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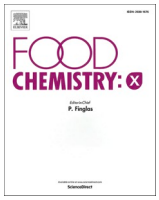

Comparison of Omega-3 polyunsaturated fatty acids bioavailability in fish oil and krill oil: Network Meta-analyses

Thi-Phuong-Thao Pham [a,b,1], Thi-Van Hoang [b,c,1], Phuc-Thao-Nguyen Cao [d,1], Thi-Thuy-Duong Le [e], Van-Thao-Nguyen Ho [e], Thi-Mai-Hoa Vu [f], Thi-Hoai-Thu Le [g], Huynh-Thien-Xuan Pham [e], Thanh-Thien Tran [h], Okti Ratna Mafruhah [i], Thi-Thuy-Linh Pham [c,j], Min-Tsang Hsieh [b,k,l,*], Hai-Anh Ha [c,**]

[a] *K24YDH3, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[b] *School of Pharmacy, China Medical University, Taichung 406040, Taiwan*
[c] *Faculty of Pharmacy, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[d] *K25YDH4, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[e] *K26YDH2, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[f] *K25YDH1, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[g] *K25YDH3, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[h] *K27YDH1, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam*
[i] *Department of Pharmacy, Universitas Islam Indonesia, Daerah Istimewa, Yogyakarta 55584, Indonesia*
[j] *Chungbuk National University College of Pharmacy, Osong, Cheongju 28160, Republic of Korea*
[k] *Drug Development Center, China Medical University, Taichung 406040, Taiwan*
[l] *Chinese Medicinal Research and Development Center, China Medical University Hospital, Taichung 40447, Taiwan*

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ABSTRACT

Background and Aims: Fish oil and krill oil are primary sources of Omega-3 polyunsaturated fatty acids (PUFAs), differing in their molecular forms and bioavailability. Understanding these differences can optimize their therapeutic use. This study aims to compare the bioavailability of Omega-3 PUFAs in fish oil and krill oil using a network meta-analysis approach. By evaluating various molecular forms and dosages, the study seeks to identify the most effective Omega-3 sources and dosing regimens to maximize health benefits.

Methods: The study adhered to the explanation of the PRISMA network meta-analysis 2015 (registered PROSPERO ID: CRD42024532536). The risk of bias was evaluated using the PEDro scale. This network meta-analysis incorporated data from studies published between 2003 and 2023, sourced from five databases: *ClinicalTrials.gov*, PubMed, Cochrane CENTRAL, the International Clinical Trials Registry Platform-World Health Organization, and Embase. Statistical analysis was conducted using advanced models in R software to ensure a rigorous evaluation of bioavailability.

Results: Out of 26 high-quality studies, findings reveal superior bioavailability of krill oil compared to fish oil. Specifically, fish oil above 3000 mg, in re-esterified triacylglycerol or ethyl ester formulations (100–2900 mg), and krill oil (100–1900 mg) significantly enhanced the Omega-3 index. At lower dosages (under 2000 mg), krill

Abbreviations: **AUC**, Area under the curve; **Cmax**, Maximum concentration; **DHA**, Docosahexaenoic acid; **EMB**, Emulsion type B; **EMN**, Emulsion type N; **EMS**, Emulsion type S; **EPA**, Eicosapentaenoic acid; **FO**, Fish oil without specific molecular form information; **FO-EE**, Fish oil ethyl ester; **FO-EM**, Fish oil emulsion; **FO-rTAG**, Fish oil re-esterified triacylglycerol; **FO-TG**, Fish oil triglycerides; **ICTRP-WHO**, International Clinical Trials Registry Platform - World Health Organization; **KO**, Krill oil without specific molecular form information; **KO-HPL**, Krill oil high phospholipid; **KO-LPL**, Krill oil low phospholipid; **KO-PL/FFA**, Krill oil phospholipid/free fatty acid; **MFO-PS**, Fish oil microencapsulated powder (sugar - milk protein: encapsulating agent); **MFO-PSRS**, Fish oil microencapsulated powder (resistant starch - milk protein: encapsulating agent); **NMA**, Network meta-analysis; **O3i**, Omega-3 index; **PUFAs**, Polyunsaturated fatty acids; **Tmax**, Time to maximum concentration; **< 2**, Doses (DHA + EPA) 100–1900 mg per day; **< 3**, Doses (DHA + EPA) 2000–2900 mg per day; **> 3**, Doses (DHA + EPA) above 3000 mg per day..

* Corresponding author at: School of Pharmacy, China Medical University, Taichung 406040, Taiwan.
** Corresponding author at: Faculty of Pharmacy, College of Medicine and Pharmacy, Duy Tan University, Da Nang 550000, Viet Nam.
E-mail addresses: t21917@mail.cmu.edu.tw (M.-T. Hsieh), hahaianh@dtu.edu.vn (H.-A. Ha).
[1] T.P.T. Pham, T.V. Hoang and P.T.N. Cao as co-first authors.

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oil shows superior Omega-3 absorption compared to fish oil. Using fish oil ethyl ester at doses between 2000 and 2900 mg may be the most effective for reducing Tmax. However, this finding should be interpreted with caution due to high heterogeneity and limited statistical significance. The highest AUC values were observed in krill oil phospholipid/free fatty acid formulation. Emulsion forms of fish oil are more effective in increasing Cmax than other formulations. These results were supported by robust statistical evidence (Egger's test, $p > 0.05$), highlighting the effectiveness of specific formulations and doses in optimizing Omega-3 absorption.

Conclusion: The research highlights the importance of understanding the bioavailability of Omega-3 PUFAs from fish oil and krill oil. The findings suggest that low-dose krill oil and fish oil emulsions (under 2000 mg) are effective and potentially safer alternatives to high-dose fish oil, potentially minimizing the risk of adverse effects.

1. Introduction

Omega-3 polyunsaturated fatty acids (PUFAs), specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known for their substantial health benefits, including mitigating cardiovascular risk and enhancing mental health and developmental outcomes (Shahidi & Ambigaipalan, 2018; Van Dael, 2021). Recent research has expanded the understanding of the extensive health advantages provided by these essential nutrients (Calder, 2017; Elagizi et al., 2021).

Marine foods, such as fish and krill, are the primary natural sources of Omega-3 PUFAs. Products derived from these sources, such as fish oil (FO) and krill oil (KO) represent primary natural sources of long-chain omega-3 PUFAs, whereas vegetable oils contain larger amounts of alpha-linolenic acid, an 18-carbon precursor (Calder & Yaqoob, 2009; Wang et al., 2019; Xie et al., 2019). Both FO and KO contain EPA and DHA in various molecular forms, which influence their bioavailability and health effects (Pham, Hoang, et al., 2024; Sung et al., 2020). FO formulations typically consist of triglycerides (FO-TG), re-esterified triacylglycerols (FO-rTAG), ethyl esters (FO-EE) (Vosskötter et al., 2023), emulsions (FO-EM), and microencapsulated powders (MFO-PS, MFO-PSRS) (Colletti et al., 2021). In contrast, KO contains EPA and DHA primarily in phospholipid form, including high-phospholipid (KO-HPL) and low-phospholipid (KO-LPL) formulations, as well as phospholipid/free fatty acid combinations (KO-PL/FFA) (Kroupova et al., 2020; Shahidi & Abad, 2024).

Both oils are recognized for their health-promoting properties. Clinical studies on FO began in the late 1970s, notably with Danish researchers Bang and Dyerberg (Liao et al., 2022), who investigated the low incidence of cardiovascular disease among Greenland Inuit populations consuming a diet rich in marine oils. Their research highlighted the potential health benefits of Omega-3 fatty acids found in fish oil (Liao et al., 2022). The first clinical study on KO commenced far later than FO in 2003, marking the onset of research into its effects on human health, particularly cardiovascular health, inflammation, and cholesterol-related issues (R. K. Berge et al., 2015; Pham, Hoang, et al., 2024; Xie et al., 2019).

Despite the recognized benefits, there is a significant gap in comprehensive research comparing the bioavailability of FO and KO. Health practitioners lack a clear understanding of which source or formulation of Omega-3 PUFAs is most effective for absorption at various dosage levels.

Several sample types can be used to assess Omega-3 levels in the blood, including whole plasma, whole blood, platelets, leukocytes, and specific plasma lipid classes such as phospholipids, cholesteryl esters, triglycerides, and free fatty acids (J. P. Schuchardt et al., 2022). The Omega-3 index (O3i), defined as the EPA + DHA content of red blood cells (RBCs) as a percentage of total identified fatty acids, is the preferred biomarker for assessing long-term Omega-3 PUFA status in clinical practice and research (Vosskötter et al., 2023). Other metrics, such as Cmax (maximum concentration), Tmax (time to maximum concentration), and AUC (area under the curve), are commonly used in pharmacokinetic studies to evaluate the bioavailability of drugs and biological compounds (Atkinson, 2012). These metrics reflect the efficiency with which the body absorbs Omega-3 from FO and KO sources (Djuricic & Calder, 2023; Watanabe & Tatsuno, 2021).

This study aims to bridge this critical research gap by comparing the bioavailability of Omega-3 across various molecular forms, formulations, and dosages of fish and krill oils using four measures of bioavailability: O3i, AUC, Tmax, and Cmax. By exploring bioavailability, this study seeks to refine dietary recommendations and improve product formulations. The insights derived are anticipated to spur further research into personalized nutritional strategies, potentially revolutionizing dietary approaches to health maintenance and disease prevention (Tseng et al., 2024).

2. Material and methods

2.1. Protocol and registration

The NMA adhered to the PRISMA for network meta-analysis 2015 checklist (Hutton et al., 2015), followed guidelines from the "Doing Meta-Analysis with R" guide (Ebert et al., 2021) as described previously (Pham, Le, et al., 2024), and was registered with PROSPERO under ID: CRD42024532536.

2.2. Eligibility criteria

- Inclusion criteria:

- Studies have characteristics that include (following the PICOS criteria):

  - P - Participants: Any participants, all subjects regardless of race or gender.
  - I - Interventions: Interventions consist of fish oil, krill oil.
  - C - Comparations: placebo (soybean oil, sunflower oil, corn oil, olive oil, flaxseed oil or vegetable oil mixture) or comparison between different molecular forms, formulations, and dosages.
  - O - Outcomes: The O3i is measured in red blood cells (RBCs), whereas the AUC, Tmax, and Cmax outcomes are assessed in plasma.
  - S - Study design: Randomized controlled trials (RCTs) or multi-arm trials.

- Studies are documented in English-language articles.

- Exclusion criteria:
  - Unfinished studies.
  - Without full-text articles.
  - Studies with withdrawn registrations.
  - Insufficient information on analyzed variables (O3i, Tmax, AUC, or Cmax).
  - Interventions with Omega-3 PUFAs but not supplemented in the form of fish oil or krill oil.

2.3. Search strategy

This research strategy involves examining the bioavailability of

clinical studies on both FO and KO, published between January 2003 and December 2023. Identified keywords: "Fish Oil", "Krill Oil", "Polyunsaturated fatty acid", "Bioavailability", and "Omega-3". All synonyms were found in the MeSH database, and a search algorithm was executed using OR and AND. Searches were performed across five databases: *ClinicalTrials.gov*, PubMed, Cochrane CENTRAL, International Clinical Trials Registry Platform (ICTRP), and Embase. The specified criteria were adhered to, based on the PICOS questionnaire, to identify relevant studies (details in **Supplementary Tables S1** and **S2**).

2.4. Study selection (screening), data collection and data items

The screening process employs the Covidence semi-automatic screening system, assessing titles, abstracts, and full texts.

The collected data was exported to MS Excel (2016), including continuous variables represented as Mean ± Standard Deviation, and the number of participants in each group for outcomes such as AUC, O3i, Tmax, and Cmax.

Data items: The basic characteristics of the included studies were collected, including the country of origin, interventions, daily dose of DHA + EPA per intervention (categorized as low doses: 100 mg to 1900 mg, medium doses: 2000 mg to 2900 mg, high doses: above 3000 mg), health characteristics of the participants, dosing regimen (single or multiple doses), and outcomes measured in each study.

Reasons for separating the dosage include:

- Data analysis: studies on KO and FO often use varying dosages to evaluate their effects. These dosage ranges were selected based on the actual distribution of doses used in available studies.
- Rational grouping: categorizing dosages into specific ranges facilitates the comparison of efficacy and safety across different study groups and helps identify if there is an optimal dosage threshold in correspondence with clinical recommendations:

+ **Low dosage** (100–1900 mg): Typically used in recommendations for general health maintenance and cardiovascular prevention.

+ **Medium dosage** (2000–2900 mg): Suitable for recommendations for treating high triglycerides and other inflammatory issues.

+ **High dosage** (above 3000 mg): Often used in studies to test maximum efficacy, though caution is advised due to potential side effects such as digestive issues, bleeding, or immune system impacts.

2.5. Risk of bias within individual studies

Using the PEDro scale with 11 questions corresponding to 10 points: "Poor" with a score of 0–3, "Moderate" with a score of 4–5, "Good" with a score of 6–8 and "Excellent" with a score of 9–10 to evaluate the quality of selected articles.

Processes: Study selection, data collection, and study quality assessment were performed independently by five team members (T.P.T. Pham, T.V. Hoang, P.T.N. Cao, T.T.D. Le and V.T.N. Ho). Differences were resolved through discussion and consensus.

2.6. Summary measures - planned methods of analysis

The study was conducted on R and R Studio software (version 2023.12.0 + 369), performing regular network meta-analysis using the netmeta package (Ebert, 2021).

Main summary measures:

- *Heterogeneity assessment:* Total heterogeneity (Q-total) and degrees of freedom (df) were calculated, along with I^2, tau^2, and tau values to assess the variability in effect estimates that could not be attributed solely to sampling error.
- *Publication bias assessment*: To assess publication bias, funnel plots and Egger's test were used. Funnel plots compare study effect sizes to their standard errors, with symmetrical plots suggesting no bias and asymmetry indicating possible underreporting of smaller studies with non-significant results. Egger's test statistically assesses funnel plot symmetry, where non-significant *p*-values ($p > 0.05$) indicate a low likelihood of bias. Publication bias assessment involved calculating the *Z*-score and *P*-value from the meta-analysis results, with further testing using the Egger's test (t) and Standard Error (SE) analysis to identify asymmetries.
- *Treatment rankings* are evaluated by using SUCRA score, according to the method by Crippa and Orsini (Crippa & Orsini, 2016) for continuous variable (detail in **Supplementary Fig. S1** & **Table S3**).
- *Additional analyses*: If the geometry of the network is not well-defined, sensitivity or subgroup analyses will be conducted and presented.

3. Results

3.1. Study selection

After initial screening, 1385 studies were identified from five databases. The Covidence tool eliminated duplicates ($n = 53$), non-RCT articles ($n = 1065$), and those not meeting criteria ($n = 34$). Among the remaining 233 studies, 141 were excluded. After full-text screening of 92 studies, 60 were excluded for various reasons such as inaccessibility or withdrawal. Six studies lacked sufficient data, leaving 26 studies for the network meta-analysis (NMA) (Fig. 1).

3.2. Study characteristics

The basic characteristics and references of the studies are summarized in **Supplementary Table S4**. Outcome variables included the O3i (22 studies), AUC (5 studies), Tmax (4 studies), and Cmax (5 studies) (Fig. 2a). Molecular forms of KO included phospholipids (75 %), PL/FFA forms (9 %), HPL (8 %), and LPL (8 %) (Fig. 2b). FO were mostly capsules without specific molecular form information (48 %), followed by EE (16 %), TG (8 %), rTAG (16 %), EM (8 %), and FO-PL (4 %) (Fig. 2c). Control groups mostly consisted of oils without pharmacological effects, such as corn oil, olive oil, sunflower oil, and placebo capsules **(Supplementary Table S4)**. In non-specific dosing regimens, fourteen studies employed a once-daily dosing schedule, while twelve studies used a dosing regimen of 2–3 times per day (Fig. 2d**)**. Studies were conducted across 8 countries, with the USA contributing the most (8 studies), followed by Australia (6 studies), Germany (5 studies), and Canada (3 studies) (Fig. 2e).

3.3. Risk of bias within studies

Nine studies (34 %) were assessed as having excellent quality, 15 studies (58 %) as good quality, and 2 studies (8 %) as moderate quality (Fig. 3b). Most studies met criteria for eligible participants, statistical comparison methods, and score/variability measures. Two studies had moderate quality due to lack of information on intention-to-treat analysis, allocation concealment, or blinding (Fig. 3a and details in **Supplementary Table S5**).

3.4. The network-graph results

The O3i network model included 14 interventions and 59 pairwise comparisons (Fig. 4a). FO formulations had various doses from low to high, while krill oil used lower doses (100–1900 mg). Heterogeneity between studies was high ($tau^2 = 1.7890$, $I^2 = 97.1$ %, Q total = 1255.57, $p < 0.0001$, Table 1). For Tmax (Fig. 4b), data from four studies (only two of them were suitable for NMA) included 21 comparisons across five interventions, indicating high heterogeneity ($tau^2 = 111.7406$, $I^2 = 94.8$ % [92.9 %; 96.3 %], $p > 0.05$, Table 1). The NMA of AUC (Fig. 4c & 5d) incorporated data from five studies, 62 comparisons

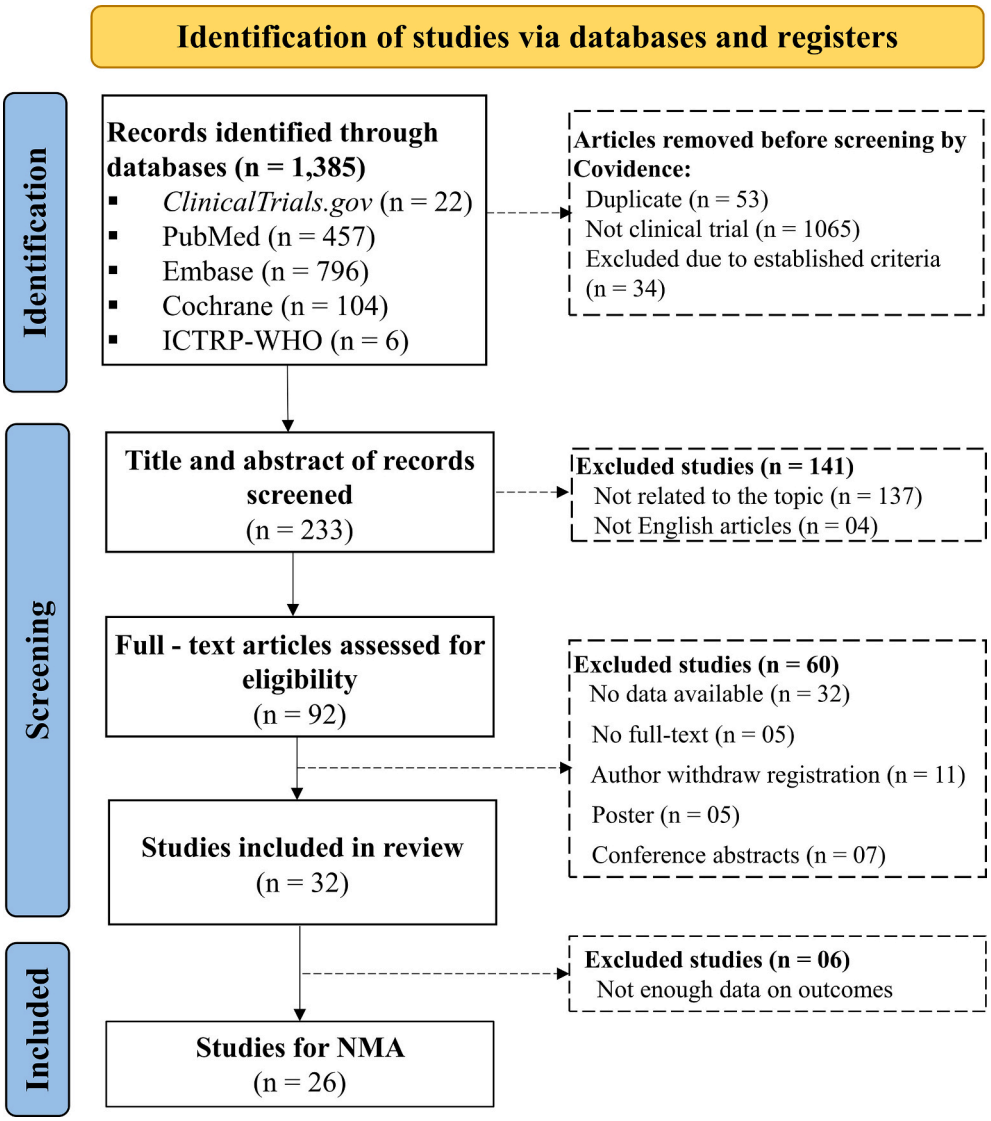

Fig. 1. Flow diagram illustrating the study selection process, from identification to inclusion in the meta-analysis, detailing numbers at each stage.
Notes: RCT: Randomized Controlled Trial; ICTRP-WHO: International Clinical Trials Registry Platform- World Health Organization, NMA: Network meta-analysis.

across 12 interventions, showing no significant differences ($tau^2 = 0$, $I^2 = 0$ %, $p > 0.05$, Table 1). For Cmax (Fig. 4e & 5f), five studies provided data for 42 comparisons across 10 interventions, divided into two subgroups. The first subgroup (**Sub 1**) showed low heterogeneity ($tau^2 = 0$, $I^2 = 0$ % [0.0 %; 60.2 %]), while the second subgroup (**Sub 2**) revealed high heterogeneity ($I^2 = 78.5$ %) (Table 1).

The meta-analysis results in **Table 2** provide a comprehensive comparison of various treatments for different outcomes:

O3i: Most FO interventions led to a higher O3i compared to placebo ($p < 0.05$). However, FO-EE at doses above 3000 mg did not significantly improve O3i (MD = 1.9, CI 95 % = [−0.49; 4.30], z = 1.56, $p = 0.1198$). KO capsules under 2000 mg per day effectively increased O3i, while KO-HPL and KO-LPL at doses below 2 g did not show significant improvement (KO-HPL: MD = 1.61, CI 95 % = [−1.13; 4.35], z = 1.15, $p = 0.2487$; KO-LPL: MD = −0.22, CI 95 % = [−2.96; 2.52], z = −0.16, $p = 0.8751$).

Tmax: FO-EE at doses above 3000 mg significantly decreased Tmax compared to KO-PL/FFA at doses below 2 g (MD = −8.47; 95 % CI = [−17.09; 0.16], z = −1.92, $p = 0.0543$). Other forms of FO (EE, rTAG, and TG) did not significantly decrease Tmax more than KO-PL/FFA at the same dose, and all of results lacked statistical significance ($p > 0.05$).

AUC: All interventions were compared at doses under 2000 mg. In **Sub 1**, no interventions showed statistically significant differences. In **Sub 2**, KO-PL/FFA significantly increased AUC compared to FO-rTAG (MD = −14.26, 95 % CI = [−24.88; −3.63], z = −2.63, $p = 0.0085$) and FO-EE (MD = −18.63, 95 % CI = [−29.49; −7.77], z = −3.36, $p = 0.0008$).

Cmax: Emulsion forms of FO (Types M and N) significantly increased Cmax compared to FO capsules ($p < 0.05$). Other FO forms (MFO-PS and FO - EMB) showed slight effectiveness without statistical significance ($p > 0.05$) in **Sub 1**. In **Sub 2**, KO-PL/FFA slightly increased Cmax compared to FO-rTAG, FO-EE, and FO-TG, but these results were not statistically significant ($p > 0.05$).

3.5. Treatment ranking (SUCRA score)

The treatment ranking results were estimated using the SUCRA score (Table 3). The most effective interventions will be showed:

O3i: The most effective interventions for increasing the O3i were FO > 3 (SUCRA = 14.71 %), FO-rTAG <2 (SUCRA = 16.20 %), and FO-EE < 2 (SUCRA = 18.40 %). Most FO formulations were more effective in increasing the O3i compared to KO formulations.

AUC: The interventions fish oil in emulsion forms (types N and B) yielded superior results compared to other interventions, with SUCRA

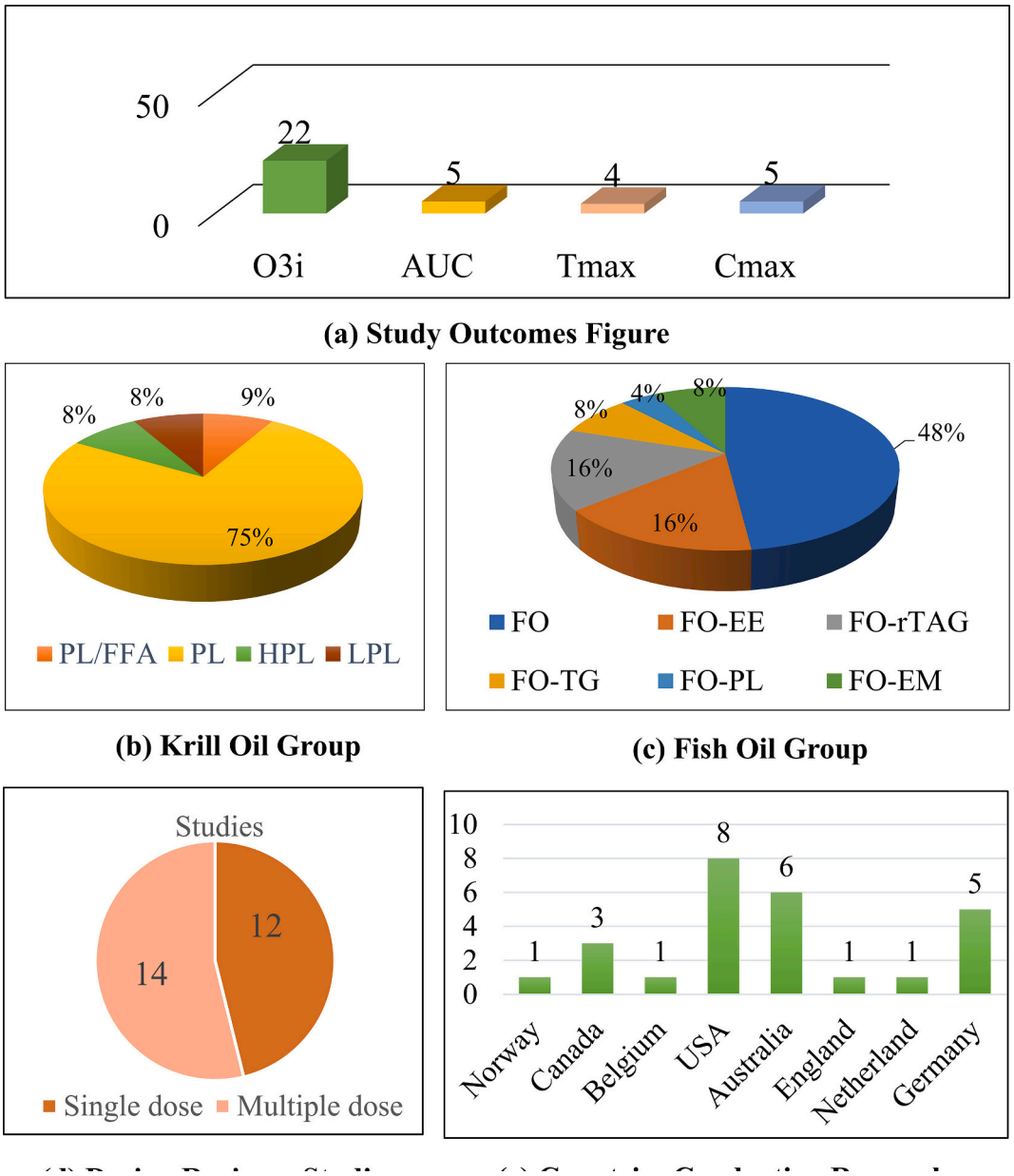

Fig. 2. Basic characteristics of the included studies.
Notes: KO: krill oil capsule without specific molecular form information; PL/FFA: krill oil phospholipid/free fatty acid; PL: phospholipid; HPL: high phospholipid; LPL: low phospholipid; FO: fish oil capsule without specific molecular form information; rTAG: re-esterified triacylglycerol; MFO: fish oil microencapsulated; EE: ethyl ester; EM: emulsion; TG: triglycerides.

scores of 16.92 % and 22.72 %, respectively **(results in Sub 1**). Within the dose range of 100–1900 mg, KO-PL/FFA < 2 (SUCRA = 11.40 %) was the most effective in increasing the AUC compared to other molecular forms of fish oil (including FO-TG, FO-EE, and FO-rTAG) (**result in Sub 2**).

Cmax: Emulsion FO forms were more effective in increasing Cmax compared to other fish oil formulations, with FO-EMS having the highest score (SUCRA = 2.3 %) in **Sub 1**. In **Sub 2**, KO-PL/FFA (SUCRA = 10.73 %) was the most effective in increasing Cmax compared to FO-EE, FO-rTAG, and FO-TG at doses under 2000 mg.

Tmax: FO-EE at doses ranging from 2000 to 2900 mg had the highest score for decreasing Tmax, with a SUCRA score of 95.22 %. Other formulations of FO-EE, FO-rTAG, and FO-TG were less effective compared to KO-PL/FFA at doses under 2000 mg. KO-PL/FFA ranked second in effectiveness, with a SUCRA score of 55.90 %.

3.6. *Publication bias*

Publication bias was assessed using a funnel plot with Egger's test (Fig. 5**).** Our analyses showed no significant publication bias ($p > 0.05$), as funnel plots were symmetrical and Egger's tests were non-significant. This suggests our findings are robust, though future research should consider trim-and-fill analysis for further validation.

4. Discussion

This research provides a comprehensive overview of direct and indirect comparisons, focusing on four key indicators: O3i, AUC, Cmax, and Tmax.

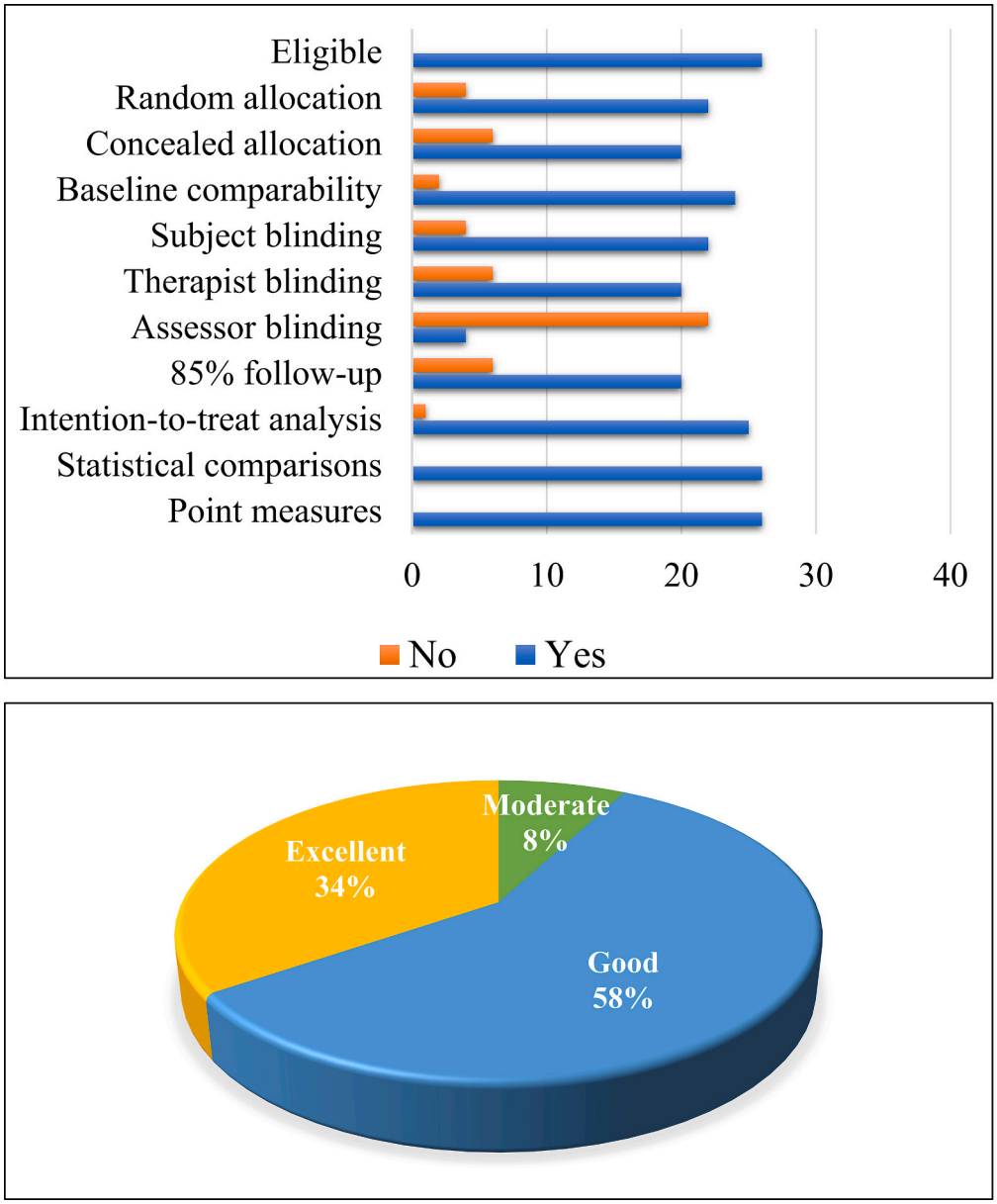

Fig. 3. Risk of bias assessment of the included studies.
(a) Proportion of 11 criteria in individual studies **(b)** Quality percentage in studies.
Notes: *Summarizing the risk of bias within included studies according to the PEDro scale, including individual criteria assessments.*

4.1. Omega-3 index

Our analysis indicates that high-dose FO interventions generally increase the O3i more effectively than lower-dose FO and KO formulations. Specifically, FO with a combined DHA + EPA content of 4400 mg per day is highly effective for boosting the O3i in red blood cells. FO-rTAG or FO-EE at doses ranging from 100 to 2900 mg also significantly improve the O3i (Fig. 4a, **Table 2**). When comparing FO and KO at the same dosage (100–1900 mg), KO tends to increase the O3i more effectively, even at lower doses. Studies such as Vosskötter et al. (2023) with 286 mg/day (Vosskötter F et al., 2023), Laidlaw et al. (2014) with 240 mg/day (Laidlaw et al., 2014), and Berge et al. (2014) with 1156 mg/day (K. Berge et al., 2014) demonstrate effectiveness of KO (K. Berge et al., 2014). Conversely, FO interventions typically use a minimum daily dose of 600 mg, with the highest reported at 1800 mg, suggesting that low-dose KO is more effective than higher-dose FO.

High-dose FO supplementation is not necessarily a direct replacement for KO, as shown in SIDE analysis (**Supplementary Table S9**). Analyzing Q' Cochrane statistics to assess inconsistencies between study designs (**Supplementary Table S8**) revealed significant inconsistencies when comparing KO < 2, FO < 2, and FO < 3 with the placebo group ($p < 0.0001$). After separating these groups, the inconsistency decreased significantly (Q = 965.61 to 6.32, $p = 0.0035$), though heterogeneity remained.

Beyond cardiovascular benefits, Omega-3 PUFAs positively impact brain health, ophthalmology, bone and joint health, and certain skin conditions (Bernhard et al., 2024; Bhargava et al., 2023; Christen et al., 2022; Gaengler et al., 2024; Huang et al., 2023; Lin et al., 2024; Stonehouse et al., 2022). Harris et al. (2017) found that raising the O3i to 4 % – 8 % can reduce the risk of death in individuals with coronary artery disease by approximately 30 % (Harris et al., 2017). Thus, increasing the O3i may significantly impact various health-related issues.

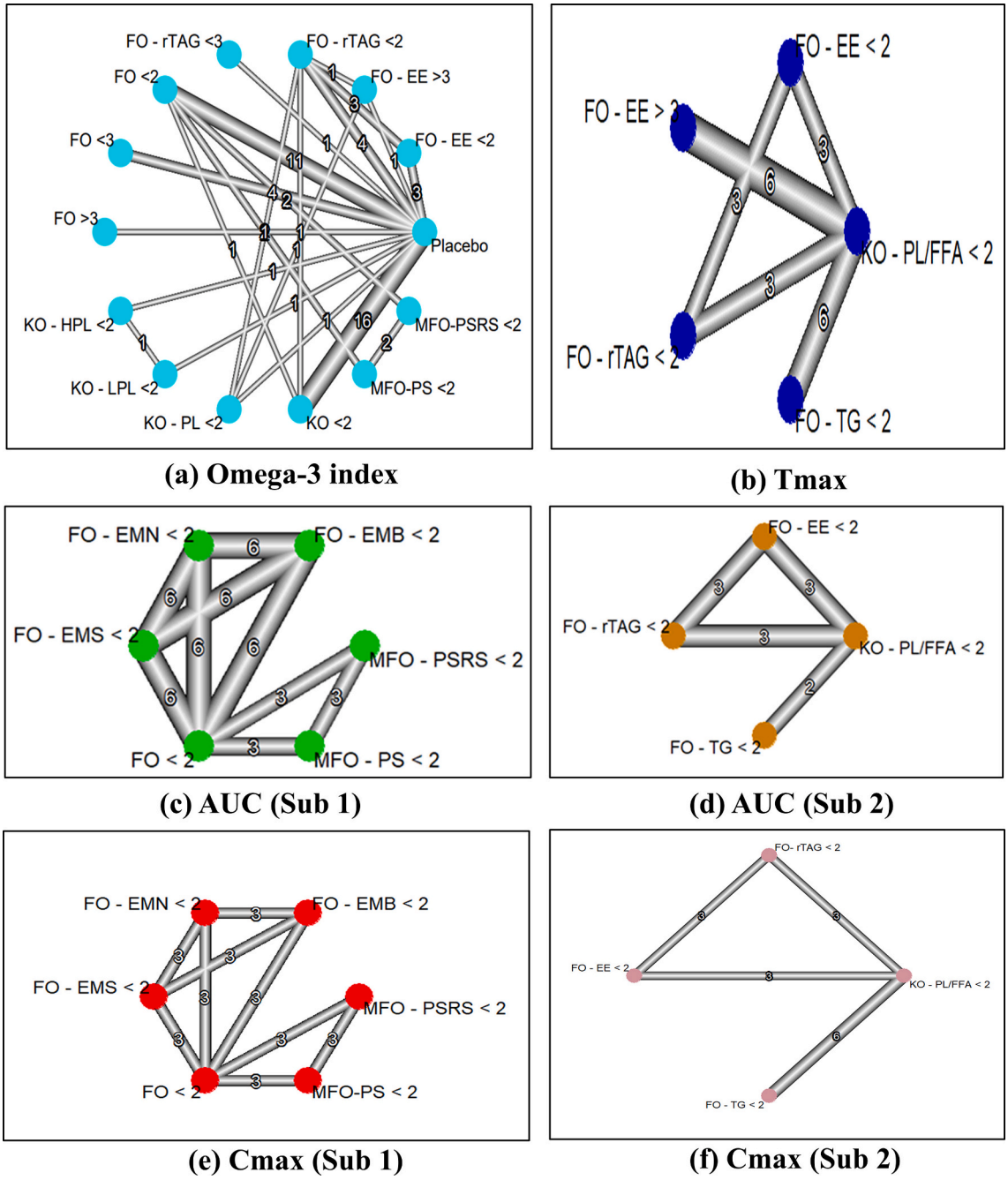

Fig. 4. Net graph estimates the effect of intervention oils on **(a)** O3i, **(b)** Tmax, **(c, d)** AUC, and **(e, f)** Cmax (random effect model).
Notes: The buttons correspond to different treatments. Edges represent observed treatment comparisons, with varying thickness indicating the frequency of each comparison in the network.

4.2. Time to maximum concentration - Tmax

The findings suggest that FO-EE at dosages between 2000 and 2900 mg may be the most effective for reducing Tmax, indicating a faster absorption rate (Fig. 4b, Table 3). Nutrition practitioners should consider this evidence when recommending Omega-3 supplements for rapid plasma fatty acid elevation. However, due to significant heterogeneity and limited statistical significance in some outcomes, these recommendations should be approached with caution. Analyzing Q' Cochrane statistics (**Supplementary Table S21**) showed inconsistencies mainly from comparing KO – PL/FFA < 2 with FO – EE > 3 ($p < 0.0001$), but the Q statistic value between study designs was zero, indicating no heterogeneity between studies. Other forms of FO, such as FO-rTAG and FO-TG, showed lower efficacy compared to KO in the PL/FFA formulation at doses below 2000 mg.

4.3. Area under the curve - AUC

KO in the PL/FFA form significantly increases plasma fatty acid concentrations, as indicated by a higher AUC index compared to FO molecular forms such as TG, EE, and rTAG within the same dose range of 100–1900 mg (Fig. 4c, **Table 2**). This conclusion is supported by SIDE analysis (**Supplementary Table S13**), which provides direct evidence for the efficacy of KO-PL/FFA.

Despite a comparable dose range, KO in the PL/FFA formulation generally requires a lower dose than equivalent FO forms to achieve

Table 1
The results of exploration for inconsistency of the Omega-3 index, Tmax, AUC, and Cmax outcomes.

Omega-3 Index
Quantifying heterogeneity / inconsistency
$tau^2 = 1.7890$ tau = 1.3375 **$I^2 = 97.1\ \%$ [96.6 %; 97.6 %]**
Tests of heterogeneity (within designs) and inconsistency (between designs)

	Q	d.f.	p - value
Total	**1255.57**	**36**	**< 0.0001**
Within designs	**965.61**	**32**	**< 0.0001**
Between designs	**289.96**	**4**	**< 0.0001**

AUC – Sub 1
Quantifying heterogeneity / inconsistency:
$tau^2 = 0$ tau = 0 **$I^2 = 0\ \%$ [0.0 %; 48.0 %]**
Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	4.44	19	0.9998
Within designs	4.44	19	0.9998
Between designs	0.00	0	–

Cmax – Sub 1
Quantifying heterogeneity / inconsistency
$tau^2 = 0$ tau = 0 **$I^2 = 0\ \%$ [0.0 %; 60.2 %]**
Tests of heterogeneity (within designs) and inconsistency (between designs)

	Q	d.f.	p-value
Total	5.72	10	0.8380
Within designs	5.72	10	0.8380
Between designs	0.00	0	–

Tmax
Quantifying heterogeneity / inconsistency
$tau^2 = 111.7406$ tau = 10.5707 **$I^2 = 94.8\ \%$ [92.9 %; 96.3 %]**
Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	**270.85**	**14**	**< 0.0001**
Within designs	**270.85**	**14**	**< 0.0001**
Between designs	0.00	0	-

AUC – Sub 2
Quantifying heterogeneity / inconsistency:
$tau^2 = 0$ tau = 0 **$I^2 = 0\ \%$ [0.0 %; 74.6 %]**
Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	3.83	5	0.5741
Within designs	3.83	5	0.5741
Between designs	0.00	0	–

Cmax – Sub 2
Quantifying heterogeneity / inconsistency
$tau^2 = 0.0919$ tau = 0.3032 **$I^2 = 78.5\ \%$ [60.9 %; 88.2 %]**
Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	**41.92**	**9**	**< 0.0001**
Within designs	**41.92**	**9**	**< 0.0001**
Between designs	0.00	0	–

Notes: * Statistically significant results highlighted in bold; **"-"**: no data; **"d.f".:** degrees of freedom.

similar bioavailability. This enhanced bioavailability is due to the presence of free fatty acids and phospholipids, which promote superior absorption and utilization of Omega-3 fatty acids (Köhler et al., 2015). This finding highlights the efficiency of the KO-PL/FFA form in maximizing bioavailability even at lower doses.

4.4. Maximum concentration - Cmax

Emulsion forms of FO are more effective in increasing the Cmax of Omega-3 fatty acids in plasma compared to traditional FO capsules. This suggests emulsion formulations should be prioritized in nutritional practices where peak plasma concentrations of Omega-3 are essential, particularly for rapid therapeutic purposes. Additionally, KO-PL/FFA may be an effective alternative to FO, especially at lower doses, benefiting those who experience adverse effects from higher FO doses.

The strength of the Cmax results lies in the inclusion of multiple interventions and comparisons, enhancing the robustness of the findings. The low heterogeneity in **Sub 1** adds confidence to the efficacy of emulsion FO forms (Fig. 4e and Table 1), indicating consistent bioavailability across studies. Conversely, the high heterogeneity in **Sub 2** (Table 1) suggests significant variability among the included studies, affecting the reliability of these results. This variability indicates unaccounted factors influencing Cmax outcomes. The lack of statistical significance in several comparisons highlights the need for further research to validate these findings.

4.5. Comparative analysis with existing literature

Our findings regarding the superior bioavailability of phospholipid-bound omega-3 in KO are consistent with previous research (Ulven & Holven, 2015). The molecular structure of FO consists predominantly of triglyceride, while KO contains Omega-3 fatty acids mainly in the form of phospholipids (Kim et al., 2020). These phospholipids in KO are more easily absorbed due to their amphiphilic properties, enhancing bioavailability compared to the triglyceride form in FO, which requires more processing in the body (Cook et al., 2016). The difference in absorption efficiency between these molecular structures explains why KO formulations, despite lower EPA and DHA content, can exhibit higher bioavailability than FO (Köhler et al., 2015; Schuchardt et al., 2011). Our study extends these insights by employing a network meta-analysis that synthesizes data across multiple dosages and formulations, revealing that KO's phospholipid form consistently outperforms other forms, particularly at lower dosages.

Furthermore, while a recent study reported similar bioavailability among KO, FO, and calanus oil(Vosskötter et al., 2023), our results indicate that KO provides superior absorption, particularly when administered in phospholipid form at lower doses. This highlights the importance of molecular structure and dosage in optimizing Omega-3 bioavailability, aligning with ealier findings (Elagizi et al., 2021), which emphasized the cardiovascular benefits of Omega-3 , thereby supporting the clinical utility of KO in rapidly elevating plasma Omega-3 levels.

4.6. The influence of chemical structure and molecular form on bioavailability

The difference in bioavailability between FO and KO can be primarily attributed to the chemical structure of the Omega-3 fatty acids they contain (Schuchardt et al., 2011; Yurko-Mauro et al., 2015). In this study, we analyzed clinical data from various molecular forms of FO and KO, including FO-TG, FO-EE, FO-rTAG, and FO-EM, as well as KO-HPL, KO-LPL, and KO-PL/FFA formulations. Our findings demonstrate that KO formulations, particularly those rich in phospholipids, offer superior absorption and bioavailability compared to the triglyceride-based FO forms. Phospholipids in KO facilitate more efficient absorption across cell membranes than the triglyceride and ethyl ester forms in FO (Köhler et al., 2015; Schuchardt et al., 2011).

While emulsified forms of FO (FO-EMB, FO-EMN, FO-EMS) can improve bioavailability, they still require additional processing to match the efficiency of phospholipid-bound omega-3 in KO. This structural distinction explains the higher bioavailability of KO, even at lower EPA and DHA concentrations, as shown in our study (see **Table 2**, Fig. 4c).

Phospholipids possess amphiphilic properties, allowing them to dissolve more readily in the aqueous environment of the body, leading to better absorption and metabolism of Omega-3 fatty acids (Ahmmed

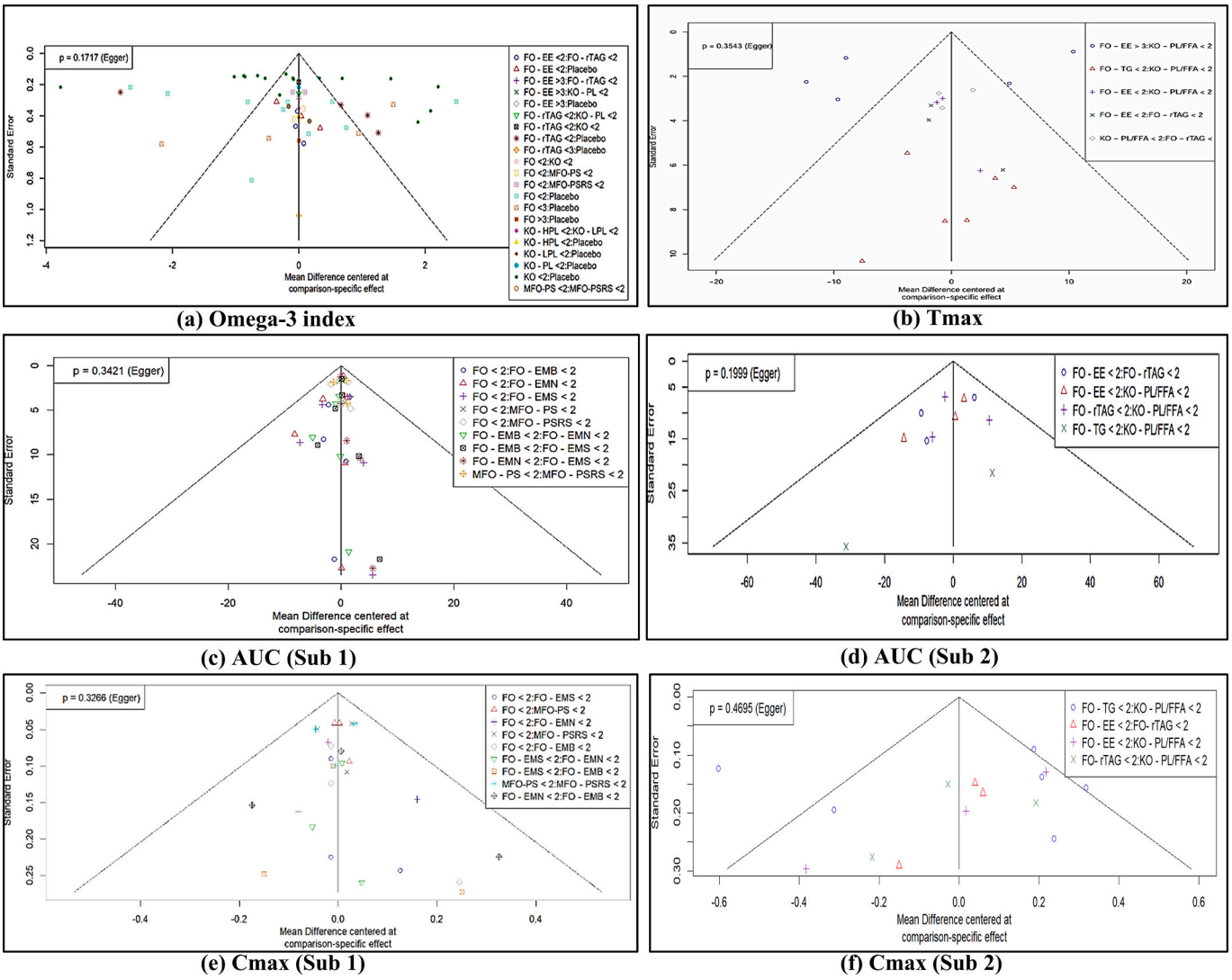

Fig. 5. Funnel plot showing the results of the publication bias analysis for the O3i **(a),** Tmax **(b)**, AUC **(c, d),** and Cmax **(e, f),** by Egger's test. ***Notes:*** *The standard error (SE) of the intervention estimate is displayed on the vertical axis, while the mean difference of the specific comparison effect is on the horizontal axis. The edges of the triangle represent the 95 % confidence interval (CI) of the studies. The more the studies are concentrated towards the top and within the 95 % CI, the higher the reliability.*

et al., 2023; Burri et al., 2012; Köhler et al., 2015). This enhanced absorption may explain why KO can elevate blood Omega-3 levels more effectively than FO, even when administered at lower doses (Kim et al., 2020; Yurko-Mauro et al., 2015; Schuchardt et al., 2011).

4.7. Clinical applications, implications for nutritional practice

A thorough understanding of the bioavailability differences between FO and KO is essential for both clinical practice and the development of effective nutritional supplements. Phospholipids in KO facilitate better integration into cell membranes, leading to faster and more efficient Omega-3 delivery to tissues, particularly in situations requiring rapid therapeutic effects, such as in the management of cardiovascular diseases or chronic inflammatory conditions (Elagizi et al., 2021; K. Berge et al., 2014; Maki et al., 2009). On the other hand, FO's triglyceride form, while absorbed more slowly, is effective for maintaining stable, long-term Omega-3 levels (Harris & Von Schacky, 2004; Vonschacky & Harris, 2007). This nuanced understanding is critical for optimizing the efficacy of Omega-3 supplements. By comparing the various molecular forms and dosages, our study helps to identify the most effective strategies for maximizing health benefits, particularly in cardiovascular health, inflammation reduction, and cholesterol management. Such insights allow clinicians to tailor supplementation strategies to individual needs, improving both efficacy and safety.

Furthermore, while health organizations recommend a daily intake of 250 mg to 3000 mg of combined EPA and DHA for adults, the molecular form in which these fatty acids are delivered significantly impacts their effectiveness and safety (Kang et al., 2023). Consuming large doses of FO can lead to several side effects, including gastrointestinal discomfort, diarrhea, and an increased risk of bleeding due to the anticoagulant properties of Omega-3 fatty acids (Lange et al., 2019; V. Kim et al., 2016; Detopoulou & Papamikos, 2014). Similar side effects have been observed with high doses of KO, although its lower dosage efficacy may reduce these risks (Van Der Wurff et al., 2019). High doses of FO, particularly above 3000 mg per day, have been associated with adverse events (Lange et al., 2019), which highlights the importance of considering both the molecular form and dosage when prescribing Omega-3 supplements. KO, although similar in composition, may offer a reduced risk profile due to its higher bioavailability, allowing for effective outcomes at lower doses (Colletti et al., 2021). However, our findings suggest that lower doses of KO or FO in emulsion forms can achieve similar, if not superior, therapeutic outcomes with fewer side effects. This evidence highlights the importance of selecting the appropriate form and dosage of Omega-3 , contributing to the development of

Table 2
The network meta-analysis results for Omega-3 index, Tmax, Area Under the Curve levels, and Cmax outcomes

Omega-3 Index				
k	**m**		**n**	
22	59		14	
Comparison: other treatments vs 'Placebo'				
Interventions	**MD**	**95 %-CI**	**z**	**p-value**
FO - EE < 2	**3.9472**	**[2.4451; 5.4493]**	**5.15**	**< 0.0001**
FO - EE > 3	1.9029	[− 0.4947; 4.3005]	1.56	0.1198
FO - rTAG < 2	**4.0440**	**[2.8252; 5.2628]**	**6.50**	**< 0.0001**
FO - rTAG < 3	**4.1700**	**[0.8498; 7.4902]**	**2.46**	**0.0138**
FO < 2	**2.6158**	**[1.7869; 3.4447]**	**6.19**	**< 0.0001**
FO < 3	**2.1041**	**[0.7061; 3.5021]**	**2.95**	**0.0032**
FO > 3	**4.5000**	**[1.6574; 7.3426]**	**3.10**	**0.0019**
KO - HPL < 2	1.6100	[− 1.1259; 4.3459]	1.15	0.2487
KO - LPL < 2	- 0.2200	[− 2.9629; 2.5229]	- 0.16	0.8751
KO - PL < 2	0.8919	[− 1.4902; 3.2740]	0.73	0.4631
KO < 2	**1.6439**	**[1.0015; 2.2864]**	**5.02**	**< 0.0001**
MFO - PS < 2	**2.6633**	**[0.5625; 4.7641]**	**2.48**	**0.0130**
MFO - PSRS < 2	**3.0212**	**[0.9618; 5.0807]**	**2.88**	**0.0040**
'Placebo'	**-**	**-**	**-**	**-**
Tmax				
k	**m**		**n**	
2	21		5	
Comparison: other treatments vs 'KO-PL/FFA < 2'):				
Interventions	**MD**	**95 %-CI**	**z**	**p-value**
FO-EE < 2	3.0251	[−9.8464;15.8966]	0.46	0.6451
FO-EE > 3	−8.4671	[−17.0903;0.1560]	−1.92	0.0543
FO-rTAG<2	2.5996	[−9.8167;15.0159]	0.41	0.6815
FO-TG < 2	5.0794	[−5.3702;15.5290]	0.95	0.3407

AUC – Sub 1				
k		**m**		**n**
4		45		6
Comparison: other treatments vs 'FO < 2'				
Interventions	**MD**	**95 %-CI**	**z**	**p-value**
FO-EMB < 2	1.5453	[−0.9005; 3.9912]	1.24	0.2156
FO-EMN < 2	1.6677	[−0.4173; 3.7528]	1.57	0.1169
FO-EMS < 2	0.3950	[−1.7959; 2.5859]	0.35	0.7238
MFO-PS < 2	−0.0334	[−2.3535; 2.2867]	−0.03	0.9775
MFO-PSRS <2	−0.9476	[−3.5157; 1.6204]	−0.72	0.4695
AUC – Sub 2				
k	**m**	**n**		
3	11	4		
Comparison: other treatments vs 'KO-PL/FFA < 2'				
Interventions	MD	95 %-CI	z	p-value
FO-EE < 2	**−18.6285**	**[−29.4905; −7.7665]**	**−3.36**	**0.0008**
FO-rTAG < 2	**−14.2551**	**[−24.8765; −3.6336]**	**−2.63**	**0.0085**
FO-TG < 2	−6.5811	[−42.7140; 29.5518]	−0.36	0.7211

Cmax - Sub 1				
k	**m**	**n**		
3	27	6		
Comparison: other treatments vs 'FO < 2'				
Interventions	**MD**	**95 %-CI**	**z**	**p-value**
FO - EMB < 2	0.0596	[−0.0595; 0.1787]	0.98	0.3267
FO - EMN < 2	**0.1902**	**[0.0800; 0.3003]**	**3.38**	**0.0007**
FO - EMS < 2	**0.2901**	**[0.1366; 0.4436]**	**3.70**	**0.0002**
MFO-PS < 2	0.0228	[−0.0319; 0.0775]	0.82	0.4140

(*continued on next page*)

Table 2 (*continued*)

MFO - PSRS <2	−0.0041	[−0.0639; 0.0557]	−0.13	0.8929
Cmax - Sub 2				
k	**m**	**n**		
2	**15**	**4**		
Comparison: other treatments vs 'KO - PL/FFA < 2'				
Interventions	**MD**	**95 %-CI**	**z**	**p-value**
FO- rTAG <2	−0.1708	[−0.5821; 0.2404]	−0.81	0.4155
FO - EE < 2	−0.4096	[−0.8230; 0.0039]	−1.94	0.0522
FO - TG < 2	−0.2172	[−0.4910; 0.0565]	−1.56	0.1199

Notes
* Statistically significant results highlighted in bold.
- "95 %-CI": 95 % Confidence Interval; **"vs":** Versus;
Number of studies: **k;** Number of pairwise comparisons: **m;** Number of treatments: **n;** Treatment estimate: sm = **'MD'**: Mean Difference;
- Effect size: **Random model effect**.

Table 3
Treatment ranking (SUCRA %) for O3i, AUC, Cmax, and Tmax.

Omega-3 Index		AUC		C_{max}		T_{max}	
Treatment	SUCRA	Sub 1	SUCRA	Sub 1	SUCRA	Treatment	SUCRA
Placebo	92.35	MFO-PSRS <2	82.50	MFO - PSRS <2	81.78	FO - EE > 3	95.22
KO-LPL < 2	98.70	FO < 2	64.26	FO < 2	80.18	KO - PL/FFA < 2	55.90
KO-PL < 2	77.23	MFO-PS < 2	63.06	MFO-PS < 2	65.82	FO - rTAG <2	39.08
KO < 2	67.12	FO-EMS < 2	55.40	FO - EMB < 2	51.44	FO - EE < 2	36.25
KO-HPL < 2	64.29	FO-EMB < 2	22.72	FO - EMN < 2	18.48	FO - TG < 2	23.55
FO-EE > 3	58.27	FO-EMN < 2	16.92	FO - EMS < 2	02.30	–	–
FO < 3	55.64	**Sub 2**	**SUCRA**	**Sub 2**	**SUCRA**	–	–
FO < 2	44.42	FO-EE < 2	81.87	FO - EE < 2	86.63	–	–
MFO-PS < 2	42.68	FO-rTAG <2	62.83	FO - TG < 2	56.77	–	–
MFO-PSRS <2	38.14	FO-TG < 2	43.90	FO- rTAG <2	45.87	–	–
FO-rTAG <3	19.68	KO-PL/FFA < 2	11.40	KO - PL/FFA < 2	10.73	–	–
FO-EE < 2	18.40	–	–	–	–	–	–
FO-rTAG <2	16.20	–	–	–	–	–	–
FO > 3	14.71	–	–	–	–	–	–

Notes: "-": *No data; Outcomes including O3i, AUC, and Cmax: High ranking from bottom to top, and Tmax variable in reverse, ranking from top to bottom.*

more effective and personalized nutritional supplements that enhance clinical outcomes.

4.8. Strengths and limitations

This study possesses several strengths. To the best of the authors' knowledge, this is the first NMA assessing the bioavailability of Omega-3 PUFAs in both KO and FO, specifically comparing molecular forms, formulations, and dosages. The inclusion of numerous studies offers a comprehensive overview of PUFA bioavailability from these sources. The absence of publication bias, as indicated by the analyses, supports the reliability of these results (Fig. 5). These findings are valuable for informing nutritional practice and guiding future research.

Regarding limitations, high heterogeneity was observed in several analyses, particularly for Tmax and Cmax. The limited number of studies and the narrower dose range for KO compared to FO constrain some conclusions. While FO has been studied at dosages exceeding 3000 mg/day, KO has only been evaluated at lower doses under 1900 mg/day. Consequently, there is a lack of evidence to compare the bioavailability of FO and KO at higher doses above 2000 mg.

Future research should explore KO supplementation in different molecular forms with higher daily doses. Standardizing methodologies across studies will be crucial to reduce heterogeneity and enhance reliability. Additional studies focusing on the long-term effects and impact on different populations are necessary to validate and enhance the applicability of these findings in nutritional practice.

5. Conclusion

This study highlights the critical importance of understanding the bioavailability differences between FO and KO, particularly in terms of their molecular forms. Our findings reveal that KO, with its phospholipid-bound Omega-3 , offers superior absorption and efficacy at lower doses compared to the triglyceride-bound Omega-3 in FO. High-dose FO (above 3000 mg, up to 4400 mg per day of DHA + EPA) is most effective for increasing the O3i. At lower dosages (under 2000 mg), KO shows superior Omega-3 absorption compared to fish oil. KO-PL/FFA is preferred for increasing AUC, while emulsion forms of FO are more effective for Cmax. The study demonstrates that low-dose Omega-3 fatty acids from KO and emulsion FO forms can be as effective and safer than high-dose FO, potentially reducing adverse effects. Future research should build on these findings by exploring the long-term impacts of different Omega-3 formulations to develop more personalized and effective nutritional interventions.

CRediT authorship contribution statement

Thi-Phuong-Thao Pham: Conceptualization, Methodology, Data curation, Software,Resources, Visualization, Writing - original draft. **Thi-Van Hoang:** Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Phuc-Thao-Nguyen Cao:** Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Van-Thao-Nguyen Ho:** Software, Resources, Methodology, Data curation. **Thi-Mai-Hoa Vu:** Software, Resources, Formal analysis, Data curation. **Thi-Hoai-Thu Le:** Software, Resources, Methodology, Data curation. **Huynh-Thien-Xuan Pham:** Software, Resources, Formal analysis, Data curation. **Thanh-Thien Tran:** Software, Resources, Data curation, Conceptualization. **Okti Ratna Mafruhah:** Resources, Investigation, Formal analysis. **Thi-Thuy-Linh Pham:** Writing – original draft,

Visualization, Software, Methodology, Data curation, Conceptualization. **Min-Tsang Hsieh:** Writing – review & editing, Supervision, Software, Funding acquisition, Data curation. **Hai-Anh Ha:** Writing – review & editing, Supervision, Software, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data included within manuscript and supplementary documents

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fochx.2024.101880.

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