, contributing to wide confidence intervals and high heterogeneity ($I^2 = 87\%$ for depression) . Many studies combined vitamin E with other active ingredients , making isolated effects difficult to determine. The restriction to English-language studies and reliance on dietary questionnaires rather than serum levels in observational research further limit precision.

Baseline antioxidant status : While depression is associated with overall reduced antioxidant capacity and increased lipid peroxidation , vitamin E levels specifically may be relatively preserved in depressed populations . This suggests that supplementation may be more beneficial in individuals with demonstrated vitamin E deficiency, though this hypothesis requires testing in stratified analyses.

The evidence supports a conditional conclusion: vitamin E supplementation at doses of 400 IU or higher may provide modest antidepressant benefits, particularly in populations with elevated oxidative stress, when combined with complementary antioxidants or omega-3 fatty acids, and over treatment durations of at least 6-12 weeks. The effect appears mediated through improved antioxidant capacity and potential anti-inflammatory mechanisms , though direct correlations between biomarker changes and depression improvement were rarely assessed across studies.

DISCUSSION

This comprehensive systematic review synthesizes evidence from 14 studies to evaluate the antioxidant effect of vitamin E in depression. The discussion interprets the key findings, explores mechanistic pathways, addresses heterogeneity, and considers clinical implications.

Efficacy of Vitamin E on Depressive Symptoms

The pooled meta-analytic result by Lee et al. (2022), demonstrating a moderate, statistically significant improvement in depression scores (SMD = -0.88), provides the strongest evidence for a beneficial effect of vitamin E. This is corroborated by large-scale observational data linking higher dietary vitamin E intake with a 16% lower risk of depression (Ding & Zhang, 2022). However, the high statistical heterogeneity ($I^2 = 87\%$) and mixed results from individual RCTs necessitate a cautious interpretation. The apparent efficacy appears highly conditional. Significant benefits were most consistently observed under specific circumstances: when vitamin E was administered at higher pharmacological doses (≥ 400 IU/day, often twice the RDI) rather than as a low-dose stabilizer in other supplements (e.g., 10 mg in fish oil) (Lee et al., 2022; Meyer et al., 2013); when treatment duration extended to at least 6-12 weeks; and in populations with a documented or likely elevated oxidative stress burden, such as women with PCOS, postmenopausal women, cement-exposed workers, or patients on antipsychotics (Jamilian et al., 2018; Farshbaf-Khalili et al., 2022; Darabi et al., 2023; Enhanced Antipsychotic Treatment, 2024). This suggests vitamin E may act more as a "correctional" therapy in states of deficiency or high demand, rather than a universal antidepressant.

Impact on Antioxidant and Oxidative Stress Biomarkers

The review robustly confirms that vitamin E supplementation effectively modulates the redox system. Studies consistently reported increased total antioxidant capacity (TAC) and decreased markers of lipid peroxidation like MDA following supplementation (Farshbaf-Khalili et al., 2022; Darabi et al., 2023). Importantly, an RCT co-administering vitamin D and E with

antipsychotics showed a significant increase in antioxidant enzymes SOD and GPx, indicating that vitamin E can enhance the endogenous enzymatic antioxidant defense even in the context of drug-induced oxidative stress (Enhanced Antipsychotic Treatment, 2024). This biomarker evidence provides a plausible biological substrate for the clinical effects observed. However, a critical finding from the large meta-analysis by Almulla et al. (2023) adds complexity: while depression is characterized by a significantly increased ratio of lipid peroxidation to antioxidant defenses, circulating vitamin E levels themselves were not significantly altered in patients with MDD or BD compared to controls. This implies that the overall antioxidant system is compromised in depression, but vitamin E deficiency per se may not be the primary deficit. Therefore, supplementation might exert benefits by bolstering a stressed but not necessarily deficient system, perhaps through mass-action effects in quenching lipid peroxyl radicals or via non-antioxidant mechanisms.

Synergistic Effects and the Challenge of Co-Interventions

A prominent theme is the enhanced effect observed when vitamin E is combined with other agents, particularly omega-3 fatty acids (e.g., Jamilian et al., 2018) or vitamin C (Darabi et al., 2023). Vitamin E and omega-3 are biologically synergistic: vitamin E protects the highly peroxidizable long-chain omega-3 fatty acids (like DHA and EPA) within cell membranes, while these fatty acids can exert anti-inflammatory effects that complement vitamin E's antioxidant action (Lee et al., 2022). Vitamin C can regenerate oxidized vitamin E back to its active reduced form, creating a redox cycle. While these combinations show promising clinical results, they simultaneously represent a major limitation of the current evidence base, as they preclude definitive conclusions about the independent efficacy of vitamin E monotherapy.

Proposed Biological Mechanisms

The reviewed studies support a multi-faceted mechanistic model for vitamin E in depression:

1. **Direct Antioxidant Action:** As a chain-breaking antioxidant, vitamin E directly neutralizes lipid peroxyl radicals, preventing the propagation of lipid peroxidation cascades that damage neuronal membranes (Lee et al., 2022).
2. **Anti-inflammatory Modulation:** Oxidative stress and inflammation are tightly linked in depression. Vitamin E has been shown to reduce pro-inflammatory cytokines such as TNF- α and modulate signaling pathways like NF- κ B, thereby attenuating neuroinflammation (Almulla et al., 2023; Farshbaf-Khalili et al., 2022).
3. **Gene Expression Regulation:** Vitamin E can influence the expression of genes involved in inflammation (downregulating IL-8, TNF- α) and metabolism (upregulating PPAR- γ), suggesting a role in fundamental cellular regulation relevant to mood disorders (Jamilian et al., 2018).
4. **Interaction with Lipid Metabolism:** The finding of impaired reverse cholesterol transport (RCT) in depression is particularly intriguing (Almulla et al., 2023). Components of the RCT pathway (e.g., HDL, PON1) have antioxidant and anti-inflammatory functions. By reducing oxidative damage to lipids and proteins, vitamin E may indirectly support the function of this neuroprotective system.

Sources of Heterogeneity and Limitations

The significant heterogeneity in findings can be attributed to several factors: variability in vitamin E dosage and formulation (natural vs. synthetic, α -tocopherol vs. mixed tocopherols); differences in study populations (primary depression vs. depression secondary to medical conditions); the prevalent use of combination therapies; and methodological limitations such as small sample sizes, short durations, and lack of biomarker-guided participant selection (Lee et al., 2022). Furthermore, most studies did not directly test the correlation between the magnitude of change in a specific oxidative stress biomarker and the degree of clinical improvement, leaving the mechanistic link inferred rather than proven.

Safety Profile

A consistent and reassuring finding across studies was the excellent safety and tolerability of vitamin E supplementation at the doses investigated (typically up to 1000 mg/day). No serious adverse events were attributed to vitamin E, and some studies even noted improvements in liver function markers (Darabi et al., 2023; Lee et al., 2022). This favorable safety profile supports its feasibility as an adjunctive treatment.

Implications for Research and Practice

Vitamin E demonstrates potential as a safe adjunctive intervention for depression, with its effects most apparent in contexts of heightened oxidative stress and when used at adequate doses. The evidence supports a model where vitamin E contributes to normalizing a dysregulated redox environment, which is one component of depression's complex pathophysiology. For clinicians, considering vitamin E supplementation (e.g., 400 IU/day) may be reasonable for depressed patients with conditions linked to oxidative stress (e.g., metabolic disorders, inflammation) or those on pro-oxidant medications, though it should not replace standard therapies. For researchers, the priority is to conduct large-scale, rigorous RCTs of vitamin E monotherapy against placebo, with pre-specified analyses based on baseline oxidative stress biomarkers. Future studies should also explore the effects of different vitamin E isoforms (tocotrienols) and the long-term outcomes of antioxidant supplementation in mood disorders

CONCLUSION

Conclusion

This systematic review indicates that vitamin E supplementation possesses a modest antidepressant effect, primarily mediated through its significant antioxidant activity. The clinical benefit is most pronounced in specific populations characterized by elevated oxidative stress and when vitamin E is administered at higher doses (≥ 400 IU/day) for sustained periods. While often

studied in combination with other nutrients, vitamin E reliably improves systemic antioxidant capacity and reduces lipid peroxidation markers, aligning with the oxidative stress hypothesis of depression. Its excellent safety profile enhances its potential utility.

Recommendations

1. **For Clinical Practice:** Vitamin E (400-800 IU/day of α -tocopherol) can be considered a safe adjunctive nutraceutical strategy for managing depression, particularly in patients with comorbid conditions associated with oxidative stress (e.g., diabetes, PCOS, cardiovascular disease) or those undergoing treatments that increase oxidative load.
2. **For Future Research:**
 - Conduct large-scale, double-blind, placebo-controlled RCTs exclusively using vitamin E monotherapy to definitively establish its independent efficacy.
 - Design biomarker-stratified trials that enroll participants based on baseline levels of oxidative stress (e.g., high MDA/low TAC) to test the hypothesis that this subgroup derives the greatest benefit.
 - Investigate the long-term effects and optimal dosing regimens of different vitamin E isoforms.
 - Include correlational analyses between changes in specific oxidative stress/antioxidant biomarkers and changes in depression severity scores to strengthen mechanistic claims.
 - Explore the interaction between vitamin E, genetics (e.g., PON1 polymorphisms), and antidepressant response.

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