SAR Journal of Psychiatry and Neuroscience

Abbreviated Key Title: *SAR J Psychiatry Neurosci*
Home page: https://sarpublication.com/journal/sarjpn/home
DOI: https://doi.org/10.36346/sarjpn.2026.v07i01.001

ISSN 2707-7764 (P)
ISSN 2709-6939 (O)

Original Research Article

Omega-3 Fatty Acids in Depression: A Systematic Review of Human Studies with Supporting Evidence from Preclinical Models

Tolga Tasci[1], Linhong Yuan[2], Zheng Feei Ma[3], Shaobo Zhou[1]*

[1]School of Science, Faculty of Engineering and Science, University of Greenwich, Central Avenue, Chatham ME4 4TB, UK
[2]School of Public Health, Capital Medical University; Beijing Key Laboratory of environment and aging; China-British Joint Laboratory of Nutrition Prevention and Control of Chronic Diseases, You'anmen Street, Beijing, 100069, China
[3]Centre for Public Health, School of Health and Social Wellbeing, University of the West of England Faculty of Health and Applied Sciences, Bristol, UK

***Corresponding Author:** Shaobo Zhou
School of Science, Faculty of Engineering and Science, University of Greenwich, Central Avenue, Chatham ME4 4TB, UK

Article History: | Received: 03.12.2025 | Accepted: 29.01.2026 | Published: 02.02.2026 |

Abstract: ***Background***: Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are essential for brain function and have been increasingly studied for their potential preventive and therapeutic roles in depression. ***Methods***: A systematic review was conducted in accordance with PRISMA guidelines, focusing on recent human studies evaluating the effects of n-3 PUFA supplementation and Mediterranean dietary patterns on depression-related outcomes. Studies were identified through electronic databases and manual searches and critically appraised using the Joanna Briggs Institute Checklist for Randomized Controlled Trials. To contextualize human data, relevant preclinical animal studies were also reviewed. ***Results***: The review identified mixed and context-dependent evidence for the efficacy of n-3 PUFAs in depression prevention among general populations. In contrast, more consistent therapeutic effects were observed in treatment studies, particularly when EPA-predominant formulations were used as adjunctive interventions. However, many studies lacked statistical power or did not achieve significance. Six preclinical studies demonstrated robust antidepressant and anxiolytic effects of EPA and DHA across models of nicotine withdrawal, chronic stress, aging, and neurotrophin deficiency. These effects were linked to anti-inflammatory, neuroprotective, and neurotrophic mechanisms. ***Conclusions***: Omega-3 PUFAs—especially EPA—may offer modest yet clinically relevant benefits as adjunctive treatments for depression. While preventive efficacy remains unclear, preclinical data provide strong mechanistic support. Future large-scale, biomarker-informed human trials are warranted to clarify efficacy and optimize dosing strategies

Keywords: n-3 Fatty Acids, Depression, Systematic Review, Mediterranean Diet, Adjunctive Therapy, Animal Models, EPA, DHA.

INTRODUCTION

Depression, also known as major depressive disorder, is a common and debilitating mental health condition characterised by persistent low mood, loss of interest or pleasure in daily activities, and a range of emotional and physical symptoms that impair an individual's ability to function (WHO, 2023). According to the World Health Organization, an estimated 5% of adults worldwide experience depression (WHO, 2023). Liu *et al*., (2024a) reported that approximately 280 million people were affected by depression in 2019, with projections indicating that mental disorders — including depression — are likely to become one of the leading global health burdens by 2030. The Global Burden of Disease study also noted an increase in depression cases from 182 million in 1990 to 290 million in 2019 (a 59% rise), largely attributed to population growth and ageing (Liu *et al*., 2024b).

Unlike transient emotional responses to life events, depression persists over time and can affect nearly all aspects of life, including personal relationships, occupational performance, and community participation. Depression is recognised as the leading cause of

disability worldwide, contributing substantially to the global burden of disease (WHO, 2023) and within the UK context (Baker & Kirk-Wade, 2024). Although depression can affect individuals of any age and background, certain groups are at elevated risk. Women, for example, have approximately a 50% higher prevalence of depression compared to men, and more than 10% of women who are pregnant or postpartum report depressive symptoms (WHO, 2023). Additionally, individuals who have experienced trauma, significant loss, or prolonged stress demonstrate a heightened vulnerability to depressive conditions (Meng *et al*., 2019).

The prevalence of depression varies regionally. In the United States, rates are estimated between 5% and 10%, with higher prevalence observed in specific populations (Breslow *et al*., 2019). In China, the China Mental Health Survey documented a 3.6% prevalence, with consistently higher rates among women compared to men (Lu *et al*., 2021). In the UK, depression represents an escalating public health issue; data from the Office for National Statistics (ONS, 2022) indicate that in autumn 2022, 16% of adults reported moderate to severe depressive symptoms, up from 10% prior to the COVID-19 pandemic. This upward trend is supported by findings from the Adult Psychiatric Morbidity Survey, which has charted rising rates of mental health disorders since the 1990s (Park & Zarate, 2019; Baker & Kirk-Wade, 2024).

Certain subgroups within populations show disproportionately high rates of depressive symptoms. ONS (2022) reports elevated prevalence among economically inactive individuals due to long-term illness (59%), unpaid carers providing more than 35 hours of care per week (37%), disabled adults (35%), young adults aged 16–29 (28%), and residents of socioeconomically deprived areas (25%) (Baker & Kirk-Wade, 2024). Socioeconomic stressors — such as difficulty meeting basic living expenses — are associated with significantly higher rates of depression, with affected individuals reporting nearly three times the likelihood of depressive symptoms compared to those without financial hardship.

Mental illnesses such as depression have worsened globally, with the COVID-19 pandemic contributing significantly to population mental health decline (Taquet *et al*., 2021; Covid-19 Mental Disorders Collaborators, 2021). Depression arises from a complex interplay of social, psychological, and biological factors. Its core clinical feature — prolonged, pervasive depressed mood — is often accompanied by comorbid conditions including tuberculosis and cardiovascular disease (Park & Zarate, 2019; Meng *et al.,* 2019; Zhang *et al*., 2023) and can also manifest with disturbances in sleep and appetite (Bhatt *et al*., 2020; Liu *et al*., 2021).

Despite the availability of effective treatments, over 75% of individuals in low- and middle-income countries do not receive appropriate depression care, due to barriers such as resource scarcity, limited trained professionals, and persistent stigma (WHO, 2023). Consequently, depression prevention and treatment are major global health priorities. Encouragingly, many observational and clinical studies have reported positive effects of dietary modifications on depressive symptoms (Ljungberg *et al*., 2020; Quirk *et al*., 2013; Lassale *et al*., 2019; Parletta et al., 2019), underscoring the potential role of nutrition in mental health interventions.

The etiology of depression is multifaceted, involving genetic, biological, psychological, social, and environmental factors (Bhatt *et al*., 2020). Recognised as a heterogeneous disorder, depression presents with a broad spectrum of cognitive and somatic symptoms, including impaired cognitive performance, anhedonia, mood disturbances (Schmidt *et al*., 2011), sleep disruption, and fatigue (Bhatt *et al*., 2020). Moreover, depression is associated with increased risk of premature mortality and greater incidence of cardiovascular disease (Zhang *et al*., 2023). Individuals with depression often exhibit severe symptoms that may reflect disruptions in adaptive biological processes (Katon *et al*., 2003).

Biologically, genetic predisposition and neurochemical imbalances, particularly involving serotonin regulation and the stress response system, are well-documented contributors (Otte *et al*., 2016; Wray *et al*., 2018). Psychologically, traits such as high neuroticism and maladaptive cognitive styles are linked to greater depression risk (Remes *et al*., 2021). Social and environmental factors such as adverse childhood experiences, isolation, and chronic stress also play significant roles (Otte *et al.,* 2016; Remes *et al*., 2021). Additionally, lifestyle behaviours including substance use and poor sleep are consistently associated with increased depression risk (Hertenstein *et al*., 2019).

Given this multifaceted etiology, effective depression management requires a holistic approach that integrates pharmacological treatments (e.g., antidepressants) with psychological therapies such as cognitive behavioural therapy, each targeting different aspects of the disorder (Vasile *et al*., 2020; Cuijpers *et al*., 2023). Integrating dietary and environmental interventions may further enhance treatment effectiveness, particularly considering established links between nutrition and mental health.

Omega-3 fatty acids comprise a family of polyunsaturated fatty acids (PUFAs) defined by a double bond at the third carbon from the methyl end of the carbon chain. The most functionally significant omega-3s — alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) — play critical structural and functional roles in brain and cardiovascular physiology. ALA is abundant in

plant sources but has limited conversion to EPA and DHA in humans (Brenna *et al*., 2009). EPA and DHA, which are more biologically active, are found predominantly in oily fish and marine oils, and contribute to neuronal membrane fluidity, synaptic function, and anti-inflammatory processes.

Dietary sources of omega-3s vary by type: ALA is common in flaxseed, chia seeds, walnuts, soybeans, and canola oil, while EPA and DHA are abundant in salmon, sardines, mackerel, anchovies, fish oil, and algal oil supplements. Algal oil provides a vegetarian/vegan DHA alternative. Omega-3s have been extensively studied for broad health benefits, including cardiovascular protection through triglyceride reduction, blood pressure modulation, and anti-inflammatory effects, supported by regulatory endorsement (Mozaffarian & Wu, 2011). DHA is also essential for cognitive and visual development, with ongoing evidence for continued brain health support in adulthood.

Interest in the role of omega-3 fatty acids in mental health — particularly depression — has increased in recent years. EPA and DHA are integral to neuronal membranes and neuroplasticity, processes often disrupted in depression (Bazinet & Layé, 2014). Their anti-inflammatory properties may counteract neuroinflammation implicated in depressive pathophysiology (Kiecolt-Glaser *et al*., 2011). Several randomised controlled trials and meta-analyses report beneficial effects of EPA-dominant supplementation on depressive symptoms, especially in major depressive disorder populations (Grosso *et al*., 2014; Mocking *et al.,* 2016).

The balance between n-3 and n-6 PUFAs may influence depression risk because they share common metabolic enzymes, leading to competitive interactions (Schmitz *et al*., 2008). Although some studies found no association between the n-6/n-3 ratio and depression (Kesse-Guyot *et al*., 2012), others demonstrate that a higher n-3/n-6 ratio is associated with reduced depression risk (Lucas *et al*., 2011; Da Rocha *et al*., 2012). A meta-analysis reported that a higher n-6/n-3 ratio was positively associated with depression, although this finding was limited to gestational populations (Lin *et al*., 2017). Therefore, broader investigations are needed to define the impact of PUFA balance on depression prevention and treatment strategies.

Despite these promising insights, evidence remains mixed. Large-scale trials such as the VITAL-DEP study found limited benefits of marine omega-3 supplementation in preventing depression in healthy adults (Okereke *et al*., 2021). Responses to supplementation vary by individual factors including baseline inflammation, EPA: DHA ratio, dose, and intervention duration, with stronger effects often observed in clinically depressed populations. Heterogeneity in study design, population, and outcome measures further complicates interpretation.

Nutritional psychiatry has emerged as an adjunctive discipline addressing intersections between mental health, stress response, and nutrition, though identifying specific causal pathways remains challenging (Adan et al., 2019). Dietary interventions may mitigate depressive symptoms and reduce risk across diverse age groups by targeting biological and psychological mechanisms (de Oliveira Meller *et al*., 2021). The Mediterranean diet — rich in omega-3s, monounsaturated fats, and polyphenols — demonstrates potential protective effects against depression (Jacka *et al*., 2017; Ventriglio *et al*., 2020), though evidence is limited by a lack of large, high-quality trials.

Understanding the independent and combined effects of omega-3 fatty acids is essential for evaluating their role in depression prevention and management. This review aims to synthesise evidence on omega-3 fatty acids, both as supplements and as components of dietary patterns such as the Mediterranean diet, in the prevention and treatment of depressive symptoms.

METHODS

This study first adhered to a protocol developed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2022 updated statement (Page *et al.,* 2021). This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), ID: **CRD4201270107.**

Search Procedure, Inclusion and Exclusion Criteria

The following databases were systematically searched: PubMed, Web of Science, and ScienceDirect. The search strategy incorporated keywords including “Mediterranean Diet,” “Depression,” “Major Depressive Disorder,” “Clinical Depression,” “Omega-3 Fatty Acids,” and “Anti-Inflammatory,” with searches conducted in English or in studies with an available English translation. Original studies investigating the effects of n-3 fatty acids on depressive symptoms, published from 2014 onward, were included in the review. This review included sources of n-3 fatty acids found in Mediterranean diet food groups and their impact on depression symptoms. Food groups such as fish, nuts, seeds, and vegetables, which are major components of the Mediterranean diet, were included due to their n-3 content, including: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Due to their alignment with the natural sources of n-3s in the Mediterranean diet, both fish oil supplementation and naturally occurring n-3s were considered.

Articles were excluded from the review if they lacked an English publication or translation, did not address depressive disorders, did not provide original

research or follow a randomized controlled trial (RCT) design, did not measure depression using a validated rating scale, lacked documentation of a pre-existing clinical diagnosis of depression in participants, or focused on less common n-3 fatty acids such as docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), and stearidonic acid (SDA).

Screening and Data Collection

The initial search across the three selected databases identified 25,444 total results based on the specified keywords. A total of 17,570 articles were excluded by automated filters in each database for not meeting the eligibility criteria. The remaining 7,874 articles were further screened based on titles and abstracts for relevance to the review criteria, research methodology, and keywords. A total of 54 articles underwent full-text screening for final inclusion, of which 42 were excluded based on the eligibility criteria, resulting in 11 articles being included in the final analysis. Figure 1 presents the PRISMA flow diagram detailing the screening and data collection process.

Additionally, a few suitable studies were identified using the electronic databases PubMed, Google Scholar, and Scopus by combining the search terms "Clinical Depression," "Mediterranean Diet," and "Omega-3 fatty acids" in in vitro and in vivo experimental contexts. The articles were assessed to determine the most relevant findings. **Table 1** summarizes studies' intervention method and duration, depression measurement scale, and effects on depressive symptoms. While **Table 2** summarizes studies (2020–2025) that have demonstrated key components of the Mediterranean Diet (MD). This systematic literature review aims to establish the association between n-3 fatty acids and depressive symptoms.

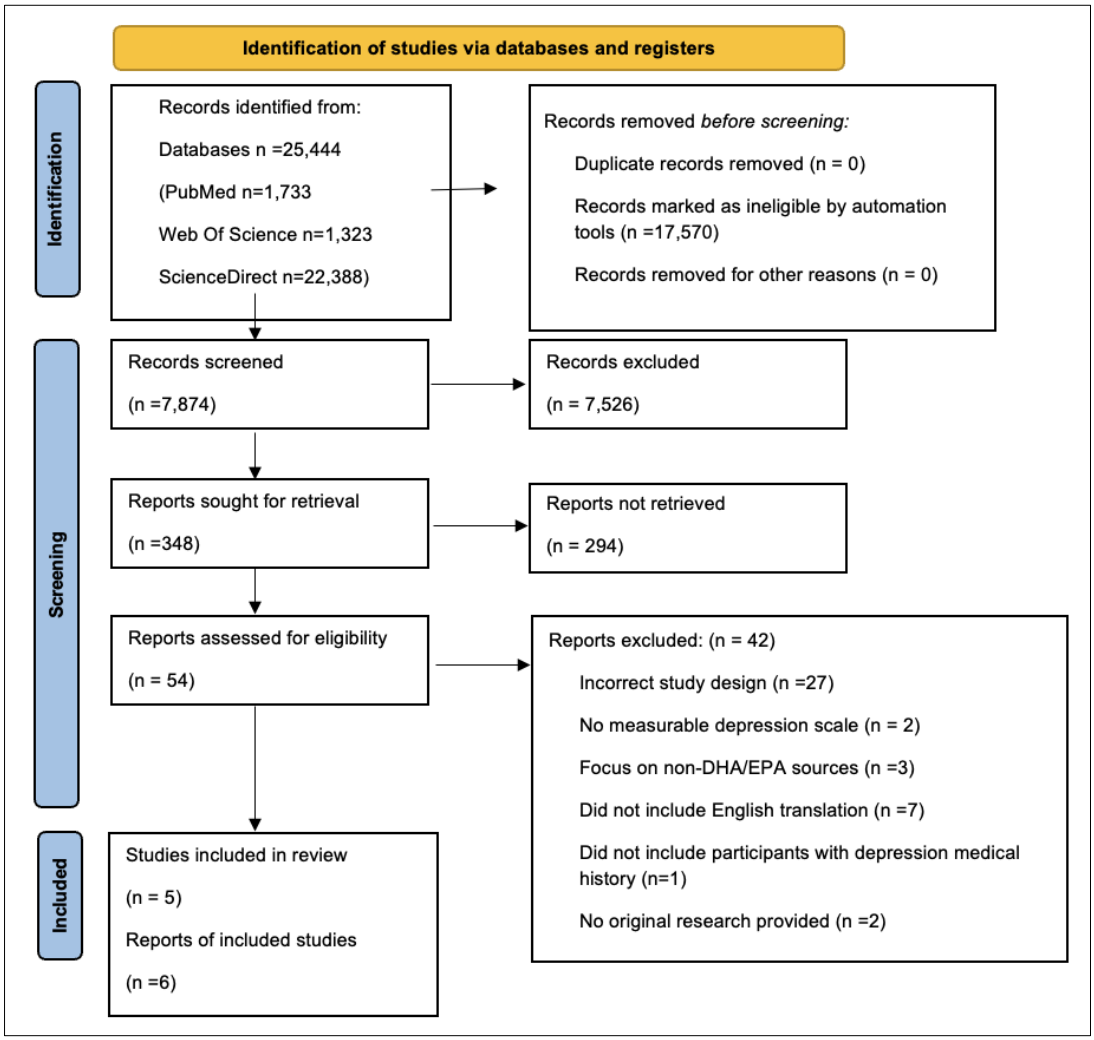


Figure 1: PRISMA flowchart outlining the selection process of studies included in the systematic review. Literature search flow chart

Critical Appraisal and Risk of Bias

All 11 included articles were appraised for methodological quality and consistency using the Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials, to enhance the rigour of the review (Barker *et al.,* 2023).

Inclusion of Animal Studies

To complement and contextualize the findings from human studies, a selection of relevant preclinical animal studies was manually identified and included. The aim was to provide mechanistic insights and support the biological plausibility of n-3 fatty acids in the treatment or prevention of depression. These studies were identified through targeted searches using electronic databases including PubMed, Scopus, and Google Scholar, with search terms such as "n-3 fatty acids," "EPA," "DHA," "animal models of depression," "BDNF," "inflammation," and "anxiolytic effects."

Only original research articles published in peer-reviewed journals from 2014 onwards were included. Studies were selected based on their relevance to the review objective, particularly those employing well-established animal models of depression, such as chronic stress, nicotine withdrawal, BDNF deficiency, or age-related depression, and those examining EPA and/or DHA supplementation. Studies were included if they reported on behavioural outcomes (e.g., depression-like or anxiety-like behaviours) and assessed underlying biological markers (e.g., neuroinflammation, BDNF levels, HPA axis activity).

The animal studies were not subjected to the same PRISMA protocol as the human studies, given their exploratory and supportive nature. However, they were critically assessed for methodological rigour, relevance to human mechanisms, and clarity of reported outcomes. A summary of the findings is presented in **Table 4**, and a synthesis is integrated into the discussion section to highlight translational relevance.

RESULTS

Characteristics of Studies

All studies presented in Table 1 involved human participants and were conducted using randomized controlled trials (RCTs) or variations thereof, providing quantitative data. All RCT designs included a placebo group, except for one study, which incorporated a control group due to the nature of its design. Omega-3 fatty acids—EPA and DHA—were used as interventions in all studies. Participants across studies varied in age, sex, and type of depression. While 10 of the 11 studies had relatively small sample sizes (each with fewer than 200 participants), one study was a significant outlier, including 18,353 participants. This outlier substantially skewed the average, resulting in a mean sample size of 1,750.

Participant sex distribution varied considerably between studies, with several studies demonstrating an imbalance favoring either male or female participants. All studies assessed depressive symptoms using at least one validated measurement tool, including the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Edinburgh Postnatal Depression Scale (EPDS), Center for Epidemiological Studies Depression Scale (CES-D), Depression Anxiety and Stress Scale (DASS), Patient Health Questionnaire-8 (PHQ-8), Hospital Anxiety and Depression Scale (HADS), or the Children's Depression Rating Scale-Revised (CDRS-R).

Using the Joanna Briggs Institute Checklist for Randomized Controlled Trials, each study in Table 1 was critically appraised based on the following 13 criteria:

1. Whether true randomization was used for participant assignment
2. Whether allocation to treatment groups was concealed
3. Whether treatment groups were similar at baseline
4. Whether participants were blinded to treatment assignment
5. Whether those delivering treatment were blinded to group assignment
6. Whether outcome assessors were blinded
7. Whether treatment groups were treated identically, apart from the intervention
8. Whether follow-up was complete and adequately described
9. Whether participants were analysed in their original groups
10. Whether outcomes were measured uniformly across groups
11. Whether outcomes were measured reliably
12. Whether appropriate statistical analysis was used
13. Whether deviations from standard RCT design were addressed in conduct and analysis

Of the 11 studies, only two—Tayama *et al*., (2019) and Parletta *et al*., (2019)—did not meet the 7th criterion, as it was unclear whether both groups received identical treatment apart from the intervention. All other criteria were met across all studies. This means that 9 of the 11 studies received 13 'Yes' responses, indicating robust RCT design and high methodological quality, while the remaining 2 studies received 12 'Yes' responses.

Table 1: Summary of study design, intervention method and duration, depression measurement scale, and effects on depressive symptoms

Reference	Study design and region intervention dosages, duration, and participant characteristics	Depression measurement scale(s)	Effect on depression
Su *et al.,* (2014)	Design: Randomized, double-blind controlled trial Location: Taiwan, China Participants: 152 (108 males) with interferon-alpha-induced major depressive episode (MDE) Intervention: EPA group: 3.5 g/day, 24 weeks (n = 50) DHA group: 1.75 g/day, 24 weeks (n = 51) Placebo group: Olive oil 4 g/day, 24 weeks (n = 51)	The Hamilton Depression Rating Scale, Every 2 weeks during first 8 weeks, then 4 weeks till end of the study to assess the occurrence of major depressive episode with the structured Mini-International Neuropsychiatric Interview.	EPA significantly reduced the risk of interferon-alpha-induced depression in HCV patients. EPA delayed the onset of depression more effectively than DHA or placebo. Lower HAMD scores were observed in the EPA group at weeks 4 and 8. Findings support EPA as a promising anti-inflammatory, preventive intervention for inflammation-related depression.
Ginty and Conklin (2015)	Design: Randomized, placebo-controlled trial Location: United States Participants: 23 (5 males) with depressive symptoms Intervention: Omega-3 group: 1.4 g/day (1000 mg EPA + 400 mg DHA), 21 days Placebo group: Corn oil, 21 days	The Beck Depression Inventory	21 days of low-dose long-chain n-3 polyunsaturated fatty acids supplementation significantly reduced depression in young adults, with 67% of participants no longer meeting depression criteria, compared to 20% in the placebo group.
Vaz *et al.,*	Design: Randomized, placebo-controlled trial Location: Brazil Participants: 60 pregnant women Intervention: Omega-3 group: 1.8 g/day (1.08 g EPA + 0.72 g DHA), from 22–24 weeks gestation to 6 weeks postpartum (~20 weeks) Placebo group: Soybean oil capsules, same duration	The Edinburgh Postnatal Depression Scale	A 16-week daily fish oil supplementation (1.8 g n-3 PUFAs) did not prevent postpartum depression overall but significantly reduced depressive symptoms among women with a history of depression during pregnancy.
Watanabe *et al*., (2018)	Design: Randomized, placebo-controlled trial Location: Japan Participants: 80 female nurses Intervention: Omega-3 group: 2000 mg/day (1200 mg EPA + 600 mg DHA), daily for 52 weeks Placebo group: Rapeseed oil + medium-chain triglycerides, same duration	The Center for Epidemiologic Studies Depression Scale	13-week n-3 supplementation in junior nurses showed no significant effect on overall mental state at 26 weeks but improved depression scores at 52 weeks, reduced insomnia at 13 weeks, and enhanced presenteeism at 26 weeks, indicating selective long-term benefits without consistent overall efficacy
Keshavarz *et al*., (2018)	Design: Randomized, placebo-controlled trial Location: Iran Participants: 65 women with co-morbid obesity and mild to moderate depression Intervention: Omega-3 group: 300 mg/day (180 mg EPA + 120 mg DHA), fish oil capsules, daily for 12 weeks	The Beck Depression Inventory-II	12-week n-3 supplementation (1.8 g/day EPA + DHA) significantly reduced both depression scores and body weight in women with co-morbid obesity and depression compared to placebo, though it did not prevent weight regain post-treatment; the supplement was well tolerated, supporting its

Reference	Study design and region intervention dosages, duration, and participant characteristics	Depression measurement scale(s)	Effect on depression
	Placebo group: Paraffin oil capsules, same duration Note: Both groups followed a weight-loss diet alongside supplementation.		potential as a safe adjunct therapy.
Tayama *et al*., (2019)	Design: Double-blind randomized controlled trial (2×2 factorial design) Location: Japan Participants: 91 adults (52 males) Intervention Groups: Omega-3 only: 1064 mg EPA + 558 mg DHA daily for 12 weeks Psychological intervention only: Stress management education + placebo capsules Combined group: 500 mg/day n-3 PUFAs + stress management education Placebo group: Rapeseed oil placebo capsules, no psychological intervention	The Beck Depression Inventory-II	12-week n-3 supplementation (1000 mg EPA + 500 mg DHA/day) combined with psychoeducation reduced depression severity in workers with mild to moderate depression, though no significant difference was found compared to psychoeducation plus placebo, suggesting limited added benefit from n-3s in this context.
Parletta *et al*., (2019)	Design: Randomized controlled trial Location: Australia Participants: 152 adults (47 males) with depression Intervention: Intervention group: Mediterranean-style dietary program (cooking workshops, food hampers, dietary advice) + fish oil (100 mg EPA + 450 mg DHA) daily for 6 months Control group: Social group intervention (e.g., games, discussions), no dietary changes or fish oil supplementation (no placebo)	Beck Depression Inventory-II with additional use of Center for Epidemiologic Studies Depression Scale and Depression, Anxiety, and Stress Scale	A Mediterranean-style diet plus fish oil significantly improved diet quality, reduced depression, and enhanced quality of life in adults with depression over 3 to 6 months, with improvements linked to increased intake of nuts, legumes, and vegetable diversity, and changes in n-3/omega-6 fatty acid profiles.
Okereke *et al*., (2021)	Design: Randomized placebo-controlled trial Location: United States Participants: 18,353 adults (9,330 males) Intervention: Omega-3 group: 1 g/day marine n-3 fatty acids (465 mg EPA + 375 mg DHA) in capsule, median follow-up of 5 years Placebo group: Soybean oil capsules, same duration *Note:* Part of a 2x2 factorial design (vitamin D also studied); this analysis focused on n-3 vs. placebo	Patient Health Questionnaire-8	In a large trial of adults aged 50+ without depressive symptoms at baseline, n-3 supplementation over 5.3 years did not prevent depression or improve mood and was unexpectedly linked to a slightly increased depression risk, suggesting limited preventive value in the general population.
Savard *et al*., (2023)	Design: Double-blind, placebo-controlled trial Location: Canada Participants: 130 males with	Hospital Anxiety and Depression Scale	In men post-prostatectomy, 12-month n-3 (MAG-EPA) supplementation did not reduce depression or psychological

Reference	Study design and region intervention dosages, duration, and participant characteristics	Depression measurement scale(s)	Effect on depression
	prostate cancer and depressive symptoms Intervention: Omega-3 group: 3.75 g/day n-3 fatty acids (including 500 mg EPA), for 12 weeks Placebo group: Sunflower oil high in oleic acid, for 12 weeks		symptoms more than placebo, with only the placebo group showing improved perceived cognitive function, indicating limited psychological benefit in this population.
Wu *et al*., (2024)	Design: Randomized, placebo-controlled trial Location: Taiwan, China Participants: 60 (10 males) with major depressive disorder Intervention: Omega-3 group: 3.2 g/day n-3 fatty acids (2.1 g EPA + 1.1 g DHA), for 12 weeks Placebo group: Soybean oil capsules, for 12 weeks	The Hamilton Depression Rating Scale	In a 12-week trial, n-3 PUFAs (3.2 g/day) as monotherapy significantly reduced depression severity in MDD patients compared to placebo; although remission and response rates were higher, they did not reach statistical significance, supporting n-3s as a potential alternative therapy.
Li *et al*., (2024)	Design: Randomized controlled clinical trial Location: China Participants: 71 (33 males) diagnosed with major depressive disorder Intervention: Omega-3 group: 2.7 g/day n-3 fatty acids (1941 mg EPA + 759 mg DHA), for 12 weeks Control group: Anti-depressant medication, for 12 weeks	The Montgomery-Asberg Depression Rating Scale	In adolescents with depression, 12-week n-3 supplementation alongside Paxil (paroxetine) significantly reduced depressive symptoms and improved cognitive function, memory, and niacin skin flushing response, supporting its role as an effective complementary therapy with cognitive and physiological benefits.

Food Groups in the Mediterranean Diet and Effect on Mental Health

Table 2 summarizes recent studies (2020–2025) that have demonstrated how key components of the Mediterranean diet—such as vegetables, fruits, whole grains, legumes, fish, olive oil, nuts, and moderate consumption of red wine—are associated with improved mental health outcomes. These foods are rich in antioxidants, anti-inflammatory compounds, and essential nutrients including n-3 fatty acids, B vitamins, and polyphenols, all of which have been linked to a reduced risk of depression and anxiety. Both clinical and observational evidence supports their role in mood regulation, neuroprotection, and the reduction of psychological distress, highlighting the Mediterranean diet's potential as a dietary strategy for promoting mental well-being.

Table 2: Summary of Mediterranean diet food groups, key nutrients, effect on mental health

Reference	Food group	Key nutrients	Effect on mental health
Dharmayani *et al.,* 2022	Vegetables	Folate, fiber, vitamins a, c, e	Improved mood, lower depression risk, cognitive protection
Yan *et al.,* 2023	Fruits	Vitamin c, polyphenols, b vitamins	Anti-inflammatory, mood elevation, reduced depression/anxiety
Ross *et al.,* 2023	Whole grains	B vitamins, fiber, magnesium	Better mood, less anxiety, gut–brain support
Alfaro-González *et al.,* 2023	Legumes	Tryptophan, folate, magnesium, iron	Serotonin synthesis, mood stabilization, fewer emotional problems
Morales-Suárez-Varela *et al.,* 2023	Fish	Omega-3 (epa, dha), vitamin d, protein	Antidepressant, anti-inflammatory, cognitive protection
Daneshzad *et al.,* 2025	Poultry & eggs	Tryptophan, b6, b12, protein	Enhanced serotonin production, antidepressant effects, cognitive support

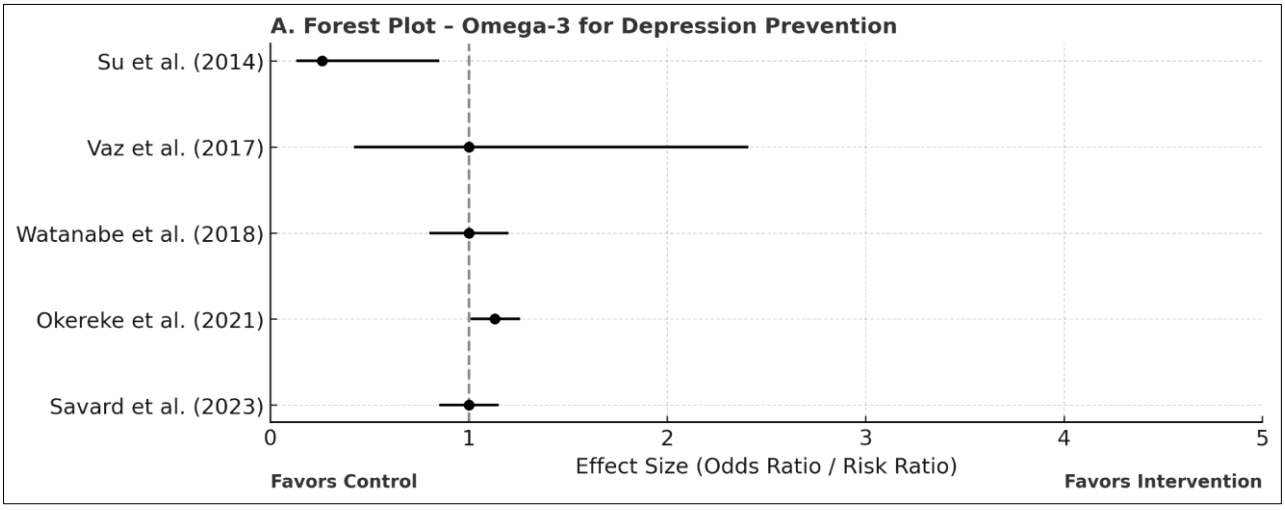
Reference	Food group	Key nutrients	Effect on mental health
Foshati *et al.,* 2022	Olive oil	Monounsaturated fats, Polyphenols	Anti-inflammatory, neuroprotective, improved depression outcomes
Fernández-Rodríguez *et al.,* 2022	Nuts & seeds	Ala, magnesium, zinc, vitamin	Lower depression risk, mood enhancement, neuroprotective antioxidant effects
Liang *et al.,* 2021	Red Wine (moderate)	Resveratrol, polyphenols	Reduced depression risk (at low doses), cognitive benefits (excess intake above limit intake considered detrimental)

Prevention and Treatment of Depression with N-3: Summary of Findings

Of the 11 articles summarized in Table 3, five focused on the role of n-3 fatty acids in the prevention of depression. Among these, two found no statistically significant effects, two reported mixed outcomes, and one observed no change in depressive symptoms following n-3 supplementation. In contrast, all six studies investigating n-3 supplementation for the treatment of depression reported statistically significant improvements in depressive symptoms.

Table 3: Impact of n-3 on depression prevention and treatment

Article author	Statistical significance in depression prevention or treatment with n-3 intervention	No statistical significance in depression prevention or treatment with n-3 intervention	Varying results	No observable change	Study type (Treatment or Prevention)
Su *et al*.,			X		Prevention
Ginty and Conklin	X				Treatment
Vaz *et al*.,			X		Prevention
Watanabe *et al*.,		X			Prevention
Keshavarz *et al*.,	X				Treatment
Tayama *et al*.,	X				Treatment
Parletta *et al*.,	X				Treatment
Okereke *et al*.,				X	Prevention
Savard *et al*.,		X			Prevention
Wu *et al*.,	X				Treatment
Li *et al*.,	X				Treatment



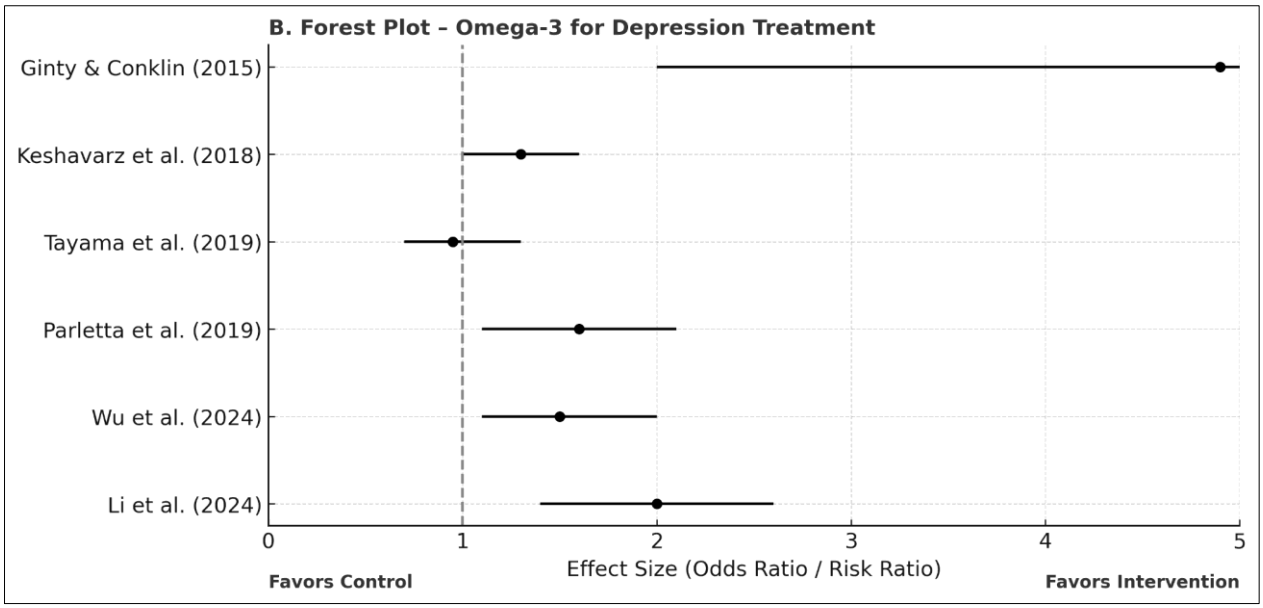


Figure 2: A total of 11 RCTs examining the impact of n-3 fatty acid supplementation on depression were included in this systematic review. The studies were classified into prevention (n = 5) and treatment (n = 6) categories. Forest plots were constructed for each group to produce effect sizes and their 95% confidence intervals (CI), as shown in Figure 2A and 2B.

Omega-3 for Prevention of Depression

Among the five prevention-focused studies, sample sizes ranged widely from 60 participants in smaller trials to 18,353 in the large-scale VITAL-DEP trial (Okereke *et al.,* 2021), highlighting significant variability in study scale and design. Three trials (Su *et al.,* 2014; Vaz *et al.,* 2017; Watanabe *et al.,* 2018) reported no significant preventive effects of n-3 supplementation. However, Su *et al.* (2014) observed a protective effect of EPA supplementation in patients undergoing interferon-alpha-induced depression treatment (OR = 0.26, 95% CI: 0.13–0.85). Due to its substantial sample size, the VITAL-DEP trial had the highest weighting in the analysis and found a modest but statistically significant increase in depression risk among participants receiving n-3 supplementation (HR = 1.13, 95% CI: 1.01–1.26). Savard *et al.,* (2023) found no significant difference in depressive symptoms over 12 months among men with prostate cancer. This meta-analysis examined the relationship between a high dietary n-6/n-3 PUFAs ratio and depression risk. Based on 12 studies involving 66,317 participants, results showed that a higher n-6/n-3 ratio is significantly associated with increased depression risk (OR = 1.21). Notably, this association was significant for dietary intake (OR = 1.32) but not for blood levels of PUFAs. These findings suggest that reducing dietary n-6/n-3 ratios may help in preventing depression (Wang *et al*., 2022).

Table 4: Effects of EPA and DHA on depression-related outcomes in animal models

Article author, year published	Animal model and sample size (n)	EPA:DHA ratio, dosage, method. duration	Observed efficacy	Biomarkers of effect	Relevance to human mechanism
Strekalova *et al.,* 2024	Male mice (30 days old) subjected to controlled ultrasound-induced stress (n=40)	EPA:DHA ratio 1:1 (0.55 mg each), administered orally for 3 weeks	Alleviated depression- and anxiety-like behaviours through anti-inflammatory mechanisms influenced by n-3 supplementation.	Inhibited TNF-α and IL-1β elevation; prevented corticosterone surge.	Demonstrates anti-inflammatory and stress-modulating effects relevant to human depression mechanisms.
Amiry *et al,* 2023	Male adolescent rats (nicotine withdrawal	3:2 (180 mg EPA: 120 mg DHA); Oral dietary administration;	N-3 pre-treatment prevents nicotine withdrawal-induced anxiety and depression by	Assessed oxidative stress, inflammation, BDNF, serotonin levels, and MAO-A activity	Supports n-3 supplementation as a safe intervention for reducing nicotine withdrawal symptoms

Article author, year published	Animal model and sample size (n)	EPA:DHA ratio, dosage, method. duration	Observed efficacy	Biomarkers of effect	Relevance to human mechanism
	model) (n=60)	No specific duration stated, pre-treatment at three doses before nicotine withdrawal	normalising biochemical imbalances		and post-cessation depression through biochemical and behavioural pathways
Tung *et al.,* 2023	Induced aging with D-galactose and stress via chronic unpredictable mild stress in 6-week-old male mice (n=36, 6 groups)	2% fish oil (EPA/DHA ratio not specified); Oral dietary administration for 8 weeks	Improvement depression-like behaviors and cognitive function compared to control	Reduced pro-inflammatory cytokines, increased IL-10 in the prefrontal cortex; preserved serotonin levels in the hippocampus by preventing increases in kynurenine and 5-HIAA; reduced microglial (Iba-1) and astrocytic (GFAP) activation	Suggests fish oil may reduce aging-related depression by modulating neuroinflammation and normalising cytokine and neurotransmitter pathways associated with late-life depression
Peng *et al.,* 2020	Chronic stress induced depression (rat model) (n=40, 4 groups)	EPA and DHA administered separately at 1% oil mixed in food; oral dietary administration for 45 days	Both n-3 oils showed antidepressant-like effects, with EPA producing greater improvements in locomotor activity and body weight	Normalised corticosterone levels; increased noradrenaline and hippocampal 5-HT; reduced neuroinflammation via suppressed microglial activity; EPA significantly lowered IL-6 and TNF-α levels; restored BDNF–TrkB signalling; increased anti-apoptotic Bcl-2 and reduced pro-apoptotic markers	Supports the antidepressant potential of EPA over DHA by reducing inflammatory cytokines and enhancing neurotrophic signalling, aligning with mechanisms observed in human depression pathology
Palmieri et al., 2025	Female rats exposed to a high n-6/low n-3 PUFA diet since fetal stage, reintroduced to n-3 PUFAs from week 8 to week 16	n-3 PUFA-rich diet administered from week 8 to week 16 (exact ratio not specified)	Improved diet-induced depressive-like behaviour (Forced Swimming Test); reversed central neurochemical alterations caused by n-3 deficiency; modulated central neurotrophins and amyloid oligomers	Increased levels of nerve growth factor, brain-derived neurotrophic factor (BDNF), and synaptophysin in the prefrontal cortex (PFC) and hippocampus; partial recovery of amyloid oligomers and amyloid-beta precursor protein; enhanced calmodulin-dependent protein	Replenishment of n-3 PUFAs reduced plasma 3-hydroxykynurenine levels (a pro-oxidant of the tryptophan/kynurenine pathway) but did not restore serotonin levels or kynurenine/tryptophan ratio; suggests late-life n-3 intervention benefits CNS function, though some neurotoxic effects may remain irreversible

Article author, year published	Animal model and sample size (n)	EPA:DHA ratio, dosage, method. duration	Observed efficacy	Biomarkers of effect	Relevance to human mechanism
				kinase II levels in PFC	
Zemdegs *et al.,* 2018	One-month-old BDNF-deficient knockout mice (n=5 per group)	Fish oil (ratio not specified); oral dietary administration for 12 weeks	Exhibited antidepressant and anxiolytic effects; mice on fish oil showed reduced depression-like behaviour compared to controls	Normalisation of the BDNF/ERK pathway; restoration of low basal ERK phosphorylation in the hippocampus; enhanced 5-HT transmission through upregulation of serotonin transporter; increased density of immature neurons and evidence of pro-neuroplastic effects	Highlights omega-3's potential to induce antidepressant and neuroplastic changes; suggests use in treatment-resistant depression via normalisation of neurotransmission and enhancement of neuroplasticity, supporting its role as an adjunctive therapy to improve treatment outcomes

A synthesis of six preclinical studies highlights the consistent antidepressant and anxiolytic effects of *n*-3 polyunsaturated fatty acids—particularly EPA and DHA—across diverse animal models of depression, including nicotine withdrawal, chronic stress, age-related depression, and BDNF deficiency. These studies (Amiry *et al*., 2023; Peng *et al*., 2020; Strekalova *et al*., 2024; Tung *et al*., 2023; Zemdegs *et al*., 2018) demonstrate that oral supplementation with EPA, DHA, or fish oil improves behavioral outcomes such as increased locomotor activity, enhanced memory performance, and reduced immobility.

Mechanistically, these effects are linked to reductions in neuroinflammation (e.g., decreased TNF-α, IL-1β, IL-6, and increased IL-10), restoration of neurotransmitter balance (e.g., elevated 5-HT and noradrenaline, reduced MAO-A activity), and enhanced neurotrophic signaling, notably via upregulation of BDNF and TrkB expression. Additional findings include mitigation of oxidative stress, reductions in neurotoxic metabolites, and normalization of hypothalamic-pituitary-adrenal (HPA) axis activity, as evidenced by lower corticosterone levels.

Although the dosage and EPA:DHA ratios varied across studies, oral delivery was the consistent mode of administration. Notably, EPA frequently demonstrated superior efficacy over DHA in modulating inflammatory and neurotrophic pathways, reinforcing its potential clinical relevance in the context of depression. Moreover, findings from models simulating treatment-resistant depression, ApoE4-associated vulnerability, and age-related cognitive decline offer strong translational implications, supporting the integration of gene–diet–neuroinflammation frameworks in future clinical research.

DISCUSSION

This systematic review aimed to evaluate the efficacy of n-3 fatty acids in both the prevention and treatment of depression across human clinical studies and preclinical animal models. Overall, the findings reveal mixed and context-dependent evidence regarding the effectiveness of n-3 fatty acids—particularly DHA and EPA—administered at varying doses and formulations in reducing depressive symptoms. While the available evidence does not support a consistent preventive effect of n-3 supplementation in non-clinical or general populations, there is emerging support for a potential therapeutic role of n-3 fatty acids in the treatment of depression, especially in clinically diagnosed populations and experimental animal models.

Across human studies, preventive trials generally demonstrated null or inconsistent effects, with effect estimates clustering around the line of no effect. In contrast, treatment-focused studies more frequently reported modest but favorable improvements in depressive symptom severity, particularly when EPA-predominant formulations were used and when supplementation was applied as an adjunct to standard care. These findings suggest that the efficacy of n-3 fatty acids may be influenced by baseline depressive status, formulation characteristics (e.g., EPA:DHA ratio), dosage, and individual metabolic or inflammatory profiles. The observed divergence between prevention and treatment outcomes highlights the importance of distinguishing between these clinical contexts when interpreting the role of n-3 fatty acids in depression.

Mechanistic evidence from both human biomarker studies and animal models provides biological plausibility for these clinical observations. n-3 PUFAs, especially DHA and EPA, are integral to neuronal membrane structure, synaptic plasticity, mitochondrial

integrity, and neurochemical regulation—processes that are frequently disrupted in depressive disorders. Clinical and epidemiological studies consistently report lower circulating levels of EPA and DHA, as well as reduced n-3 to n-6 PUFA ratios, in individuals with depression and bipolar disorder. Complementary preclinical evidence further demonstrates that n-3 supplementation can attenuate neuroinflammation, normalize neurotransmitter systems, regulate hypothalamic–pituitary–adrenal (HPA) axis activity, and enhance neurotrophic signaling, with EPA often exhibiting greater antidepressant-like effects than DHA. Collectively, these findings support the hypothesis that n-3 fatty acids may exert therapeutic benefits through anti-inflammatory, neuroprotective, and synaptic mechanisms, rather than through primary disease prevention.

Importantly, the results of this review also reinforce the relevance of dietary context. Observational evidence suggests that adherence to dietary patterns naturally rich in n-3 fatty acids—most notably the Mediterranean diet—is associated with a reduced risk of depression (Alfaro-González *et al*., 2025), whereas isolated n-3 supplementation alone appears insufficient to replicate these effects in randomized trials. This discrepancy underscores the likelihood that synergistic interactions among multiple nutrients, food matrices, and lifestyle factors contribute to the mental health benefits observed in whole-diet approaches. Taken together, the findings of this review suggest that while n-3 fatty acids may not function as a universal preventive intervention, they hold promise as adjunctive therapeutic agents within broader dietary and clinical strategies for depression, warranting further targeted and mechanistically informed investigation.

Biological Mechanisms of n-3 Fatty Acids in Depression

N-3 PUFAs, particularly DHA and EPA, are increasingly recognized for their critical roles in maintaining brain health and modulating neurobiological processes relevant to the pathophysiology of depression. Their influence extends across several domains, including neuronal membrane composition, synaptic structure and function, mitochondrial integrity, neurotransmitter regulation, and neuroinflammatory modulation.

DHA is a major structural component of neuronal membranes and plays an essential role in maintaining synaptic membrane fluidity and the synthesis of phosphatidylserine, a key phospholipid involved in membrane signaling and neurotransmitter release (Kim *et al*., 2022). Experimental studies have shown that DHA enhances the expression of synaptic proteins such as drebrin and postsynaptic density protein-95 (PSD-95), which are integral to dendritic spine formation and synaptic plasticity—processes closely linked to cognitive function and emotional regulation (Zhou *et al*., 2022). In addition, DHA helps preserve mitochondrial function by protecting cardiolipin from oxidative damage, thereby supporting cellular energy metabolism and limiting apoptosis.

EPA, while less prevalent than DHA in brain tissue, appears to exert more potent anti-inflammatory effects, which may underpin its superior antidepressant properties in some studies. EPA modulates inflammation through its metabolic conversion into bioactive lipid mediators via the cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 pathways, leading to the production of resolvins and protectins—lipid compounds with neuroprotective and anti-inflammatory properties (Malau *et al*., 2024). EPA also influences the expression of synaptic amides and indirectly supports neurotransmission by reducing inflammatory cytokines that impair monoamine activity.

Clinical evidence further supports the relevance of these mechanisms. Numerous studies have documented significantly lower serum levels of EPA and DHA in individuals with major depressive disorder (MDD) and bipolar disorder compared to healthy controls (Gao *et al*., 2024). Additionally, epidemiological data indicate that a reduced dietary intake of n-3 PUFAs and a low n-3 to n-6 ratio are consistently associated with an increased prevalence of depressive disorders (Wang *et al*., 2022; Gao *et al*., 2024). These findings suggest that insufficient n-3 availability may disrupt essential neurobiological pathways that contribute to mood regulation.

Emerging neuroimaging data offer further mechanistic insight. A 52-week randomized controlled trial demonstrated that DHA supplementation significantly modulated brain entropy in the left posterior cingulate gyrus—an area implicated in self-referential processing and depression pathogenesis (Lin *et al*., 2024). These alterations in brain network complexity could reflect improved synaptic integration and functional connectivity resulting from DHA's structural and neurochemical effects.

Preclinical models have also provided compelling evidence of the antidepressant potential of n-3 PUFAs. In a chronic unpredictable mild stress (CUMS) model, DHA and EPA supplementation attenuated behavioral signs of depression, normalized hippocampal serotonin (5-HT) levels, and reduced plasma corticosterone, suggesting regulation of the HPA axis (Peng *et al*., 2020). Notably, EPA produced stronger antidepressant-like effects than DHA, possibly due to its more robust impact on inflammatory cytokines such as IL-6 and TNF-α. Similarly, in models of sleep deprivation, DHA supplementation reversed depressive-like behaviors and restored the expression of cannabinoid receptor type 1 (CB1), further highlighting the neuromodulatory capacity of n-3 PUFAs.

The relevance of these findings is reinforced by studies examining lifelong n-3 deprivation and repletion. For instance, in a rodent model of perinatal n-3 deficiency, reintroducing DHA and EPA from adolescence significantly improved depressive-like behaviors and restored levels of neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in the prefrontal cortex and hippocampus (Palmieri *et al*., 2025). While some neurochemical deficits—such as serotonin levels and the kynurenine/tryptophan ratio—were only partially recovered, the results suggest that n-3 supplementation may offer substantial neuroprotective benefits, even when introduced after developmental critical windows.

Despite these mechanistic insights, clinical outcomes remain mixed, particularly in prevention trials. The variability in study results likely reflects heterogeneity in factors such as dosage, duration, the ratio of EPA to DHA, baseline n-3 status, comorbidities, and depression subtypes. A recent clinical cohort study combining EPA/DHA and vitamin D supplementation failed to show significant improvement in depressive symptoms relative to placebo, underscoring the potential influence of formulation or synergistic nutrient interactions. Nevertheless, the cumulative evidence strongly supports the involvement of n-3 fatty acids in structural and biochemical pathways that are disrupted in depression, providing a biologically plausible rationale for their use as adjunctive treatments in mood disorders.

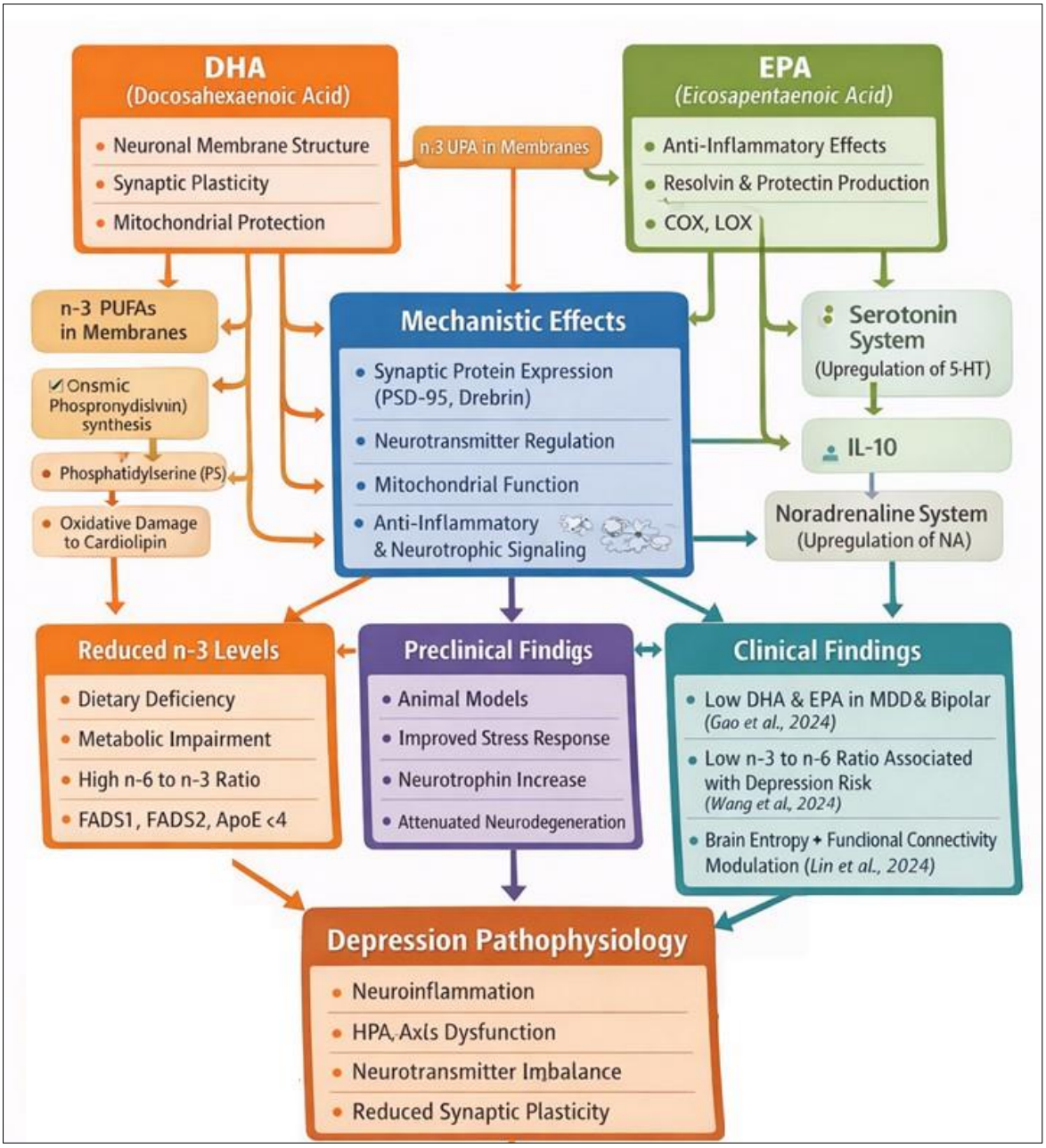


Figure 4: Biological Mechanisms of Omega-3 Fatty Acids (EPA & DHA) in Depression: Molecular Pathways and Neurobiological Effects

Evidence from Human and Animal Studies

Evidence from human studies suggests that the efficacy of omega-3 fatty acids in depression is highly context-dependent. Preventive trials, such as the VITAL-DEP study (Okereke *et al*., 2021), found no significant reduction in depression incidence with n-3 supplementation in general populations, and in some cases observed neutral or slightly adverse outcomes. Similarly, a clinical cohort study examining combined EPA/DHA and vitamin D supplementation reported no significant symptom reduction compared to placebo, highlighting the influence of dosage, formulation, and baseline participant characteristics on outcomes.

In contrast, treatment-focused trials demonstrate more encouraging results. A 52-week RCT by Lin *et al*., (2017; 2025) found that DHA supplementation significantly reduced brain entropy in the left posterior cingulate gyrus, a region associated with depression, suggesting potential modulation of neural connectivity. Additionally, Ginty & Conklin (2015) reported a statistically significant reduction in depressive symptoms with omega-3 supplementation. While other trials showed non-significant results, point estimates generally favored n-3s when used as adjunctive therapy. These findings support a modest therapeutic role for omega-3s, particularly EPA-rich formulations, when incorporated into comprehensive treatment strategies.

Animal studies offer strong mechanistic support for the antidepressant effects of n-3 fatty acids. In a chronic stress model, EPA and DHA supplementation reduced plasma corticosterone levels and restored hippocampal serotonin (5-HT), with EPA showing superior efficacy in enhancing neurotrophic signaling (e.g., BDNF–TrkB) and suppressing inflammatory cytokines such as IL-6 and TNF-α (Peng *et al*., 2020). In sleep-deprived rats, DHA reversed depressive-like behaviors and normalized cannabinoid receptor 1 expression, demonstrating neuromodulatory effects. Additional models of long-term n-3 deficiency revealed persistent depressive behaviors and synaptic disruption, which were partially rescued by postnatal n-3 repletion. Reintroduction of EPA/DHA improved neurotrophin levels (NGF, BDNF), increased synaptic protein expression, and reduced pro-oxidant metabolites, though some impairments—such as reduced serotonin levels and increased amyloid-related markers—were only partially reversible (Palmieri *et al*., 2025).

Collectively, these animal studies underscore the biological plausibility of omega-3s as therapeutic agents in depression, aligning with observed improvements in neuroinflammatory, neurochemical, and neuroplastic pathways also implicated in human pathophysiology.

Dietary Context and Mediterranean Diet

The dietary context in which omega-3 fatty acids are consumed plays a critical role in modulating their potential impact on mood and depression outcomes. Observational studies consistently report that greater adherence to the Mediterranean diet—a dietary pattern naturally rich in omega-3 sources such as fatty fish, olive oil, nuts, and leafy greens—is associated with a significantly reduced risk of depression (Lassale *et al*., 2019; Shafiei *et al*., 2019). These findings suggest that omega-3 intake, when embedded within a broader, nutrient-rich dietary framework, may confer synergistic benefits that extend beyond those of isolated supplementation.

However, randomized controlled trials (RCTs) present a more complex picture. Large-scale studies such as Deane *et al*., (2021) found no significant preventive effect of n-3 supplementation in healthy adults (RR 1.01), indicating that supplementation alone may not be sufficient to reduce depression risk in non-clinical populations. This aligns with the preventive forest plot (Figure 2A), where effect sizes cluster around the null value, reflecting the limited efficacy of n-3 supplementation as a standalone preventive intervention.

In contrast, RCTs targeting the treatment of depression (Figure 2B) demonstrate more favorable outcomes, particularly when EPA-predominant formulations are used. Meta-analyses have shown that EPA-rich interventions yield greater reductions in depressive symptom severity, particularly in individuals with major depressive disorder (Hallahan *et al*., 2016; Appleton *et al*., 2021). These findings support the therapeutic rather than preventive utility of n-3s, especially in clinical populations.

Importantly, emerging evidence suggests that whole-diet approaches may offer superior benefits compared to isolated nutrient supplementation. Dietary interventions based on the Mediterranean diet have been associated with improvements in mood and cognitive function, likely due to the synergistic effects of multiple bioactive compounds—including polyphenols, fiber, and antioxidants—alongside omega-3 fatty acids (Firth *et al*., 2019). Additionally, Mediterranean diet adherence is often accompanied by health-promoting behaviors, such as increased physical activity and social eating patterns, which may further enhance mental health outcomes.

In sum, while isolated n-3 supplementation shows modest therapeutic potential in depression treatment, dietary patterns like the Mediterranean diet appear to offer a more holistic and sustainable strategy for mental health promotion. Future research should continue to explore how nutrient interactions and lifestyle factors contribute to these effects and whether comprehensive dietary interventions can outperform pharmacological or supplement-based approaches in the long term.

Effect of EPA: DHA Ratio and Dosage Considerations

Emerging evidence suggests that the efficacy of n-3 PUFAs in alleviating depressive symptoms is highly dependent on both the EPA: DHA ratio and the absolute dosage of supplementation. Multiple meta-analyses, including the comprehensive review by Mocking *et al*., (2016), have demonstrated that EPA-predominant formulations—particularly those with an EPA: DHA ratio of 2:1 or higher—consistently show greater efficacy in reducing depressive symptoms than DHA-predominant or balanced formulations.

Mechanistically, EPA is thought to exert more potent anti-inflammatory and neuroprotective effects than DHA, likely due to its action on eicosanoid pathways and subsequent modulation of pro-inflammatory cytokines (Martins, 2009). These mechanisms are particularly relevant in depression, which is increasingly recognized as a disorder with significant neuroinflammatory components. Supporting this, observational studies have linked low dietary intake of EPA to an elevated risk of developing depressive-like states (Morgese *et al*., 2017).

However, alternative hypotheses have proposed that the absolute dose of EPA, rather than the EPA: DHA ratio per se, may be the more critical factor in determining therapeutic outcomes. Guu *et al*., (2019) emphasize that higher EPA doses, regardless of ratio, may lead to more robust antidepressant responses. This view aligns with findings from several trials included in this review, where studies employing higher total doses of EPA—either alone or in combination with DHA—reported more favorable outcomes.

Despite these promising results, the current body of evidence is not entirely consistent. For instance, large-scale randomized controlled trials (RCTs) involving non-clinical or general population samples have often failed to detect significant benefits from n-3 supplementation (Appleton *et al*., 2021). This variability in findings may reflect the influence of other moderating factors, including baseline n-3 status, co-existing medical or psychiatric conditions, or concurrent treatments. Furthermore, animal studies offer important insights into the nuanced role of EPA versus DHA. For example, in a chronic unpredictable mild stress (CUMS) model of depression, Peng *et al*., (2020) found that while both DHA and EPA exerted antidepressant effects, EPA was significantly more effective in normalizing corticosterone levels and elevating hippocampal 5-HT, noradrenaline, and BDNF levels. These neurochemical effects underline EPA's superior efficacy in modulating the biological underpinnings of depression.

Overall, the evidence underscores the need for more targeted research to determine the optimal EPA: DHA ratio and total dosage for different populations. Factors such as depression subtype, patient age, comorbidities, and baseline PUFA levels may all influence the response to omega-3 supplementation. Until these parameters are better defined, clinicians should consider both the ratio and total dose of EPA when recommending omega-3 interventions for depressive symptoms, with a particular emphasis on EPA-dominant regimens.

Evaluation of n-3 Efficacy in Depression Prevention

This systematic review synthesised data from five studies (Su *et al*., 2014; Vaz *et al*., 2017; Watanabe *et al*., 2018; Okereke *et al*., 2021; Savard *et al*., 2023) to evaluate the efficacy of n-3 PUFAs in the prevention of depression. The forest plot generated for these studies (Figure 2A) demonstrated that none of the trials yielded statistically significant findings, as all 95% confidence intervals (CIs) crossed the line of no effect (odds ratio or risk ratio = 1). Although individual point estimates varied—with some marginally favouring the intervention (e.g., Vaz et al., 2017; Savard *et al*., 2023) and others favouring the control (e.g., Su *et al*., 2014; Okereke *et al*., 2021)—the overall pattern indicates an inconclusive and inconsistent preventive effect of n-3 supplementation on depression risk.

Several methodological and biological factors may contribute to this observed lack of efficacy. Firstly, significant heterogeneity was noted across the included studies regarding sample size, population characteristics, supplementation dosages, durations, and baseline nutritional status. Such variability complicates the ability to generalise findings and may obscure potential benefits for specific subpopulations. For example, individuals with low baseline levels of EPA and DHA may respond more robustly to supplementation, whereas those with adequate baseline status might derive limited additional benefit, thereby diluting overall treatment effects in mixed cohorts. Furthermore, differences in study design and outcome measures also play a role in the inconsistent results. Most trials were not stratified by depression risk level or by dietary patterns that may modulate n-3 PUFA bioavailability and efficacy. Inadequate control for confounding variables, such as co-occurring nutritional deficiencies, psychosocial stressors, and inflammatory markers, may also contribute to variability in outcomes.

In summary, current evidence does not support the routine use of n-3 PUFAs for the primary prevention of depression in unselected populations. However, this does not rule out the potential for preventive efficacy in targeted subgroups, such as individuals with known n-3 deficiency, chronic low-grade inflammation, or genetic predisposition to depression. Future prevention-focused trials should adopt stratified randomisation designs and incorporate biomarker assessments to better elucidate the contexts in which n-3 PUFAs may confer preventive benefit.

Evaluation of n-3 Efficacy in Depression Treatment

The evaluation of n-3 PUFAs for the treatment of depression reveals more consistent, though still mixed, evidence compared to their use in prevention. In this review, six randomized controlled trials (RCTs)—Ginty & Conklin (2015), Keshavarz *et al*., (2018), Tayama *et al*., (2019), Parletta *et al*., (2019), Wu *et al*., (2024), and Li *et al*., (2024)—were included in the treatment-focused forest plot (Figure 2B). Of these, Ginty & Conklin (2015) reported a statistically significant benefit of n-3 supplementation, with a confidence interval (CI) entirely favoring the intervention, suggesting a robust effect on reducing depressive symptoms. The remaining studies showed point estimates generally favoring n-3 supplementation, although with CIs that crossed the line of no effect, indicating a lack of statistical significance.

These findings suggest a modest but potentially meaningful benefit of n-3 supplementation for depression treatment, particularly in specific clinical subgroups. The results support the hypothesis that EPA and DHA, the primary bioactive components of n-3s, contribute to mood improvement through anti-inflammatory and neuroprotective mechanisms (Dighriri *et al*., 2022). These mechanisms include the modulation of neurotransmitter systems (e.g., serotonin and dopamine), attenuation of neuroinflammation, and support of neuronal membrane integrity—processes all implicated in the pathophysiology of depression.

However, variability in treatment outcomes remains, potentially due to differences in study design, sample size, baseline depression severity, n-3 dosage and formulation (notably EPA: DHA ratios), and concurrent antidepressant therapies. For example, wide CIs in studies such as Keshavarz *et al*., (2018) and Wu *et al*., (2024) may reflect small sample sizes or limited statistical power, reducing confidence in their findings. Furthermore, the inclusion of mixed populations—some on pharmacological treatments and others not—may obscure the isolated effects of n-3 supplementation.

The significant results in Ginty & Conklin (2015) highlight the possibility that n-3s may be most effective as adjunctive treatments, particularly in individuals with partial response to standard therapies. The generally favorable trends across the remaining studies support this interpretation, even when statistical significance was not achieved. These trends suggest that, while n-3 supplementation may not serve as a standalone intervention for depression, it could enhance existing treatment regimens.

In sum, the findings provide encouraging, though not definitive, evidence supporting the use of n-3 fatty acids in the treatment of depression, particularly for targeted subgroups. Future research should prioritize larger, adequately powered trials with standardized dosing protocols, clearly defined depression subtypes, and stratified participant profiles. Integration of biomarker analyses (e.g., inflammation, neurotransmitters, and neurotrophins) will also be critical in elucidating the biological underpinnings of treatment response and optimizing clinical application.

Neurobiological and Genetic Insights

Emerging evidence underscores the intricate neurobiological and genetic mechanisms through which n-3 PUFAs, particularly EPA and DHA, influence the pathophysiology of depression. DHA plays a foundational role in neuronal membrane composition, stabilizing phosphatidylserine and promoting efficient synaptic transmission through the enhancement of synaptic proteins like drebrin and PSD-95, which facilitate dendritic spine formation and plasticity (Kim *et al*., 2022; Zhou *et al*., 2022). Additionally, DHA preserves mitochondrial function by protecting cardiolipin from oxidative damage, thereby supporting cellular energy metabolism and neuronal resilience.

EPA complements these actions by modulating key inflammatory pathways—cyclooxygenase, lipoxygenase, and cytochrome P450—leading to the production of lipid mediators with neuroprotective and anti-inflammatory properties (Malau *et al*., 2024). Collectively, these molecular effects contribute to homeostasis in neurotransmitter systems, particularly serotonin and noradrenaline, which are dysregulated in depressive disorders. Clinical studies consistently demonstrate that individuals with major depressive disorder or bipolar disorder exhibit reduced serum concentrations of EPA and DHA compared to healthy controls (Gao *et al*., 2024). Moreover, a lower dietary intake of n-3 fatty acids, and an imbalanced n-3 to omega-6 ratio, have been linked to higher depression prevalence (Wang *et al*., 2022; Gao *et al*., 2024).

Preclinical research reinforces these findings. Animal studies have shown that n-3 PUFA supplementation mitigates neuroinflammatory responses, normalizes elevated corticosterone, and restores hippocampal serotonin levels in chronic stress models (Peng *et al*., 2020). Furthermore, EPA appears to outperform DHA in modulating these effects, particularly in the regulation of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and enhancement of neurotrophic signaling via the BDNF–TrkB pathway.

From a genetic perspective, genome-wide association studies (GWAS) have implicated fatty acid desaturase (FADS) genes, which regulate PUFA metabolism, as risk factors for bipolar disorder. Alterations in FADS genes can disrupt arachidonic acid concentrations, potentially exacerbating inflammatory cascades implicated in mood disorders (Gao *et al*., 2024). Additionally, animal models deprived of n-3 PUFAs since fetal development display significant cognitive deficits and depressive-like behaviors. Reintroduction of n-3s enhances neurotrophin levels, boosts synaptic protein expression, and partially reverses amyloid

accumulation—though some neurotoxic damage may remain irreversible (Palmieri *et al*., 2025).

These converging lines of evidence underscore the critical role of n-3 PUFAs in maintaining neurobiological integrity and regulating gene–diet interactions that contribute to the onset and course of depression. Further research is warranted to delineate how individual genetic variations in lipid metabolism influence therapeutic responses to n-3 supplementation and to clarify the long-term impact of early-life PUFA deprivation on mental health outcomes.

Limitations in Review Design and Study Inclusion

Several important limitations must be acknowledged in the design and execution of this systematic review, which may affect the strength and generalizability of its conclusions. First, the review was conducted by a single reviewer, raising the possibility of selection and interpretation bias. While standardized criteria were applied, the absence of a second reviewer may have limited the robustness and objectivity of study selection and data extraction. Second, the review did not conduct a formal meta-analysis or include pooled effect estimates, which are essential for quantifying overall effect sizes and evaluating heterogeneity across studies. As a result, the ability to determine the precise efficacy of n-3 fatty acids in depression prevention or treatment is limited. Third, substantial variability exists among the included studies in terms of sample characteristics, intervention duration, n-3 dosage, EPA: DHA ratios, and the specific subtype or severity of depression being treated. Such heterogeneity complicates the synthesis of findings and may explain the lack of consistent results. Notably, some studies may have included participants with sufficient baseline n-3 levels, thereby reducing the observable impact of supplementation. Fourth, most studies included in this review had relatively small sample sizes, as evidenced by the wide confidence intervals in their results. Smaller trials may be underpowered to detect statistically significant effects and are more susceptible to random error. The only exception was the large-scale trial by Okereke *et al*., (2021), which had sufficient power but did not detect a significant preventive effect. Fifth, many studies lacked diversity in participant demographics, limiting the applicability of findings to broader populations. This includes underrepresentation of diverse ethnic, age, and socioeconomic groups, which may experience different baseline nutritional statuses, metabolic responses, and risk factors for depression. Finally, the review includes studies addressing a wide range of depressive disorders, from major depressive disorder to perinatal and subthreshold depression. This inclusion of multiple depression subtypes introduces further variability and may obscure differential treatment responses. According to DSM-5, depressive disorders encompass heterogeneous conditions with distinct symptom profiles and pathophysiologies (Bains and Abdijadid, 2020). Thus, pooling outcomes across such varied conditions may limit the interpretability of findings. Overall, these limitations underscore the need for cautious interpretation of results and highlight the importance of future studies with larger, more diverse populations, standardized protocols, and stratified analyses based on depression subtype and baseline nutritional status.

Implications for Clinical Practice and Future Research

This review suggests that while n-3 PUFA supplementation is not currently justified as a universal preventive strategy for depression, it may offer therapeutic benefits in select contexts. The strongest support lies in its role as an adjunctive treatment. For example, Ginty & Conklin (2015) found a statistically significant reduction in depressive symptoms, and other studies reported favorable, though non-significant, trends. This points to modest but clinically meaningful effects, particularly when combined with standard treatments.

Evidence also supports potential benefits in high-risk groups, such as individuals with low baseline n-3 levels or chronic inflammation. Given the favorable safety profile and cardiovascular benefits of omega-3s, clinicians may consider supplementation in these subgroups as part of a multimodal treatment strategy.

From a public health perspective, greater emphasis should be placed on promoting whole-food dietary patterns, like the Mediterranean diet, which are naturally rich in n-3 sources. Observational studies (Lassale *et al*., 2019; Shafiei *et al*., 2019) consistently show reduced depression risk with better diet adherence, though RCTs have yielded mixed results.

Future research should address current limitations by:

- Targeting specific subgroups, such as those with n-3 deficiency or treatment-resistant depression;
- Standardizing dosing protocols for EPA:DHA ratios and treatment durations;
- Integrating mechanistic biomarkers (e.g., BDNF, cortisol, inflammatory markers) to complement symptom data (Strawbridge *et al*., 2017);
- Conducting meta-analyses to synthesize evidence more definitively.

Ultimately, while evidence remains mixed, n-3 fatty acids—especially EPA-rich formulations—hold promise in depression treatment contexts, particularly when tailored to individual profiles and integrated within broader dietary and clinical strategies.

CONCLUSION

This systematic review demonstrates that n-3 fatty acids do not provide consistent benefits for the prevention of depression in general populations but may offer modest therapeutic value in treatment contexts,

particularly as adjunctive interventions. Evidence from clinical and preclinical studies supports biologically plausible mechanisms involving neuroinflammation, synaptic plasticity, and neurotrophic signaling, with EPA-predominant formulations showing greater promise than DHA alone. The findings also highlight the importance of dietary context, suggesting that whole-diet approaches such as the Mediterranean diet may be more effective than isolated supplementation. Further targeted, mechanistically informed trials are required to clarify optimal formulations and responsive subgroups.

Acknowledgments: Not applicable.

Declaration of Conflicting Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Statement: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent Statements: Not applicable.

Data Availability Statement: Not applicable.

Author Contributions

Conceptualization, SZ, LY, ZM, and TT; Methodology, TT, SZ; Investigation, TT, SZ; Resources, SZ, LY; Data Curation, TT; Writing—TT, SZ; Writing—Review & Editing, SZ, TT, LY, ZM; Supervision, SZ, LY, ZM; Project Administration, SZ.

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