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THE EFFECTS OF KRILL OIL CONTENT ON ASTHMA

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ABSTRACT

Asthma is a lung disease that is increasing in the number of patients and whose severity is difficult to control. Various single antioxidants have been studied to reduce the severity and period of asthma exacerbations but the appropriate intervention compound has yet to be found. Krill oil contains various kinds of antioxidant compounds at high levels. Objective: To explain the effect of the antioxidant compounds in krill oil on asthma. Research Methods: Several journals and articles examined the effects of each antioxidant compound in krill oil on asthma. Results: several studies have shown that the effects of antioxidant compounds in krill oil can reduce inflammation and exacerbations of asthma. Conclusion: Biomolecular research is needed to determine the levels of antioxidant compounds in krill oil considering that the composition of krill oil can easily change due to various factors.

KEYWORDS *Asthma, Krill Oil, Antioxidant*

INTRODUCTION

Asthma is a global health problem as it affects 235 million people in various countries. Asthma is a chronic non-communicable lung disease with episodic or persistent respiratory symptoms and airflow limitation caused by bronchoconstriction and increased mucus with complaints of shortness of breath, wheezing, chest tightness, coughing (Papi et al., 2020). Asthma is influenced by host (immune) and environmental factors (allergens, pollution and others). These factors will trigger the appearance of asthma symptoms which correlate with increased oxidative stress in the body, especially the lungs. This oxidative stress will cause injury to cells and organs and the body's response to relieve symptoms.

The imbalance between lung cell injury due to oxidants and tissue resolution due to chronic inflammation characterizes the lung remodeling process in asthma.

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This can be inhibited by antioxidants (Abreu et al., 2018). Various antioxidants have been shown to reduce the degree of exacerbation and severity of asthma. Krill oil is rich in antioxidants. Krill oil has been shown to reduce inflammation in several diseases associated with chronic inflammation but there are also studies that prove krill oil is less beneficial in asthma (Xie et al., 2019).

This contradicts a 2023 study that found supplementation of omega-3 fatty acids, vitamin C and Zn either singly or in combination can reduce bronchial asthma severity in mild and moderate bronchial asthma patients. All of these compounds are included in the krill oil content (Barua et al., 2023).

RESEARCH METHOD

Information processing from several research journals and scientific articles collected online with publication years between 2014-2023 that describe and examine asthma disease and krill oil content that is antioxidant. Information was obtained from international (Google Scholar, PubMed, Semantic Scholar) online searches.

RESULT AND DISCUSSION

Asthma

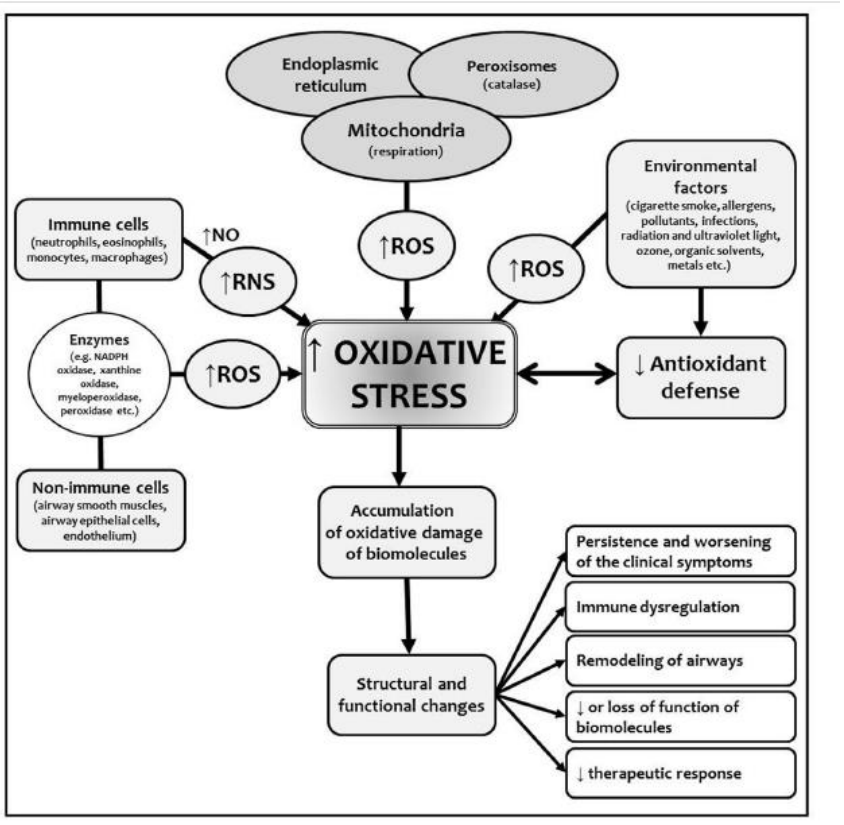
Asthma is an immune-mediated disease characterized by chronic lung inflammation and airway hyperresponsiveness. Many studies have addressed the pathophysiology of asthma and its complications but there are still no compounds that can be used for interventions capable of reversing airway remodeling (Abreu et al., 2018).

Several asthma phenotypes are categorized based on the precipitant (e.g. allergen-induced asthma, non-allergic asthma, infection-aggravated asthma, exercise-induced asthma) (Jesenak et al., 2017).

Inflammation in asthma is mediated by granulocyte effector cells such as neutrophils and eosinophils (Robb *et al.*, 2016). This determines the endotype of asthma which is categorized into type 2 and non-type 2. Type 2 is the activation of the type 2 immune response involved in the pathogenesis of allergy which is the release of specific proinflammatory cytokines and the final mediators of the inflammatory process are eosinophilic granulocytes. Non-type 2 is a type 1 immune response that acts to recognize various trigger factors (pollutants, smoke, viruses, etc.) and neutrophil granulocytes as its main effectors (Soccio *et al.*, 2023). T helper type-2 (Th2) cell immune responses play a role in the pathogenesis of asthma and other atopic diseases. Elevated levels of Th2 cells trigger the release of cytokines interleukin (IL)-4, IL-5, IL-9 and IL-13, and an increase in eosinophils and immunoglobulin E (IgE) production. This triggers inflammatory mediators that cause typical asthma symptoms of bronchospasm, airway mucosal edema, and increased mucus secretion. These symptoms can be triggered by viruses, allergens, and exercise (Quirt et al., 2018). The severity or lightness of symptoms varies within the lungs and is either spontaneously reversible or must be treated with asthma medications, namely fast-acting bronchodilators/short-

acting beta-agonists (SABAs) to reduce airway bronchoconstriction and inhaled corticosteroids (ICS) to reduce inflammation. Several factors can cause frequent exacerbations and/or increased severity of asthma, namely viral infections (Rhinovirus is the most common virus) by decreasing the lung response to steroid drugs during the inflammatory process (Papi et al., 2020). Another factor is the increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) that will trigger oxidative stress and aggravate airway inflammation.

Endogenous sources of ROS are cells (phagocytes, activated eosinophils and neutrophils, monocytes, macrophages, airway epithelial cells, endothelium), cell organelles (mitochondria, peroxisomes, endoplasmic reticulum), enzymes (e.g. cytochrome P450, NADPH oxidase, nitric oxide synthase, xanthine oxidase) and others (e.g. metal ion reactions). Exogenous sources of ROS are pollutants (conventional and e-cigarette smoke), ultraviolet light, ionizing radiation, metals, drugs (chemotherapy) and others (Jesenak et al., 2017). Exposure to allergens or other asthma triggers (e.g. infection, pollutants, exercise) triggers inflammation accompanied by an increase in ROS/RNS. Oxidative damage plays a role in all asthma phenotypes because inflammation is the basis of the pathogenesis of all forms of asthma. Increased ROS and RNS and decreased antioxidants correlate with increased degrees of bronchial hyperreactivity and decreased lung function and decreased response to asthma medications (Jesenak et al., 2017).



(Jesenak *et al.*, 2017).

This will result in an increase in the dose of medication used to manage asthma symptoms. Patients with uncontrolled asthma with low-dose ICS are switched to medium-dose ICS+LABA to reduce the risk of exacerbations and improve lung function (Cividini *et al.*, 2023).

Asthma arises as an inflammatory process in the lungs but 50% of asthma patients are also triggered by comorbidities such as obesity and oxidative stress associated with infection (Wenzel, 2016). Asthma sufferers also have other atopic disorders, for example allergic rhinitis, so it is believed that asthma is one of the signs of a systemic disease so that treatment or therapy for asthma is also applied systemically and locally (Papi *et al.*, 2020). Some studies show serum total antioxidant levels in asthmatics are lower compared to healthy controls and the addition of antioxidants (zinc, selenium, vitamin D, coenzyme Q10) correlates with a decrease in airway inflammation, namely a decrease in fractional exhaled nitric oxide (FENO) (Jesenak *et al.*, 2017).

Dietary patterns also reduce the risk of asthma both during prenatal, natal, childhood and adulthood. Diets containing fish or fish oil, higher levels of vitamin E and zinc during prenatal periods have a reduced risk of asthma in young children (Quirt et al., 2018).

Krill oil

Krill oil contains many antioxidant compounds namely omega 3 (EPA, DHA), omega 6, PL, flavonoids, vitamin A, vitamin E and astaxanthin {(Xie et al., 2019), (Tessitore, 2017)}. Lipid mediators of omega 3 and omega 6 polyunsaturated fatty acids play a role in bronchoconstriction symptoms, airway inflammation, and the recovery process in asthma (Fussbroich *et al.*, 2020).

A 2019 study found that omega-3 and omega-6 intake is associated with pediatric asthma morbidity and may alter the asthma response to indoor particulate matter (PM) i.e. increasing omega-3 intake and reducing omega-6 intake may reduce asthma morbidity. Omega-3 fatty acids are precursors of resolvins, protectins, and maresins where these molecules regulate neutrophil infiltration, coordinate the clearance of apoptotic neutrophils by macrophages, and adjust the production of cytokines that promote inflammatory resolution whereas omega-6 fatty acids play a more complex role as precursors of proinflammatory mediators. (Brigham *et al.*, 2019).

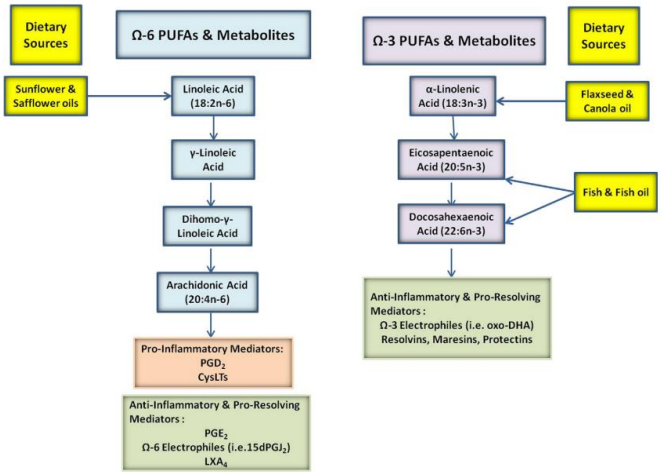


FIG 1. Lipid mediators derived from omega-6 (Ω-6) and omega-3 (Ω-3) fatty acids.

(Wenzel, 2016)

Omega 3 fatty acids (Eicosapentaenoic acid /EPA and Docosahexanoic acid /DHA in krill oil have been found to have pharmacological effects in cardiovascular, neurological and inflammatory process diseases. Omega 3 (Eicosapentaenoic acid /EPA and Docosahexanoic acid /DHA) are natural PPAR ligands that can activate peroxisome proliferator-activated receptors / PPAR. Peroxisome proliferator-activated receptors form heterodimers with retinoic receptor-X whose ligand is represented by cis-9-retinoic acid (Colleti et al., 2021).

All PPAR isoforms are mainly expressed in lung epithelium, endothelium, dendritic cells, eosinophils, fibroblasts and macrophages and play a role in bronchopulmonary homeostasis. Disruption of PPAR regulation may be a triggering factor in asthma pathogenesis (Kytikova *et al.*, 2020).

The isomeric form of PPARγ controls the release of proinflammatory mediators and enhances anti-inflammatory effects. PPARγ activation occurs in the cell and the uptake of EPA and DHA is due to the expression of FAT/CD36 (fatty acid translocase/cluster of differentiation 36) and even PPARγ also regulates the expression of FAT/CD36. This suggests that omega 3 fatty acids can increase their own uptake in fat tissue and are able to activate PPAR through non-covalent interactions, promoting a reduction in the inflammatory response, namely a decrease in TNFα and IL-6 release after lipopolysaccharide stimulation (Colleti et al., 2021).

The anti-inflammatory effects of omega-3 fatty acids may improve lung function and reduce the severity of bronchial asthma (Barua *et al.*, 2023). Nuclear factor (NF)-kappaB (NF-κB) plays an important role in inflammation by regulating cell expression and cytokine activity in the airway (Schuliga, 2015).

Table 1. Inflammatory genes regulated by NF-κB in airway cells types.

Cell Type	Genes
Lymphocytes (Th1/Th2)	Eotaxin-1, regulated and activation normal T cell expressed and secreted (RANTES), Th1 [interferon (IFN)-gamma and interleukin (IL)-2], Th2 [IL-4, IL-5 and IL-13] [46]
Eosinophils	TNF-α, IL-8, intercellular adhesion molecule (ICAM)-1 and leukocyte function-associated antigen-1 (LFA-1) [47,48]
Neutrophils	IL-8, granulocyte macrophage-colony-stimulating factor (GM-CSF), IL-1Ra [49]
Macrophages	Monocyte chemotactic protein-1 (MCP-1), IL-8 and growth-regulated oncogene-α (GROα) [50,51]
Epithelial cells	Thymic stromal lymphopoietin (TSLP), ICAM-1, vascular adhesion molecule (VCAM)-1, IL-8, IL-6, GM-CSF, chemokine (C-X-C motif) ligand (CXCL)1, RANTES, GROα, MCP-1, eotaxin-1 and MUC5AC [52–55]
Smooth muscle	TSLP, CD38, VCAM-1, ICAM-1, cyclooxygenase-2, IL-6, IL-8, CXCL10 (a chemoattractant for mast cells), GM-CSF, RANTES, MCP-1, GROα, neutrophil-activating protein-2 (NAP-2) and epithelial neutrophil activating peptide 78 (ENA-78) [56–63]

(Schuliga, 2015)

Nuclear factor (NF)-kappaB is activated by external stimuli such as UV radiation, endotoxins, oxidative stress, saturated fatty acids. Omega 3 (EPA and DHA) can reduce pro-inflammatory cytokines (TNFα, IL-1, IL-6, IL-8, and IL-12 and decrease the transcription of enzymes that trigger the inflammatory process (NO synthase and COX-2) by activating PPAR thus preventing the translocation of NF-κB into the nucleus and inducing the expression of anti-inflammatory cytokine IL-10 in a PPAR-dependent manner (Colleti et al., 2021).

Docosahexaenoic acid (DHA) is metabolized by lipoxygenase, cyclooxygenase, and epoxygenase enzymes into various specialized pro-resolving mediators (resolvins and maresins) that act as anti-inflammatory and pro-resolving mediators, reducing inflammation in the lungs (Dominguez et al., 2020). Resolvins exert anti-inflammatory and cytoprotective effects by activating Nrf2 (leading to the induction of various protective enzyme effects), decreasing NF-kappaB activation (reduced pro-inflammatory cytokine production), and inhibiting neutrophil influx (McCarty, 2016). Eliaçik et al.'s 2014 study found the importance of an EPA:DHA ratio of at least 1, but less than 2.5, showed significant results in reducing inflammation through BALF neutrophil markers and a decrease in mean basement membrane thickness (Hardy *et al.*, 2016).

The concentrations of EPA and DHA in krill oil are comparable to other fish oils but most of the EPA and DHA in krill oil are associated with PL whereas EPA and DHA in fish oil are associated with TAG. This contributes to the higher bioavailability of krill oil compared to fish oil as a source of EPA and DHA (Xie et al., 2019). The main phospholipid in krill oil is phosphatidylcholine, with 40% of the total fatty acids bound to phosphatidylcholine being eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Colleti et al., 2021).

Flavonoids comprise a diverse group of polyphenols and have functions as anti-oxidants, antibacterials, immunomodulators, anticancer, and anti-inflammatories. New flavonoid compounds were detected in krill oil that have a structure similar to 6,8-di-C-glucosyl luteolin and Sampalis' 2013 study proved that these compounds provide skin protection effects against the dangers of ultraviolet B (UVB) radiation and improvement of dyslexia and abnormal motor functions. Research shows that C-glycosylation at certain positions of flavonoids increases their antioxidant ability (Xie et al., 2019).

Vitamin A and vitamin E are fat-soluble vitamins known for their antioxidant effects. Vitamin E in krill oil is mostly (90%) in the form of α-tocopherol which is 14.74 to 63.0 mg/100 g oil. Tocopherol has antioxidant ability and synergistic effect with other bioactive components in krill oil. Another fat-soluble vitamin in krill oil is vitamin A with concentrations ranging from 16.40 to 28.55 mg per 100 g of krill oil. The vitamin A content in krill oil is higher than in fish oil (Xie et al., 2019).

Astaxanthin is a carotenoid that has strong antioxidant abilities. Astaxanthin as an antioxidant is 10 times stronger than other carotenoids such as zeaxanthin, lutein, canthaxantin, and β-carotene, 100 times stronger than α-tocopherol (Xie et al., 2019), and 550 times stronger than vitamin C (Tessitore, 2017). The amount of astaxanthin in krill oil ranges from 40 to 5000 mg/kg {(Xie et al., 2019), (Colleti et al., 2021)}. Astaxanthin reduces oxidative stress by inducing Nrf2-ARE-mediated antioxidant enzymes in various in vitro models. Nrf-2 is one of the transcription factors whose activation has the effect of increasing the production of direct antioxidant molecules and hyper-activation of antioxidant enzymes SOD, CAT, and GPX (Colleti et al., 2021).

Krill also contains minerals that can act as antioxidants, namely zinc and selenium but in small amounts (Colleti et al., 2021). Krill oil has been shown to reduce inflammation in several diseases associated with chronic inflammation such as inflammatory bowel disease, but there are studies with contradictory results, namely the lack of effect of krill oil on asthma even though asthma is included in lung diseases with chronic inflammation. (Xie *et al.*, 2019).

The following is a table of studies that contain the effects of krill oil and the content of krill oil (omega 3) on diseases due to inflammatory processes, especially in the lung organs.

Author / Years	Title	DOI	Objective	Method	Results
Vincenzo Tessitore 2017 (Tessitore, 2017)	The effects of krill oil administration on Inflammatory Bowel Diseases (IBDs): a promising new therapy	http://dx.doi.org/10.23751/pn.v19i3.6002	The use of krill oil reduces inflammation in IBD patients.	A trial conducted on 32 patients, given 3x1 capsules of 500 mg krill oil per day for 90 days.	25 out of 32 patients experienced a reduction in clinical symptoms and normalization of fecal calprotectin levels (a biomarker for intestinal inflammation).
Bomi Framroze*and Henriette Heggdal 2020 (Framroze and Heggdal, 2020)	An in vitro study to explore the modulation of eosinophil effector function in human allergic peripheral blood eosinophils using enzymatically extracted salmonid oil	http://dx.doi.org/10.31989/ffhd.v10i8.730	Comparison of prophylactic treatment using omega-3 fish oil, krill oil, and salmon oil fractions in a group of asthma patients resistant to steroid treatment (due to eosinophil dysfunction).	In vitro study measuring changes (i) in eosinophil shape in normal PMNL (ii) integrin upregulation in normal PMNL and (iii) eosinophil apoptosis in groups given omega-3 fish oil, krill oil, and salmon oil fractions.	Prophylactic treatment of human allergic peripheral blood eosinophils with 100 µg/ml salmon oil showed low modulation of eosinophil effector function. Krill oil and standard fish oil did not show low eosinophil modulation

Emily P. Brigham1 , Han Woo1 , Meredith McCormack1,2, Jessica Rice1 , Kirsten Koehler2 , Tristan Vulcain3 , Tianshi Wu1 , Abigail Koch1 , Sangita Sharma4 , Fariba Kolahdooz4 , Sonali Bose5 , Corrine Hanson6 , Karina Romero1 , Gregory Diette1,2, and Nadia N. Hansel1,2 2019 (Brigham *et al.*, 2019)	Omega-3 and Omega-6 Intake Modifies Asthma Severity and Response to Indoor Air Pollution in Children	http://dx.doi.org/10.1164/rccm.201808-1474OC.	To determine the relationship between omega-3 and omega-6 fatty acid intake and childhood asthma morbidity, and the relationship between fatty acid intake and indoor pollution strength, asthma symptoms related to PM, albuterol use, and systemic inflammation.	Analysis involved 135 children with asthma enrolled in the AsthmaDIET Study. At baseline, 3 months, and 6 months, data included: average weekly indoor home PM concentration <2.5 mm in aerodynamic diameter and PM <10 mm in aerodynamic diameter, omega-3 and omega-6 fatty acid food intake, daily symptoms, and peripheral blood leukocytes. Asthma severity and lung function were measured.	High omega-6 intake correlated with increased asthma severity (P = 0.02) and lower FEV1/FVC ratio (P = 0.01). High omega-3 intake correlated with reduced indoor PM <2.5 mm aerodynamic diameter effects on symptoms (P, 0.01), whereas high omega-6 intake correlated with enhanced indoor PM <2.5 mm aerodynamic diameter effects on symptoms and circulating neutrophil percentage (P, 0.01). Conclusion: Omega-3 and omega-6 intake is related to pediatric asthma morbidity and may modify asthma response to indoor PM.
Uttam Kumar Barua1, Pranab Karmaker2, Arup Kumar Saha3, Md. Merazul Mostofa4, Dilip Kumar Ghosh5, Kamal Krishna Biswas6* 2023 (Barua *et al.*, 2023)	The Effects of Omega-3 Fatty Acids Supplementation in Bronchial Asthma	https://doi.org/10.4236/jbm.2023.114015	Omega-3 fatty acids and combined supplementation significantly reduce bronchial asthma severity.	A randomized, double-blind, placebo-controlled study on 290 adults with mild to moderate persistent bronchial asthma given omega-3 fatty acid, vitamin C, and Zn supplementation and placebo. Subjective symptom improvement, lung function, and biochemical tests were conducted at baseline and end of therapy.	All supplements (omega-3 fatty acids, vitamin C, and Zn, and their combination) contributed more than placebo in reducing bronchial asthma severity. However, omega-3 fatty acids and combined supplements significantly improved symptoms (p <0.05). There was a significant improvement in lung function and sputum inflammatory markers with dietary supplementation (p <0.05). Thus, subjects with mild to moderate bronchial asthma can benefit from dietary supplementation containing omega-3 fatty acids, Zn, and vitamin C.

Chandrashekhar Kocherlakota a,* , Banda Nagaraju a , Narala Arjun a , Akula Srinath a , Kumar S. D. Kothapalli b,* , J. Thomas Brenna b 2022 (Kocherlakota *et al.*, 2022)	Inhalation of nebulized omega-3 fatty acids mitigate LPS-induced acute lung inflammation in rats: Implications for treatment of COPD and COVID-19	https://doi.org/10.1016/j.plefa.2022.102426	To determine if Omega 3 delivered via nebulized formulation reduces LPS-induced acute lung inflammation in male Wistar rats.	Inflammation was induced by intraperitoneal LPS injection once daily for 14 days. One hour post-injection, rats received nebulized treatment comprising O3 emulsified egg lecithin, Budesonide, and Montelukast, and a mix of O3 and Melatonin or Montelukast or Cannabidiol; O3 was free fatty acids for all groups except one with ethyl ester. Lung histology and cytokines were assessed in n = 3 rats per group on day 8 and day 15.	All groups had half or less severity of alveolar histiocytosis than the disease control (Cd) treated with LPS and saline inhalation. IL-6, TNF-α, TGF-β, and IL-10 were reduced in all O3FA groups. IL-1β was reduced in most but not all O3 groups. O3 given as ethyl ester was overall most effective in reducing LPS effects.
D. Fussbroich1,2,3, R. A. Colas4 , O. Eickmeier2 , J. Trischler2 , S. P. Jerkic2 , K. Zimmermann1 , A. Göpel1 , T. Schwenger1 , A. Schaible5 , D Henrich5 , P. Baer6 , S. Zielen2 , J. Dalli4,7, C. Beermann1 and R. Schubert2 2020 (Fussbroich *et al.*, 2020)	A combination of LCPUFA ameliorates airway inflammation in asthmatic mice by promoting pro-resolving effects and reducing adverse effects of EPA	https://doi.org/10.1038/s41385-019-0245-2	To compare the effects of dietary supplementation with LCPUFA combination or eicosapentaenoic acid (EPA) alone to investigate whether the combination has beneficial effects in asthmatic mice	Mice were sensitized with house dust mite (HDM) extract and then given a combination of LCPUFA or EPA alone in an asthma induction study. Airway hyperresponsiveness (AHR), bronchoalveolar lavage, and lung histochemistry were examined. Lipid mediator profiles were determined by liquid chromatography-tandem mass spectrometry (LC-MS-MS).	LCPUFA combination reduced AHR, eosinophilic inflammation, and inflammatory cytokines (IL-5, IFN-γ, and IL-6) in asthmatic mice, while EPA increased inflammation
Edward C. Dominguez 1 , Art J. Heires 2 , Jacqueline Pavlik 2 , Tricia D. Larsen 3 , Stephanie Guardado 1 , Joseph H. Sisson 2 , Michelle L. Baack 3,4 , Debra J.	A High Docosahexaenoic Acid Diet Alters the Lung Inflammatory Response to Acute Dust Exposure	http://dx.doi.org/10.3390/nu12082334	A high DHA diet modifies the dust-induced inflammatory response through increased production of specialized pro-resolving mediators (SPM).	Mice were pretreated with a DHA-rich diet for 4 weeks before intranasal exposure to a single dose of dust extract collected from concentrated swine feeding operations (HDE).	DHA-rich diet caused an increase in specialized pro-resolving mediators (SPM) production during acute dust-induced inflammation.

Romberger 2,5 and Tara M. Nordgren 1,2,*2020 (Dominguez *et al.*, 2020)					
Hongyun Zhao1,2, Yee Chan-Li1 , Samuel L Collins1 , Yuan Zhang3 , Robert W Hallowell1 , Wayne Mitzner2 and Maureen R Horton 2014 (Zhao *et al.*, 2014).	Pulmonary delivery of docosahexaenoic acid mitigates bleomycin-induced pulmonary fibrosis	http://www.biomedcentral.com/1471-2466/14/64	the therapeutic role of docosahexaenoic acid (DHA), an n-3 PUFA in pulmonary fibrosis.	Intratrhalal DHA was administered to the lungs of mice 4 days prior to intratraced bleomycin treatment. Weight and survival were monitored for 21 days. Bronchoalveolar fluid (BALF) and pulmonary inflammatory cells, cytokines, eicosanoids, histology and pulmonary function are determined on serial days (0, 3, 7, 14, 21) after bleomycin injury.	administration of DHA, an intratracheal single PUFA, protects mice from the development of bleomycin-induced lung inflammation and fibrosis. These results suggest that further investigation into the role of n-3 polyunsaturated fatty acids in fibrotic lung injury and repair is needed.
Leonardo Terranova1*, Patrizia Risé2 , Andrea Gramegna1,3, Christian Pinna2 , Carlo Agostoni4,5, Marie-Louise Syrén5 , Stefano Turolo6 , Paola Marchisio3,7, Francesco Amati8,9, Stefano Aliberti8,9, Angelo Sala2 and Francesco Blasi1,3 2022 (Terranova *et al.*, 2022)	Pro-resolving and pro-inflammatory fatty acid-derived mediators in sputum of stable state bronchiectasis patients	https://doi.org/10.1186/s12931-022-02301-5	Evaluating the metabolites of docosahexaenoic acid and arachidonic acid in sputum in adults with bronchiectasis determining their relationship with clinical data, bacterial counts and neutrophil elastase.	Observational and cross-sectional studies were conducted on the bronchiectasis program of the Policlinico Hospital in Milan, Italy, where patients were enrolled. Active neutrophil elastase was measured by enzyme-associated immunosorbent assays, pro-resolve and pro-inflammatory fatty acid-derived mediators were evaluated by mass spectrometry, and respiratory pathogens were assessed by real-time PCR. Analysis was carried out on the phlegm collected during the stable state and clinical data was also collected.	Levels of pro-inflammatory mediators derived from arachidonic acid metabolism showed a relationship with neutrophil elastases, comparable to the identification of Pseudomonas aeruginosa and with radiological results, while concentrations of pro-resolution mediators derived from docosahexaenoic acid were associated with a better improvement in health status, characterized by reduced markings in radiology, bacterial infections and the production of sputum volume.
Haiyan Tong1 , Siqi Zhang2 , Wan Shen3,4, Hao Chen3 , Claudia Salazar1	Lung Function and Short-Term Ambient Air Pollution Exposure Differential Impacts of	http://dx.doi.org/10.1513/AnnalsATS.202107-767OC	Evaluating whether n-3 FA intake and polyunsaturated omega 6 (n-6) FA levels in the blood may modulate the association between	Sixty-two healthy adults were put into either high or low n-3 FA groups based on n-3 FA intake and erythrocyte n-3 FA concentrations. The low and high n-6 FA groups	The lag-dependent relationship between short-term ambient air pollutants and lung function modulated differently by n-3 and n-6 FA, suggests that n-3

, Alexandra Schneider2 , Ana G. Rappold1 , David Diaz-Sanchez1 , Robert B. Devlin1 , and James M. Samet 2021 (Tong *et al.*, 2022)	Omega-3 and Omega-6 Fatty Acids		respiratory effects and short-term exposure to ambient air pollution in healthy adults.	dichotomized based on blood n-6 FA levels. Participants underwent three to five testing sessions spaced at least 7 days apart. At each session, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and markers of plasma inflammation (IL-6 [interleukin-6]) and oxidative stress (ox-LDL [oxidized low-density lipoprotein)]) were measured.	and n-6 FA counteract the respiratory response to low levels of air pollution in healthy adults.
Johnatas D. Silva1† , Miquéias Lopes-Pacheco1,5† , Ligia L. de Castro1 , Jamil Z. Kitoko1 , Stefano A. Trivelin1 , Natália R. Amorim2 , Vera L. Capelozzi3 , Marcelo M. Morales4,5, Bianca Gutfilen6 , Sergio A. L. de Souza6 , Daniel J. Weiss7 , Bruno L. Diaz2† and Patricia R. M. Rocco 2019 (Silva *et al.*, 2019)	Eicosapentaenoic acid potentiates the therapeutic effects of adipose tissuederived mesenchymal stromal cells on lung and distal organ injury in experimental sepsis	https://doi.org/10.1186/s13287-019-1365-z	investigating whether preconditioning with eicosapentaenoic acid (EPA) would potentiate mesenchymal stromal cell expression in experimental sepsis by further reducing lung and distal organ injury, thereby improving survival.	In mice induced sepsis with cecal ligation and puncture (CLP); Falsely operated animals are used as controls. Twenty-four hours after surgery, CLP mice were further randomized to receive saline, adipose tissue-derived MSCs (AD-unpreconditioned), or AD-MSCs preconditioned with EPA for 6 hours intravenously. After 24 hours, survival rate, sepsis severity score, pulmonary mechanics and histology, biomarker protein levels in lung tissue, cellularity in the blood, dystal organ damage, and MSC distribution (with technetium-99m marking) were analyzed.	Unconditioned and EPA-conditioned AD-MSCs showed similar viability and differentiation capacity, accumulating primarily in the lungs and kidneys after systemic administration. Compared with preconditioned AD-MSCs, AD-MSCs preconditioned by the EPA further reduced lung static elasticity, alveolar collapse, interstitial edema, alveolar septal inflammation, collagen fiber content, neutrophil cell count as well as levels of interleukin-1β protein and keratinocyte chemoattractants in the lungs. tissue abnormalities, and morphology in the heart (myocyte architecture of the heart), liver (hepatocyte mess and hyperplasia of Kupffer cells), kidneys (acute tubular necrosis), spleen (increased number of megakaryocytes and lymphocytes), and small intestine (disorganization of villi architecture). EPA preconditioning on MSCs results in

					increased secretion of pro-resolution and anti-inflammatory mediators (RvD1, PGE2, IL-10, and TGF-β).
Meng-Han Liu1†, An-Hsuan Lin1†, Shing-Hwa Lu2, Ruo-Yun Peng3, Tzong-Shyuan Lee1 * and Yu Ru Kou1 * 2014 (Liu *et al.*, 2014)	Eicosapentaenoic acid attenuates cigarette smoke-induced lung inflammation by inhibiting ROS-sensitive inflammatory signalling	https://doi.org/10.3389/fphys.2014.00440	examine whether the antioxidant and anti-inflammatory properties of eicosapentaenoic acid (EPA) have a beneficial effect on lung inflammation caused by cigarette smoke	The murine model was exposed to subchronic CS for 4 weeks leading to pulmonary inflammatory infiltration (total cell count in bronchoalveolar lavage fluid (BALF), an increase of 11.0-fold), an increase in pulmonary vascular permeability (protein levels in BALF, a 3.1-fold increase).), increased levels of chemokines (11.4–38.2-fold increase) and malondialdehyde (a marker of oxidative stress; 2.0-fold increase) in the lungs, as well as lung inflammation; all events caused by CS are suppressed with daily EPA supplementation	EPA's novel role in reducing oxidative stress and lung inflammation caused by subchronic CS exposure in vivo and in suppressing CSE-induced IL-8 in vitro through its antioxidant function and by inhibiting MAPKs/NF-κB signaling.
Soraia Carvalho Abreu1,2†, Miquéias Lopes-Pacheco1,3†, Adriana Lopes da Silva1†, Debora Gonçalves Xisto1 , Tainá Batista de Oliveira1 , Jamil Zola Kitoko1,4, Lígia Lins de Castro1 , Natália Recardo Amorim5 , Vanessa Martins 1 , Luisa H. A. Silva1 , Cassiano Felippe Gonçalves-de-	Eicosapentaenoic Acid Enhances the Effects of Mesenchymal Stromal Cell Therapy in Experimental Allergic Asthma	https://doi.org/10.3389/fimmu.2018.01147	investigated whether pre-treatment with eicosapentaenoic acid (EPA) potentiates the therapeutic properties of MSCs in experimental allergic asthma.	Seventy-two C57BL/6 mice were used. House dust mite extract (HDM) is administered intranasal to induce severe allergic asthma in mice. Unstimulated or EPA-stimulated MSCs are administered intratracally 24 hours after the final HDM challenge. Pulmonary mechanics, histology, biomarker protein levels, and cellular in bronchoalveolar lavage fluid (BALF), thymus, lymph nodes, and bone marrow were analyzed. The effects of EPA on the formation of lipids and the secretion of resolvin-D1 (RvD1), prostaglandin E2 (PGE2), interleukin (IL)-10, and transforming	EPA amplifies MSC-based therapy in experimental allergic asthma, which leads to increased secretion of pro-resolution and anti-inflammatory mediators (RvD1, PGE2, IL-10, and TGF-β), modulation of macrophages towards anti-inflammatory. phenotype, and reduction in the remodeling process.

Albuquerque6,7 , Hugo Caire de Castro Faria-Neto7 , Priscilla Christina Olsen4 , Daniel Jay Weiss 2 , Marcelo Marcos Morales 3,8, Bruno Lourenço Diaz 5‡ and Patricia Rieken Macêdo Rocco 2018 (Abreu *et al.*, 2018)				growth factor (TGF)-β1 by MSCs were evaluated in vitro.	
Arzu Ulua ,1 , Abigail Burr a ,1 , Art J. Heires b , Jacqueline Pavlik b , Tricia Larsenc , Pedro A. Perez ,Carissa Bravoa , Nicholas V. DiPatrizioa , Michelle Baackc,d, Debra J. Romberger e,b , Tara M. Nordgrena,b,∗ 2021 (Ulu *et al.*, 2021)	A high docosahexaenoic acid diet alters lung inflammation and recovery following repetitive exposure to aqueous organic dust extracts	https://doi.org/10.1016/j.jnutbio.2021.108797	evaluating the role of DHA in modifying airway inflammation in murine models	Murin was subjected to repeated exposure to aqueous extracts from agricultural dust (three-week exposure to pigsty/HDE dust extracts) and after a one-week solution/recovery period, levels of resolvin and cells in bronchoalveolar lavage fluid (BALF), TNFα, plasma endocannabinoid levels and related lipid mediators were measured.	Mice fed a diet high in DHA significantly increased levels of DHA-derived resolvin in bronchoalveolar lavage fluid (BALF) and decreased TNFα along with changes in plasma endocannabinoid levels and related lipid mediators. After one week of recovery, there was a significant decrease in BALF cellulity and cytokine/chemokine release along with an increase in BALF's amphiregulin and resolvin in DHA-fed mice compared to control diet-fed mice exposed to HDE.

The usefulness of krill oil content is also supported by a 2023 study that found supplementation of omega-3 fatty acids, vitamin C and Zn either singly or in combination can reduce bronchial asthma severity in mild and moderate bronchial asthma patients (Barua et al., 2023).

Krill oil has been approved by various countries and the US Food and Drug Administration (FDA) as GRAS (Generally Recognized as Safe) and can even be consumed by pregnant and lactating women. Krill oil supplementation is well tolerated by the human body as it has minimal side effects of flatulence and diarrhea (Colletti *et al.*, 2021).

CONCLUSION

This literature review aims to determine the effectiveness of antioxidant compounds in krill oil on the development of asthma. Krill oil, which is rich in antioxidant compounds, can be used as supplementation in addition to asthma medications (corticosteroids and SABA) to manage asthma symptoms and exacerbations. Several studies have shown that the levels of compounds in krill oil can differ in concentration depending on storage conditions, transportation processes, and pretreatment methods of raw materials as well as seasonal variations, environmental changes, krill breeding sites and sexual maturity of krill samples. More extensive biomolecular research is needed to determine the effect of krill oil compounds given the easy changes in the composition of krill oil despite its high antioxidant effect.

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