Evidence on the Efficacy of Omega-3 Polyunsaturated Fatty Acids as an Adjunct Therapy for Chronic Obstructive Pulmonary Disease

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Background As the fourth leading cause of death worldwide, Chronic Obstructive Pulmonary Disease (COPD) places a significant burden on healthcare-related costs. COPD is characterized by airflow impairment, including chronic bronchitis, small airway obstruction, and emphysema. COPD pathophysiology involves inflammation correlated with lung decline, body composition alteration, and decreased quality of life. Since preceding studies have shown its roles in inflammatory processes, omega-3 is proposed as a potential adjunct treatment in slowing down COPD progression.

Aim To analyze the efficacy of omega-3 as a potential adjunct therapy in COPD management.

Method A literature review was conducted by retrieving studies published from 2010-2020 through PubMed, EBSCOhost, Cochrane Controlled Register of Trials (CENTRAL), Scopus, Clinical Key, Wiley, and Science Direct that evaluate the effect of omega-3 supplementation in COPD management.

Outcome The search yielded 12 studies with a total of 6,474 subjects. Outcomes suggested that omega-3 leads to a reduction in inflammation, improved body composition, enhanced exercise capacity, higher quality of life, and lower exacerbation occurrences. Association found for lung function was weak, but this might be due to the study designs. The only potential adverse effect was diarrhea, but this is insignificant.

Conclusion To conclude, omega-3 supplementation in COPD management showed promising results, considering its efficacy in slowing down COPD progression, minimal side
effects, cost-effectiveness, and feasibility. However, the incorporation of this intervention into management guidelines requires more trials with larger samples to establish more substantial evidence and a more in-depth understanding of its roles.

**Keywords** Adjunct, COPD, Inflammation, Omega-3
Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitation involving chronic bronchitis, small airway obstruction, and emphysema. Although tobacco smoking is the most common risk factor, air pollution, exposure to chemicals, infections, and genetic alterations can also lead to COPD. COPD is the fourth leading cause of death worldwide; with an increasing prevalence of 299,398,200, the incidence of 18,475,700, and Years Lost to Disability (YLD) of 30,611,500, it poses a significant portion in the global burden of diseases. The prevalence of COPD in the Indonesian population >30 years of age was 3.8% or roughly 9.2 million in the latest survey involving COPD in 2013. Healthcare costs correlated with COPD place a significant problem; therefore, it is essential to provide effective management strategies that will diminish hospitalization rates and increase the quality of life for patients.

Symptoms of COPD include dyspnoea, wheezing, cough, and sputum production. Assessment is based on spirometry (FEV1/FVC), exacerbation, and symptoms. Inflammation is the hallmark of COPD; airway inflammation involving activation of macrophages, transcription of matrix metalloproteinases, cytokines such as IL-8 and TNF-α, recruitment of neutrophils, CD8+ T cells that produce IP-10 and CXCL10, the release of macrophage metalloproteinases, and neutrophil elastases ultimately lead to lung damage. Systemic inflammation, characterized by changes in blood neutrophils, ROS, and mediators such as IL-6, TNF-α, IL-1β, fibrinogen, and CRP, also occurs in COPD and is proposed as a mechanism for cachexia and sarcopenia. Reduced exercise capacity also occurs, as well as reduced quality of life and increased mortality.

Currently, treatment of COPD involves pharmacological use of bronchodilators such as beta2-agonists, antimuscarinics, methylxanthine, corticosteroids, phosphodiesterase-4, and mucolytic agents. However, a nutritional intervention that can further reduce inflammation and maintain muscle mass, such as omega-3 PUFAs, may prove to be more therapeutically beneficial when consumed in conjunction with smoking cessation and pharmacological approaches. This literature review is aimed at analyzing the potential of omega-3 PUFAs as an adjunct therapy for patients diagnosed with COPD to improve quality of life, slow down progression, and reduce exacerbation.

Method

Search Strategies

The authors constructed this review by retrieving and analyzing studies from PubMed, CENTRAL, Scopus, Wiley, EBSCOhost, ClinicalKey, and ScienceDirect databases published from 2010 to 10th June 2020, with the search terms: ("COPD" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Airflow Obstruction" OR "Chronic Obstructive Airway Disease") AND ("Omega 3" OR "Omega-3 Polyunsaturated Fatty Acid" OR "n-3
PUFA" OR "n-3 oil" OR "Eicosapentaenoic acid" OR "Docosahexaenoic acid" OR "Alpha-linolenic acid"). The studies were limited to human participants.

Data Extraction
Essential data were extracted, including the first author and year of publication, study location, design, intervention, measuring tool, and outcome; including the presence of inflammatory biomarkers, lung function, body composition, exercise capacity, Health-Related Quality of Life (HRQoL), COPD exacerbation, and any other reported outcome.

Study Selection
This review is constructed by analyzing 401 studies from 6 databases. Finally, the studies included consist of 5 randomized controlled trials, 5 cross-sectional studies, 1 cohort study, and 1 pilot study.

Results and Discussion
Study Characteristics
In this review, 12 studies were included with a total of 6,474 subjects. The studies were international, mostly cross-sectional, and randomized controlled trials. All studies were aimed to evaluate the effect of omega-3 in COPD management. The outcome varied; however, because relieving symptoms and preventing exacerbation are critical aspects in COPD management, most findings were focused on limiting inflammation to achieve a better quality of life. The results are shown in Table 1.

Omega-3 PUFAs
Omega-3 contains a first double bond located at the third position from the methyl terminus. Due to ineffective synthesis from endogenous precursors, omega-3 is considered to be nutritionally essential. Alpha-linolenic acid (ALA) is found in seeds, nuts, and seed oils,[8] whereas the primary exogenous sources of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are fatty fish.9

Preceding studies have shown that omega-3 is beneficial in the treatment of diseases involving inflammation, such as cardiovascular, joint, and inflammatory bowel diseases.10,11,12 For that reason, recent studies have emerged to evaluate its potent anti-inflammatory properties in the management of COPD. Doses of omega-3 supplementation evaluated for efficacy ranged from 0.6-1.5 g/day.

Role in Inflammation
Roles of omega-3 in anti-inflammatory pathways are achieved through substrate competition, receptor competition, and release of resolving metabolites (Figure 1).11,13

During substrate competition, omega-3 PUFAs prevalent on inflammation sites will contend against COX- and LOX-dependent metabolic pathways that oxidize other fatty acids (omega-6) into arachidonic acid, then eicosanoids such as prostaglandins, leukotrienes, and lipoxins. Less inflammatory-potent metabolites from omega-3 such as 3-series prostaglandins and 5-series leukotrienes will then compete with more potent omega-6 metabolites for receptors. Other
pathways produce pro-resolving mediators such as EPA-derived resolvsins (RvE1, RvE2, RvE3), DHA-derived resolvsins (RvD1, RvD2, RvD3, RvD4, RvD5, RvD6), protectins (PD1, PDX), maresins (MaR1, MaR2), and their conjugates in tissue regeneration. These promote resolution of acute and chronic inflammation through inhibition of PMNs, recruitment of macrophages that conduct efferocytosis, stimulation of phagocytosis, attenuation of Th₁ and Th₁₇ polarization, and generation of Treg in CD4 response. Other roles also exist, such as cell membrane composition amendment and gene expression regulation.

Evidence-based studies have pointed out the effect of omega-3 on COPD inflammatory markers. TNF-𝛼 plays a vital role in NF-κβ and MAPK signaling that regulate cytokine release and Receptor-Interacting Serine/Threonine Kinase 1 (RIPK1) cytotoxicity that may lead to worsening conditions in COPD. A cross-sectional study on 250 stable COPD patients by de Batlle showed that serum inflammatory markers such as TNF-𝛼 and NF-κβ DNA-binding pro-inflammatory cytokines decreased upon consumption of ALA and DHA. Furthermore, in two randomized controlled trials by Calder and Sugawara, the presence of IL-6, IL-8, and TNF-𝛼 were lower in the group receiving the omega-3 enriched supplement. It is known that IL-6 and IL-8 are produced by human bronchial epithelial cells as mediators for COPD exacerbation. C-Reactive Proteins, which lead to COPD exacerbation, also decreased in the latter study. In another study conducted by Williams, DHA and EPA supplementation combined with rosuvastatin and lycopene on COPD patients lowers plasma IL-6 and alters inflammatory gene expressions. Leukotriene B4 Receptor (LTB4R) gene, associated with the neutrophil count, was lowered back to basal level after omega-3 supplementation. This might occur as DHA and EPA can substitute arachidonic acid in cell membrane so that LTB4 is produced less; whereas LTB5, which has 10-30 fold lower neutrophil chemotactic potency, is produced more. CXCL10 (also called Interferon-g-Inducible Protein-10/IP-10), which is produced by neutrophils and functions to attract activated T-lymphocytes, also returned to basal levels. Moreover, omega-3 supplementation also reduced RIPK2, a caspase-recruitment domain involved in cell signaling and death. Conversely, there was a decreased expression of ALOX-5, a gene that codes for arachidonate 15-lipoxygenase (15-LO) involved in peroxidizing arachidonic acid into 12-hydroxyeicosatetraenoic acid (12-HETE), a neutrophil chemoattractant. Above all, it can be concluded that omega-3 can limit inflammation and promote resolution in COPD progression.
Role in Lung Function

Spirometry is the main determinant in COPD diagnosis and assessment as it reflects the severity of airflow obstruction. Forced Vital Capacity (FVC) reflects the total air that can be exhaled quickly and maximally. Meanwhile, the amount of air forcefully exhaled on the first second reflects the Forced Expiratory Volume (FEV1). In COPD-confirmed patients with FEV1/FVC <0.70, a lower FEV1 score than predicted means a more severe obstruction. The GOLD initiative describes COPD as class 1/mild when FEV1 is ≥80% predicted; class 2/moderate when 50% ≤FEV1<80% predicted; class 3/severe when 30%≤FEV1<50% predicted, and class 4/very severe when FEV1 <30% predicted.

Numerous studies have investigated the association between omega-3 supplementation with COPD progression. Two cross-sectional studies show no relationship: Choi evaluated 573 participants, while Fulton assessed only a small number of cases. In another study by Sugawara, 0.6 g omega-3 and 248 mg vitamin A intake combined with low-intensity exercise gave no significant effect on FEV1 and FVC. However, Sugawara included only 32 patients. Contrastively, in a nutritional epidemiological study by Leng comparing 2 large cohorts with 1,829 and 508 people respectively, it was concluded that higher omega-3 intake was associated with higher average FEV1 and thus better lung function. With higher EPA and DHA intake, FEV1 decline was slower; lung function was even completely protected with very high DPA intake (>20 mg/day) in one of the cohorts. Similarly, a cross-sectional study by Ng showed that people who consume more omega-3 PUFA displayed higher FEV1 and better lung function. On the whole, results are either none or positive, but no negative effect is found after omega-3 supplementation. More interventional trials are needed to provide stronger evidence.
| No | Author; Year of Publication | Study Location | Study Design | Intervention | Measuring Tool | Outcome |
|----|----------------------------|----------------|--------------|--------------|---------------|---------|
| 1  | Choi H, et al; 2020         | South Korea    | Cross-sectional | -            | • Spirometry  |
|    |                            |                |              |              | • HRQoL using |
|    |                            |                |              |              | EQ-5D         |
|    |                            |                |              |              | + No significant association between omega-3 intake and FEV1/FVC |
|    |                            |                |              |              | + HRQoL with higher omega-3 intake |
| 2  | van Beers MV, et al; 2020  | The Netherlands | Double-blind, Randomized Controlled Trial | • Phase 1 (4 months) 3 portions/day leucine, Vit D, PUFA in NUTRITION or PLACEBO • Phase 2 (8 months) +1 portion/day to NUTRITION group | • QMS  |
|    |                            |                |              |              | • Bicycle ergometry test (CET)  |
|    |                            |                |              |              | • PAL  |
|    |                            |                |              |              | • HRQoL using EQ-5D and HADS  |
|    |                            |                |              |              | • Body composition  |
|    |                            |                |              |              | + QMS score in NUTRITION |
|    |                            |                |              |              | + CET score in NUTRITION (insignificant) |
|    |                            |                |              |              | + PAL (steps per day) in NUTRITION (P=0.025) |
|    |                            |                |              |              | + EQ-5D in PLACEBO but not in NUTRITION group (P=0.009) |
|    |                            |                |              |              | + HADS score in NUTRITION (P=0.037) |
|    |                            |                |              |              | + total body weight, muscle mass, FM |
| 3  | Lemoine C, et al; 2019     | Maryland, USA  | Cross-sectional | -            | • HRQoL using SGRQ, CAT, CCQ  |
|    |                            |                |              |              | • + SGRQ (P=0.01), CAT (P=0.01), CCQ (P=0.01) score |
|    |                            |                |              |              | • + symptoms, exacerbations (P=0.03) |
| 4  | Fulton AS, et al; 2019     | South Australia| Cross-sectional | -            | • Spirometry  |
|    |                            |                |              |              | • No significant association between fish and PUFA intake with FEVI and FVC |
| 5  | Calder PC, et al; 2018     | Sweden         | Double-blind, Multicentre, Randomized Controlled Trial | 200mL TMN containing high-dose omega-3 fatty acids, vitamin D, and high-quality protein daily for 12 weeks compared with PLACEBO | • Bodyweight and composition  |
|    |                            |                |              |              | • Borg scale, 6MWD  |
|    |                            |                |              |              | • Serum inflammatory markers  |
|    |                            |                |              |              | • No notable difference in BMI, WCC, LBM, & SMI; + FM in TMN (P=0.0013) |
|    |                            |                |              |              | • + fatigue (P=0.0223), + dyspnoea (P=0.0382) in TMN |
|    |                            |                |              |              | • + concentrations of IL-6, IL-8, TNF-α |
| Study Number | Authors & Year | Location | Study Design | Intervention | Main Findings |
|--------------|---------------|----------|--------------|--------------|--------------|
| 6            | Ogasawara T, et al; 2018 | Shizuoka, Japan | Randomized Controlled Trial | 1 g/day of EPA ONS compared with EPA-free ONS | • HRQoL using SGRQ, CAT, and CCQ  
• COPD progression  
• Decreased in TMN; ↑ CRP in both groups  
• No difference in CAT & CCQ, + activity subdomain in SGRQ  
• + exacerbations in TMN; no difference in lung function/FEV1 (p=0.3689) |
| 7            | Leng S, et al; 2017 | New Mexico, USA | Cohort | - | • Spirometry  
• ↑ FEV1 with higher omega-3 intake (P<0.0001 in LSC, P=0.0011 in VSC)  
• Slower FEV1 decline with higher EPA and DHA intake (P<0.05)  
• Complete protection against FEV1 decline on high DPA intake (>20 mg/day in LSC) |
| 8            | van de Bool C, et al; 2017 | The Netherlands | Randomized Controlled Trial | ONS of leucine, vitamin D, and omega-3 fatty acids combined with supervised high-intensity training for 4 months or PLACEBO | • Plasma levels  
• Bodyweight and composition  
• PAL, 6MWD, IMS  
• QMS, CET  
• HADS  
• ↓ arachidonic acid in nutrition  
• + body mass (P=0.01), SMM (P<0.001), FM in nutrition  
• + IMS (P=0.001), + QMS (P<0.001), CET (P<0.001) score in nutrition  
• + HADS score in nutrition |
| 9            | Williams EJ, et al; 2016 | Newcastle, Australia | Pilot | Phase 1 (first 4 weeks) 20 mg/day rosuvastatin  
• Phase 2 (8 weeks) 20 mg/day rosuvastatin, 1.5g/day DHA, EPA, and 45 | • Clinical characteristics (lung function, HRQoL, BMI, blood pressure)  
• Systemic inflammatory biomarkers  
• Airway inflammatory biomarkers  
• No notable effect clinically  
• + plasma IL-6 phase1, +phase2 (P=0.0924)  
• + plasma CRP phase1, +phase2 (P=0.6862)  
• Peripheral blood counts remain similar  
• + % neutrophils, absolute count (P=0.0161) |
| Study | Authors | Location | Study Design | Intervention | Results |
|-------|---------|----------|--------------|--------------|---------|
| 10    | Ng TP, et al; 2013 | Singapore | Cross-sectional | - | • Peripheral blood gene expression |
|       |          |          |              | 10 mg/day lycopene | • ↓ % sputum macrophages \(P=0.0153\) |
|       |          |          |              |                | • ↑ LTB4R gene phase 1, phase 2 \(P=0.0103\) |
|       |          |          |              |                | • ↑ CXCL10 phase 1, phase 2 \(P=0.0176\) |
|       |          |          |              |                | • ↑ RIPK2 \(P=0.0377\), ↑ ALOX15 \(P=0.0493\) |
| 11    | de Batlle J, et al; 2010 | Spain | Cross-sectional | - | • Spirometry |
|       |          |          |              |                | • ↑ FEV1/FVC with omega-3 intake \(P=0.045\) |
|       |          |          |              |                | • ↑ TNF-\(\alpha\) level in omega-3 intake \(P=0.049\) |
|       |          |          |              |                | • ↓ NF-\(\kappa\) DNA-binding pro-inflammatory cytokines in omega-3 intake |
| 12    | Sugawara K, et al; 2010 | Akita, Japan | Randomized Controlled Trial | Nutritional drink of omega-3 PUFAs 0.6 g and vitamin A 248 mg for 12 weeks combined with low-intensity exercise or PLACEBO | • Spirometry |
|       |          |          |              |                | • No effect on FEV1 and FVC |
|       |          |          |              |                | • ↑ body weight \(P=0.0015\), fat-free mass \(P=0.0159\) in nutrition |
|       |          |          |              |                | • ↑ HRQoL using CRQ |
|       |          |          |              |                | • ↑ CRQ (dyspnea domain) in nutrition |
|       |          |          |              |                | • ↑ CRQ (dyspnea domain) in nutrition |
|       |          |          |              |                | • ↓ hsCRP \(P=0.0035\), IL-6 \(P=0.0173\), IL-8 \(P=0.0005\), TNF-\(\alpha\) \(P=0.0037\) in nutrition |

6MWD, 6-Minute Walking Distance; ALOX15, Arachidonate 15-Lipoxygenase; BMI, Body Mass Index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CET, Cycle Endurance Time; CRP, C Reactive Protein; CRQ, Chronic Respiratory Questionnaire; CXCL10, C-X-C Motif Cytokine 10; EQ-5D, European Quality of Life-5 Dimensions; FEV1, Forced Expiratory Volume in 1 s; FM, Fat Mass; FVC, Forced Vital Capacity; HRQoL, Health-Related Quality of Life; HADS, Hospital Anxiety and Depression Scale; hsCRP, High Sensitivity C-Reactive Protein; IL, Interleukin; IMS, Inspiratory Muscle Strength; LBM, Lean Body Mass; LSC, Lovelace Smokers Cohort; LTB4R, Leukotriene B4 Receptor; NF-\(\kappa\)B, Nuclear Factor-\(\kappa\)B; ONS, Oral Nutritional Supplementation; PAL, Physical Activity Level; PI\(\text{max}\), Maximal Inspiratory Pressure; QMS, Quadriceps Muscle Strength; REE, Resting Energy Expenditure; RIPK2, Receptor-Interacting Serine/Threonine-Protein Kinase; SGRQ, Saint George's Respiratory Questionnaire; SMI, Skeletal Muscle Mass Index; SMM, Skeletal Muscle Mass; TMN, Targeted Medical Nutrition; TNF-\(\alpha\), Tumor Necrosis Factor-\(\alpha\); VSC, Veteran Smokers Cohort; WCC, Waist and Calf Circumference.
evidence that confirms a positive relationship.

Role in Body Composition
Nutritional depletion and alteration in body composition are prevalent in patients suffering from COPD as a consequence of systemic inflammation that results in a reduction of muscle mass and body weight. These alterations have been linked to lower exercise capacity, distorted metabolic functions, and impaired nutritional intake. Furthermore, Fat-Free Mass (FFM) loss affects respiratory and peripheral muscle function. Progressively, these may lead to cachexia and sarcopenia. Assessment is based on Body Mass Index (BMI) and Fat-Free Mass Index (FFMI); depletion is classified as BMI ≤21, and FFMI ≤15 in females or ≤16 in males.

Three randomized controlled trials by van Beers, van de Bool, and Sugawara show improvements in body weight, muscle mass, and fat mass after omega-3 supplementation. In a similar study by Calder, fat mass increase was noticed, although the BMI increase was not significant. Further evidence is found in a meta-analysis by Ferreira, which concludes that nutritional intervention stimulates weight and FFM gain, especially when integrated with exercise programs in undernourished patients.

Role in Exercise Capacity
Skeletal muscle dysfunction is one of the extrapulmonary manifestations of COPD. It involves a decline in airway quality, loss of elastic recoil, larger ventilatory dead space, and inefficient gas exchange, which lead to ventilatory limitation, increased pressure during tidal breathing, dyspnea, dynamic hyperinflation, muscular metabolic changes, as well as inflammation, which lead to poor oxidative capacity and peripheral muscle fatigue. Consequently, exercise performance is a critical parameter that allows the prediction of functional impairment and risk of death among COPD patients.

Thus, exercise tolerance enhancement is so important that it is currently stated as one of COPD treatment goals. Relevance of omega-3 in exercise tolerance is seen as they act as natural ligands of peroxisome proliferator-activated receptors (PPARs) and PPAR-gamma coactivators (PGC)-1α, which regulate skeletal muscle morphology and oxidative metabolism.

Various measuring tools are used as determinants of long-term omega-3 impact on exercise limitation in COPD. These include Quadriceps Muscle Strength (QMS), Cycle Ergometer Training (CET), Physical Activity Levels (PAL), 6-Minute Walking Distance (6MWD), Inspiratory Muscle Strength (IMS), and Maximal Inspiratory Pressure (PImax). Studies by van Beers and van de Bool showed improved QMS scores, which are evaluated using dynamometry. PAL was also increased, measured with the number of steps per day using a tri-axial GT3X Actigraph. Data also showed higher CET scores, indicating exercise capacity improvement. Based on a study by Calder, reduction in exercise-induced muscle fatigue and dyspnea in the omega-3 group were confirmed with
improvement in 6MWD and Borg scale scores. Additionally, IMS increase was demonstrated in a randomized controlled trial by van de Bool. In another trial by Sugawara, PImax value was increased, reflecting better IMS, as well as higher QMS score in COPD patients that received omega-3 supplementation.

Role in HRQoL
COPD is a chronic condition that could severely impact HRQoL. Hence, patient-centered outcomes are necessary for assessing the effectiveness of treatment across multiple dimensions of life, including mental state, pain/discomfort, physical function, mobility, symptoms, and daily activities. These are assessed through extensive questionnaires, such as the European Quality of Life-5 Dimensions (EQ-5D), Hospital Anxiety and Depression Scale (HADS), Clinical COPD Questionnaire Score (CCQ), Saint George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and Chronic Respiratory Questionnaire (CRQ).

Based on a randomized clinical trial by van Beers, reduction in the EQ-5D score, which evaluates most of the stated dimensions, was found in the placebo but not in the omega-3 group, implying that COPD progression is halted. Focusing more on mental status, anxiety, and depression, evaluated by HADS, were reduced in the omega-3 group. Meanwhile, Lemoine showed lower CCQ and CAT scores, which imply fewer COPD-specific symptoms, such as sputum production, wheezing, dyspnea, fatigue, physical activity intolerance, and sleep disturbances. Furthermore, the SGRQ score was also reduced, which measures non-specific respiratory symptoms and physical activity disturbances. Calder showed an increased activity subdomain in the SGRQ, although CCQ and CAT scores were not much different. In another study by Sugawara, there was an improvement in the CRQ score, especially in the dyspnea domain. Above all, data obtained from all studies show improved HRQoL with the lessening of symptoms, exacerbation, and presence of comorbidities in the group with omega-3 supplementation.

Role in COPD exacerbation
During the course of the disease, acute periods of deterioration or worsening of COPD symptoms may occur; these are termed Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD). Exacerbation manifestations vary among individuals; most commonly these include shortness of breath, intensified cough, chest tightness, wheezing, increased pulmonary volume, and purulence. Non-specific symptoms, such as fatigue and general malaise, are also common. Recurrent exacerbations are significantly correlated with poor health, faster lung decline, higher morbidity, and raised mortality; therefore, it is a major concern. Lemoine showed that omega-3 intake was associated with fewer exacerbations, less COPD morbidity, and a trend towards higher lung function. Similarly, a randomized controlled trial by Calder found that the omega-3 group experienced less frequent exacerbations. It
is hence proven that omega-3 is beneficial in lessening AECOPD occurrences.

Safety
Safety endpoints measured in the studies generally concluded that omega-3 supplementation implicates no significant deteriorative effect on health. Calder\textsuperscript{18} showed that diarrhea was likely to occur; nonetheless, this was insignificant and well-tolerated, noting that the control group has more diarrhea than the one with omega-3. Blood pressure in the omega-3 group was more likely to decrease than the placebo group, but not up to the point of hypotension. Heart rates were equivalent across groups, showing no associated risks. The outcomes of physical examination, laboratory safety assessment, and adjunct medications also did not vary between groups. Additionally, habitual dietary intake did not change after supplementation; the risk of malnutrition after omega-3 supplementation is hence minimal.

Study strengths & limitations
Studies included in this review viewed the disease from many standpoints such that almost all aspects are holistically evaluated. Omega-3 as a nutritional therapy plays a pivotal role in COPD management with proven efficacy and minimal adverse risk. However, there are still limited studies performed regarding this topic and the effect on lung function was still inconclusive. This calls for further trials involving larger samples to establish stronger evidence on lung function specifically. More studies are also needed to gain a more in-depth understanding of the biomolecular mechanism on how omega-3 can slow down COPD progression and affect exercise capacity, body composition, as well as the quality of life.

Application and cost-effectiveness
As our review reflects generally positive results in various aspects of COPD-related health status, omega-3 can be proposed as a possible adjunct therapy, although further studies are needed to implement it in established COPD management guidelines. Omega-3 supplementation in clinical practice is considered cost-effective, noting that sources are mainly from fish which are prevalent in many areas.

Conclusion and Recommendation
Based on the studies included in this review, we found that omega-3 supplementation exhibits good potential as an adjunct therapy to be used together with pharmacological treatment and smoking cessation in slowing down COPD progression. Clinical trials along with cross-sectional, cohort, and pilot studies showed that omega-3 lowers inflammation and nutritional depletion, indicated by reduced pro-inflammatory biomarkers, including TNF-\(\alpha\), IL-6, and IL-8, as well as increased body weight and muscle mass. Exercise capacity and HRQoL generally improved, while exacerbations are lessened in the patients receiving omega-3 supplementation. However, no significant enhancement in lung function was found, probably because of the study designs. Diarrhea is considered to be a potential
adverse effect of omega-3 supplementation; however, it is tolerable and insignificant.

As there is still limited information available regarding the potential protective mechanisms of omega-3 consumption in COPD management, the authors recommend for more studies to be conducted in the future, especially clinical trials with a higher number of participants and investigation of even more specific roles in COPD pathophysiology. We hope that the results concluded could become a basis for further studies regarding adjunctive therapy to increase the efficacy of COPD management.

Conflict of Interest
The authors declare no conflict of interest.

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