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MINI-REVIEW

Calanus oil in the treatment of obesity-related low-grade inflammation, insulin resistance, and atherosclerosis

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Abstract

Calanus oil (COil) is a natural product extracted from marine zooplankton *Calanus finmarchicus* found in the North Atlantic Ocean. This oil is rich in wax esters of polyunsaturated fatty acids (PUFAs) and has been projected as the best alternative to fish oil because its production cannot keep pace with the demands from the growing markets. The COil is the only commercially available marine source of wax esters, whereas classic ω-3 PUFAs comes from triglycerides, ethyl esters, and phospholipids. It has, in recent decades, been seen that there is an unprecedented rise in the use of PUFA-rich oil in the aquaculture industry. A simultaneous rise in the demand of PUFAs is also observed in the health care industry, where PUFAs are suggested preventing various disorders related to lifestyles such as obesity, diabetes mellitus, chronic low-grade inflammation, atherosclerosis, and brain and cardiovascular disorders (CVDs). In this review, we will explore the metabolic aspects related to the use of COil as an antioxidant, anticholesterinemic, and anti-inflammatory dietary source and its impact on the prevention and therapy of obesity-related metabolic disorders.

Keywords Calanus oil · *Calanus finmarchicus* · Polyunsaturated fatty acid · Wax esters · Astaxanthin

Introduction

The health benefits of the consumption of seafood and marine lipids have a long time been known (Pedersen 2016). Marine animals are a great source for lipid-rich oil, with marine fishes being a common source for nutrient-rich oil till recently (Albert et al. 2016; Linder et al. 2010). The lipid-rich oil from fishes is commonly used in aquaculture, and the demand for lipid-rich oil is continuously increasing due to a thriving aquaculture industry across the globe (Abdelhamid et al. 2018). The use of fish oil in aquaculture as a feed source is very common as it contains a very high quantity of health-promoting ω-3 long-chain polyunsaturated fatty acids (φ-3 LC-PUFAs) (Turchini et al. 2010). However, fish oil production cannot keep up with the growing needs, which causes the necessity of search for promising natural materials, rich in lipids, containing ω-3 LC-PUFAs. Scientists investigate currently, as an alternative to fish oils, oil-seed plants and zooplankton to produce n-3 LC-PUFAs (Lee et al. 2019; Shanaida 2019; Venegas-Caleron et al. 2010). The ratio of ω-6/ω-3 essential fatty acids in natural oil-

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rich products is very important for the development of the human body (Simopoulos 2002). Besides their claimed potential in preventing metabolic syndrome, ω-3 PUFAs have been recently associated with cancer prevention (Aucoin et al. 2017; Fabian et al. 2015; Nabavi et al. 2015). There are very few reports about *Calanus* genus-derived PUFAs in the prevention of tumors, yet the current hypothesis is that ω3-PUFAs may be able to enhance the activity of chemopreventive drugs against cancer (Abel et al. 2014; D'Archivio et al. 2018). Probably, the fundamental key able to enable PUFAs in acting against tumors has to be retrieved in the PUFAs ability in counteracting inflammation (Marion-Letellier et al. 2015). A huge deal of literature reports, encompassing several cohorts from numerous countries and with different demographic features, cannot provide sound evidence to suggest a significant relationship between ω-3 fatty acids and cancer incidence, data are grossly scanted. According to most of these research studies, it appears that diet supplementation with ω-3 fatty acids is unlikely to prevent cancer fully. Despite this, many reviews, surveys, and experimental investigations on in vitro cell cultures and animals would suggest a significant preventive effect of ω3-PUFAs in counteracting carcinogenesis, particularly in some solid tumors such as breast, prostate, colon, and pancreas cancers.

Some authors reported yet that daily intake of ω3-PUFAs and an optimal ω3/ω6 PUFAs ration might ameliorate the prevention of chronic and inflammatory disease, particularly involving cardiovascular disease and cancer (Simopoulos 2008), although no optimal ratio was forward so far (Wang et al. 2004).

The positive effects on conditions like thrombosis, atherosclerosis, hypertriglyceridemia, hypertension, and autoimmune diseases were generally related to the long-chain PUFAs, although some controversial data were recently reported (Akbar et al. 2017; Das 2000; Ergas et al. 2002; Hande et al. 2019; Johnsen et al. 2018). FAO/WHO recommended the dietary panels for sufficient ω-3 fatty acids intake (FAO/WHO 2003).

Some authors have also suggested that the ability of ω3-PUFAs in dampening the risk of cancer is fundamentally due to their anti-inflammatory potential and inhibition of cell growth factors (Weylandt et al. 2015).

Briefly speaking, data relating cancer prevention and ω3 PUFAs intake are too scanty to fully elucidate the causative association between benefit and cancer reduction for diet-derived PUFAs, and therefore further insights are needed.

Although the consumption of these fatty acids is strongly advised, the daily intake is generally far below the suggested quantities (Calder 2015). Various dietary supplements, containing high amounts of PUFAs, are available on the market, such as cod liver oils, whole fish body oils, and plant products. Table 1 summarizes some of the very recent clinical outcomes of the use of ω3-PUFAs in the human dietary intake.

The future growth of the fish industry is highly dependent on the sustained and adequate supply of fish oil. Continuous extraction of fish oil from marine fishes is unsustainable due to an ever-increasing demand for these oil-rich fishes in the human diet. Research has shown that oils rich in ω-3 PUFAs, such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, reduce the risk of cardiovascular disorders. Beneficial effects of these oils have also been seen in weight management, treatment of dyslipidemia, hypertension, diabetes mellitus, chronic low-grade inflammation, and atherosclerosis (Crandell 2016; Garcia-Esquinas et al. 2019; Minihane et al. 2015; Turchini 2013; Turchini et al. 2010).

Zooplankton, such as copepods and krill, are the most numerous primary consumers of plankton in the marine environment (Grieve et al. 2017; Van Dinh et al. 2019). The copepod *Calanus finmarchicus* is spread in large amounts in the North Atlantic and has lipid-rich stages that can be harvested sustainably. Its oil can be used as a health-promoting nutraceutical. Recent publications indicate that oil from *C. finmarchicus* may have beneficial health effects (Höper et al. 2014; Tande et al. 2016).

These data present an opportunity to find out new sources of PUFA-rich oil from the marine ecosystem. In recent times, *C. finmarchicus,* a member of small crustaceans, has been presented as an alternative to marine fishes because of the presence of PUFA-rich oil in this zooplankton. *C. finmarchicus* acts as a critical link between the phytoplankton and other marine organisms present at the higher trophic levels in a marine food web. It is predominantly found in the North Atlantic Ocean and contains a very high quantity of long-chain ω-3 EPA and DHA (Pedersen et al. 2014). The oil extracted from *C. finmarchicus* is viscous owing to the presence of fatty acids in the wax ester form that comprises 80–90% of the oil composition. It has been observed that 20–30% fatty acids in these wax esters are long-chain fatty acids with a small number of phytosterols, antioxidants, glycerol, and free fatty acids (Pedersen et al. 2014; Salma et al. 2016). The consumption of ~250–500 mg EPA plus DHA per day lower the relative risk of mortality from coronary heart disease, and higher doses do not substantially further lower the risk (Mozaffarian and Rimm 2006). It was proved the ability of diet to positively modulate inflammation and associated health claims (Minihane et al. 2015).

The present review aims to summarize various health-promoting benefits of the COil extracted from *C. finmarchicus.*

Some insights on copepods' derived COil

C. finmarchicus, as a source of COil, is a widespread small marine crustacean constituting the major fraction of the zooplankton biomass presented in the North Atlantic Ocean (Pedersen 2016). It is a relatively small herbivorous

Table 1 Some very recent effects reported about ω3-PUFAs activity on human pathology

Source	Protocol	Actions	References
Marine ω3-PUFAs	Double-blind RCT	↓ Cardiometabolic risk in 108 Chinese hypertensive subjects	Yang et al. (2019)
Marine ω3-PUFAs, selenium, vitamins, calcium	multicenter 2 × 2 factorial randomized clinical	None Did not reduce depression and mood disorders in 1025 Caucasian patients	Bot et al. (2019)
Fish oil	RCT	None Did not reduce liver fat in 50 overweight men	Parker et al. (2019)
Fish oil	Double-blinded RCT	↑ Amelioration in the offspring growth and their BMI from 736 pregnant women	Vinding et al. (2018)
COil ω3-PUFAs	Observational study	None Eczema	Tande et al. (2016)
Marine and COil ω3-PUFAs	Multicenter RCT	↓ Aromatase inhibitors-induced arthralgia in 249 subjects with breast cancer	Shen et al. (2018)
Marine and COil ω3-PUFAs	RCT	↓ Liver steatosis in NAFLD from 20 patients	Spahis et al. (2018)
Infusion of 0.2 g/kg ω3-PUFAs	RCT	↑ Faster postoperative recovery in patients undergoing on-pump CABG in 57 patients.	Feguri et al. (2019)
Marine and COil ω3-PUFAs	RCT	↑ Cognitive decline in 50 subjects	Bowman et al. (2019)
Marine and COil ω3-PUFAs	RCT	↑ Improvement of inflammation, insulin resistance, glucose and lipid metabolism in 200 patients with impaired glucose regulation	Wang et al. (2019)
Marine and COil ω3-PUFAs	RCT	↓ Headaches and migraine in 74 subjects	Abdolahi et al. (2019)
Marine and COil ω3-PUFAs	RCT	↑ Survival in stage III colon cancer	Song et al. (2019)

crustacean, which is about 3–4 mm in size and has a life span of 1 year in boreal waters (Fig. 1).

All zooplanktons require lipids for reproduction, energy storage, and diapause. While triglycerides are an important lipid storage molecule in terrestrial organisms, wax esters are the primary lipid storage entity in the marine zooplankton living in the cold polar areas. While triglycerides fulfill the short-term energy needs of these zooplanktons, wax esters serve as a long-term energy source for these small organisms.

Wax esters are significant principles of the marine food chain since zooplankton is considered an important element of marine food webs (Cook et al. 2016; Höper et al. 2014; Lee et al. 1970).

Several methods can be applied to obtain oil from marine biomass, e.g., wet or dry rendering, hydrolysis, silage production, supercritical fluid extraction, and solvent extraction (Pedersen et al. 2014). Among these techniques, the wet rendering is applied in the most widely global manufacturing of fish and calanus oils (Bimbo 2012). The major technological stages comprise boiling, pressing, separation of the liquid phase with a further recovery of the oil, and drying of the residual protein matter. Boiling provides denaturation of the proteins and conditions for the extraction of the lipids by pressing method. The refining stage often occurs to make the edible fixed oil (Bimbo 2012).

The major active principles in the oil extracted from *C. finmarchicus* are exemplified by monoesters of LC-PUFA and fatty alcohols, namely wax esters. The calanus oil is also rich by the deep red carotenoid astaxanthin (ASX), which exhibits antioxidant effects (Davinelli et al. 2018; Zuluaga et al. 2018). The fatty acid residues of its wax esters contain

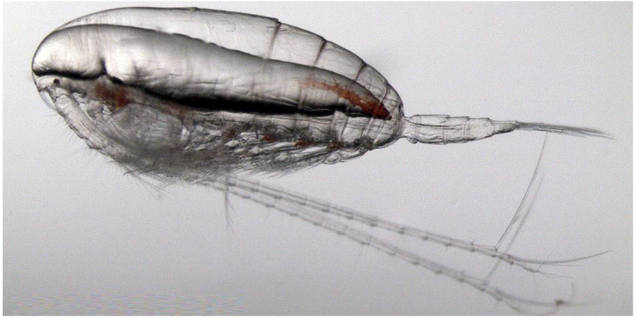

Fig. 1 Microphotograph of *Calanus finmarchicus* (Cameron Thompson, the University of Maine for courtesy)

high amounts of stearidonic acid (SDA), EPA and DHA, and also of monounsaturated fatty acids (Walker et al. 2013).

The structure of the characteristic wax ester of *C. finmarchicus* lipids, comprising fatty alcohol docosenol (22:1n-11) and PUFA, is shown in Fig. 2.

Substantial evidence shows that consumption and increased blood levels of the very LC ω-3 PUFAs (EPA, DHA, and α-linolenic acid) are associated with health benefits (Walker et al. 2013).

Triacylglycerols containing mainly the ω-3 fatty acids (Fig. 3) might reach up to 8.9% and phospholipids up to 10.3% of total lipids in COil (Pedersen et al. 2014).

Triglyceride esters of EPA and DHA are common in such animal dietary products, fish oil, and COil (Horrocks and Yeo 1999; Nakamura et al. 2014). DHA has an important impact on the growth and development of the infant's brain. The intake of DHA enhances learning skills, whereas its deficiency may lead to learning disability (Bazan 2005; Echeverria et al. 2017; Lo Van et al. 2016).

DHA and EPA have a positive effect on diseases such as hypertension, arthritis, atherosclerosis, and depression. Also, DHA is needed in adults to maintain a normal function of the brain (Cook et al. 2016; Rechenberg and Humphries 2013; Smith et al. 2018; van der Burg et al. 2019; Zehr and Walker 2018).

The intense red color of COil is due to high carotenoid astaxanthin content (Pedersen 2016). In zooplankton, ASX is the most commonly occurring carotenoid and may contribute to as much as 85–90% of the total pigment (Ambati et al. 2014; Davinelli et al. 2018). Copepods use β-carotene, obtained from phytoplankton, as a precursor for ASX synthesis (Andersson et al. 2003). The specific structure of the ASX molecule provides its ability to be esterified, higher antioxidative capacity, and a more polar configuration than other carotenoids (Guerin et al. 2003).

Thus, COil is the only commercially available marine source of wax esters, whereas classic ω-3s come as triglycerides, ethyl esters, and phospholipids. The wax esters in COil are slowly but completely digested and absorbed in the distal intestine, which permits interaction with GPR120 receptors (Im 2018; Karakula-Juchnowicz et al. 2017; Moniri 2016). The receptor interaction causes metabolic effects as well as reduction of the liver—and intra-abdominal—fat deposition and provides insulin sensitivity. Digestion of wax esters releases the unsaturated fatty acids in the colon and activates the GPR120 receptors in immune cells that secrete hormones, which controls the sugar and fat metabolism (O'Connell et al. 2017).

Of importance to be mentioned here is that the oil content of *C. finmarchicus* is regulated by the growth stage, location, and seasonal variations (Pedersen et al. 2014). The wax ester content is highest (88%) in *C. finmarchicus* during late autumn when the organism undergoes the feeding cycle and lowest (85% of the total lipids) during the winter season when the lipids are used as an energy source in gonad production (Kvile et al. 2016). Recent studies have reported that stage IV and stage V are the best developmental stages to extract the oil from *C. finmarchicus* as, during these stages, the lipids constitute as much as 60% of the total dry bodyweight of the organism (Bailey et al. 2012; Pedersen et al. 2014). The composition of wax esters varies between *Calanus* species (Graeve and Kattner 1992; Pedersen et al. 2014). For example, lipids of *C. hyperboreus* are predominantly di-unsaturated long-chain wax esters while the lipids of *C. finmarchicus* are rich in monounsaturated short-chain wax esters (Graeve and Kattner 1992).

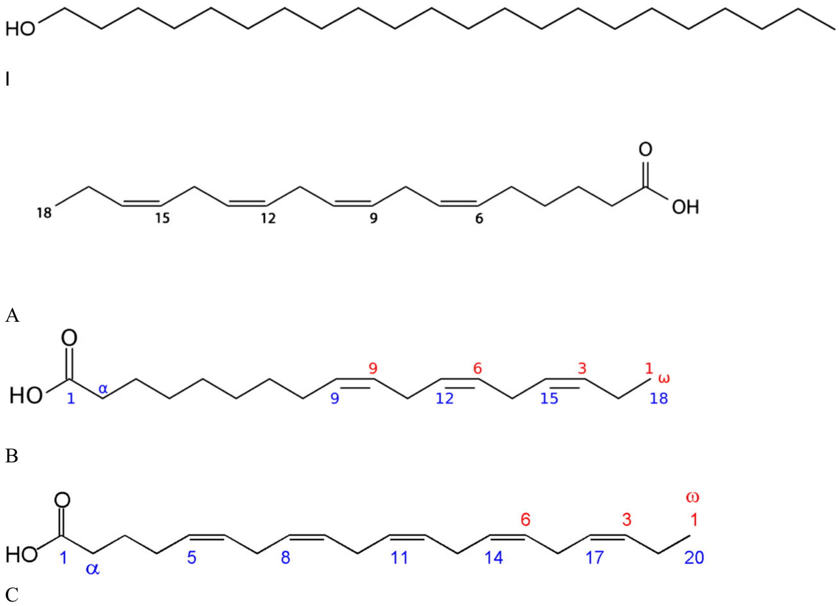

Fig. 2 Structural formulas of docosenol (1) and the PUFA (**a** stearidonic acid; **b** eicosapentaenoic acid; **c** docosahexaenoic acid) as a wax ester component of COil

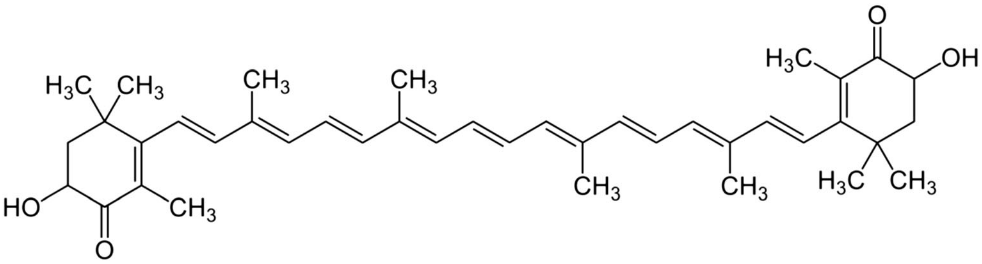

Fig. 3 The structural formula of carotenoid astaxanthin

The use of standardized proteolytic enzymes may improve the yield of COil extraction from *C. finmarchicus.* In one study, their content was higher in comparison with traditional technologies employed in fish oil extraction (Vang et al. 2013).

One more advantage of using small zooplanktons for the extraction of lipid-rich oil is the lower levels of persistent organic pollutants in these organisms. It is well-known that the concentration of persistent organic pollutants increases with higher trophic levels due to the phenomenon of biomagnification (Alava and Gobas 2012). The short life cycle of *C. finmarchicus* also contributes to the low degree of contamination by organic admixtures.

Since zooplanktons represent the lower trophic levels in a food chain, the concentration of these contaminants is significantly lower in the extracted oil comparatively to the cod feeding the various small fishes. Hence, the zooplanktons' oil does not require refining/purification steps to remove the contaminants (AMAP 2002; Pedersen et al. 2014). A majority of fatty alcohols in *C. finmarchicus* are monounsaturated with 20:1ω-9 and 22:1ω-11 constitutes up to 82% of the total fatty alcohols. In contrast, saturated alcohols constitute only 8–24% of the total fatty alcohols (Pedersen et al. 2014).

The COil in weight loss and metabolic syndrome

Obesity is a complex lipid metabolic disorder and represents currently one of the most serious global health issues since it has a negative impact on various systems in the human body. Overweight and obesity are of significant importance considering their global epidemic prevalence (over 300 million obese persons) and relatedness with type 2 diabetes, heart disease, osteoarthritis, certain forms of cancer, and some other ailments (Abdali et al. 2015; Patra et al. 2015).

The accumulation of visceral and subcutaneous fat is one of the distinguishing features of obesity that contributes to the development of cardiometabolic disorders. It has been assumed that various mechanisms, including disturbances in lipid metabolism and insulin resistance, activation of inflammatory mediators, endothelial dysfunction, and adipokine imbalance, are contributed to the development of both obesity and atherosclerosis (Lovren et al. 2015).

Obesity leads to an augmentation of excess calories in visceral fat and the allocation of high quantities of free fatty acids in different parts of the human body and can result in type 2 diabetes. Leptin, adiponectin, and cytokines altogether contribute to oxidative stress and low-grade inflammation, which occur in obesity (Abdali et al. 2015; Ellulu et al. 2017).

Dietary COil and administration of exenatide counteracted obesity-induced derangements of myocardial metabolism. COil also protected the heart from ischemia, which could have implications for the prevention of obesity-related cardiac disease (Jansen and Larsen 2017; Rashed et al. 2016).

Due to the potentially dangerous adverse effects of obesity, the necessity for natural products of animal and plant origin to combat obesity is being explored, that might be used as an alternative strategy for development of effective and safe medicines for the treatment of metabolic conditions related to obesity and hypercholesterolemia (Patra et al. 2015; Shanaida 2019).

One of the major reasons for obesity is a sedentary lifestyle characterized by lower physical activity and higher intake of energy-dense foods thus creating a scenario of positive energy balance in the body (Hruby and Hu 2015; Wang et al. 2008). According to one estimate, the prevalence of obesity may reach 85% by 2030 in the US population (Wang et al. 2008). Obesity, especially visceral obesity, has been shown to induce chronic low-grade inflammation in the body attributed to increased secretion of potent pro-inflammatory cytokines from macrophage and other cells of the immune system (Ellulu et al. 2017). The persistent low-grade inflammation is a major contributing factor in the onset and subsequent progression of insulin resistance, CVDs, and other metabolic disorders (Ellulu et al. 2017).

It has been established that dietary intake of useful fatty acids can change the inflammatory milieu in the body and dietary ratio of ω-6 (n-6) to ω-3 (n-3) can potentially determine the susceptibility of an individual for various disorders where inflammation plays a contributing role (Raphael and Sordillo 2013). The ω-6 PUFAs have been shown to exacerbate the inflammation, while ω-3 PUFAs tend to reduce body inflammation (Simopoulos 2006).

The COil is a rich source of long-chain ω-3 fatty acids, EPA and DHA, and can be used as a potential nutraceutical supplement to reduce obesity and other metabolic disorders. In a recent study, oil from *C. finmarchicus* showed anti-obesity properties in diet-induced obese mouse model C57BL/6J. It was observed that feeding mice with a supplement containing 2% *C. finmarchicus* wax esters for 11 weeks reduced weight gain in high-fat diet-fed C57BL/6J mice. Dietary supplementation with a low quantity of COil (2%) was able to prevent the excessive dependence of fatty acid oxidation for energy production in cases of obesity in mice (Pedersen et al. 2014). The wax esters of COil were hydrolyzed, and the generated free fatty acids were absorbed by both the liver and adipose tissue as reflected by the changed fatty acid composition of lipids analyzed from the liver and adipose tissue.

Moreover, the liver also generated long-chain ω-3 fatty acids from the C_{18} ω-3 fatty acids presented in the feed (Pedersen et al. 2014). In another study, C57BL/6J mice fed high-fat diet showed body weight gain, fat deposition in the abdominal region, and disrobed glucose metabolism in comparison with normal chow-fed diet. However, supplementing a high-fat diet (HFD) with 1.5% COil successfully reduced body weight and improved glucose metabolism (Hoper et al. 2013). It also prevented fat accumulation and hepatic steatosis, thus helped in improving liver health. Treatment with COil reduced the overall size of adipocytes, increased the expression levels of anti-inflammatory cytokine adiponectin, and reduced the expression of the potent inflammatory cytokines TNF-α and IL-6 (Hoper et al. 2013). This indicates that COil offers both preventive and therapeutic advantages in fighting obesity and other related disorders (Hoper et al. 2013).

Other research has shown that supplementation with wax esters was more effective in managing obesity-induced inflammation and glucose intolerance in comparison with pure EPA + DHA ethyl esters (E/D) supplementation. This indicated that the beneficial effects of COil are not attributed to only EPA and DHA content, and the other smaller components of wax esters are also responsible for the observed health benefits of COil (Höper et al. 2014).

It was reported that COil treatment significantly reduced the levels of blood glucose, plasma insulin, plasma non-esterified fatty acid, and improved glucose tolerance in comparison with a high-fat diet and pure EPA and DHA treated groups (Höper et al. 2014). The above-cited studies have demonstrated that COil can be used as a nutraceutical supplement in weight management therapies owing to its anti-obesity and anti-inflammatory properties.

COil and insulin resistance

Obesity and type 2 diabetes are significantly related to increased inflammation. Metabolic syndrome is caused by an increased inflammation of the adipose tissue with possible further systemic inflammation and type 2 diabetes. Among promising trends for the abolishment of both conditions, the administration of anti-inflammatory nutrition is proposed (Sears 2009).

It has been observed that wax esters present in COil undergo slower digestion, therefore, later reaching to the distal intestine. However, other ω-3-fatty acids do not reach distal intestinal parts due to a faster absorption rate (Höper et al. 2014). The G protein coupled receptor GPR120 is present in several cell types and body organs. It is suggested as a potential target for the management of disorders associated with low-grade inflammation; it inhibits the cellular inflammation due to its inhibitory effects of the NF-kB pathway (Karakula-Juchnowicz et al. 2017). GPR120 is also expressed in the large intestine, and studies have shown that it mediates the beneficial effects of fish oil rich in ω-3 fatty acids (Buettner 2010; Karakula-Juchnowicz et al. 2017). Studies have suggested that PUFA present in COil acts via GPR120, leading to a lowering in systemic inflammation and improved insulin activity (Pedersen 2019). Also, COil treatment reduced the size of adipocytes and therefore prevented hypoxic condition often observed in large size adipocytes (Pedersen 2019). It has been demonstrated that hypoxic conditions in adipocytes attract macrophages and create an inflammatory milieu leading to insulin resistance as well as abnormal glucose metabolism (Fujisaka et al. 2013). A close association between inflammation and insulin resistance has been well established. A higher inflammatory milieu adversely affects both the secretion of insulin from pancreatic β-cells and downstream signaling pathways in the cell by inhibiting the tyrosine phosphorylation of IRS-1 (Rehman and Akash 2016). Both these mechanisms lead to abnormal insulin secretion and function, consequently leading to disturbed glucose homeostasis (Rehman and Akash 2016). It is evident from the above-cited studies that COil prevents the secretion of pro-inflammatory cytokines and their action.

Anti-inflammatory properties of COil

Cytokines and other mediators, firstly lipids, participate in the processes for discontinuation of inflammation, not simply as disabling pro-inflammatory pathways (Hotamisligil 2006; Serhan et al. 2008). COil has been shown to possess potent anti-inflammatory properties due to the presence of ω-3-fatty acids and antioxidant molecules such as ASX. The ω-3 fatty acids of the COil act as a precursor molecule for the synthesis of anti-inflammatory eicosanoids (Pedersen 2019). Eicosanoids are oxylipins and control the host immune responses by interacting with various cellular receptors (Noverr et al. 2003). ASX present in COil is a powerful antioxidant molecule due to the presence of two oxygenated groups on each ring structure (Salma et al. 2016).

C. finmarchicus reduces macrophage infiltration and downregulates pro-inflammatory gene expression, including interleukin-6, monocyte chemoattractant protein-1, and tumor necrosis factor-α, whereas it upregulates the expression of adiponectin (Höper et al. 2014). Low-grade chronic inflammation plays an important pathological role in many chronic age-related conditions. Unresolved inflammatory responses may be involved in the early stages of disease development (Calder 2015).

SDA, another useful component of COil, reduces the synthesis of pro-inflammatory mediators synthesized from ω-6 fatty acids. Studies have reported that the anti-inflammatory effects of SDA are also mediated by its inhibition of the NF-kB pathway in macrophages (Sung et al. 2017). Furthermore, COil provides wax esters, which have been shown to reduce adipose tissue inflammation by inhibiting adipose tissue hypoxia and synthesis of inflammatory mediators (Pedersen 2019).

Moreover, the presence of ASX also prevents the oxidation of COil, thus obviates the need to add extra antioxidants to it. ASX possesses potent anti-inflammatory properties due to its inhibitory effects on cyclooxygenase-2 and inducible nitric oxide (Pedersen 2019). ASX also inhibited the expression of several inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Davinelli et al. 2018). Thus, the anti-inflammatory properties of COil have been attributed to the presence of ω-3 fatty acids, SDA, and carotenoid ASX.

The COil in the prevention of atherosclerosis, cardiovascular and brain disorders

Various biochemical processes in the cell produce reactive oxygen and nitrogen species. The formation of these free radicals is unavoidable, and their role as a mediator in several biochemical pathways has been well documented (Abdali et al. 2015; Pham-Huy et al. 2008; Salvayre et al. 2016; Yang et al. 2016).

Under general conditions, the free radicals generated have been trapped/neutralized by the antioxidant machinery of the cell that involved vitamins A, C, E, and numerous enzymes of the antioxidant pathways.

However, excessive production of free radicals can potentially damage the cellular membranes, especially lipids (de Araújo et al. 2016). This oxidative stress is an important contributing factor in the development of several lifestyle-related disorders such as obesity, cardiovascular diseases, insulin resistance, chronic inflammation, and aging (Pham-Huy et al. 2008). For example, oxidation of LDL-cholesterol by free radicals is an important step in the development and subsequent progression of atherosclerosis (Eilertsen et al. 2012; Salvayre et al. 2016). Angiotensin II infusion is a commonly used model to induce hypertension and understand the mechanism behind the induction of hypertension (Lohmeier 2012).

Dietary supplementation with an oil extracted from the zooplankton copepod *C. finmarchicus* decreased the cholesterol level in apoE-deficient (apoE(−/−)) mice and might be recommended as an effective and safe food supplement to diminish the atherosclerosis plaque formation (Eilertsen et al. 2012). Long-chain monounsaturated and n-3 polyunsaturated fatty acids decline the after-dinner lipid level in the blood and liver of rats (Halvorsen et al. 1995).

In a mice model of Ang II infusion, body weight and weights of various organs declined. It was observed that supplementation with COil successfully ameliorated the adverse effects of Ang II infusion in mice model (Salma et al. 2016). The COil supplementation also prevented the rise in blood pressure attributed to Ang II infusion. The other detrimental effects of Ang II infusion, cardiac hypertrophy, and fibrosis in the cardiac muscles were also prevented in the COil treated group. Moreover, the inflammatory response and fibrosis observed in the aorta were completely prevented in COil-treated group indicating a complete reversal of Ang II-induced cardiac abnormalities in mice model of hypertension (Salma et al. 2016). In another study, the O-GlcNAcylation of proteins induced by Ang II treatment was reduced in COil-treated group (Salma et al. 2016). Taken together, the COil treatment was successful in preventing cardiac tissue inflammation and oxidative stress, thus acted as a cardioprotective health supplement. In another study, COil supplementation has been shown to protect against obesity and obesity-associated myocardial abnormalities. The COil treatment increased the glucose oxidation and showed an improved post-ischemic functional recovery in comparison with non-treated obese mice. The study concluded that COil treatment successfully prevented myocardial health abnormalities induced by obesity (Jansen and Larsen 2017). Dietary supplementation of COil also ameliorated atherosclerosis in apoE−/− mice, as evidenced by reduced aorta atherogenesis and aortic lesions (Eilertsen et al. 2012). It was observed that supplementation with EPA + DHA was less effective in preventing atherosclerosis in comparison with COil treatment indicating that molecules other than EPA and DHA also played an important role in preventing atherosclerosis-induced damage (Eilertsen et al. 2012).

Additionally, COil supplementation also reduced the expression of several pro-inflammatory genes, such as ICAM, CCl2, and NF-kB, in the liver, indicating an anti-inflammatory action in the liver (Eilertsen et al. 2012). However, COil supplementation did not change the plasma concentrations of various biochemical parameters such as cholesterol, glucose, and TG in the present study (Eilertsen et al. 2012). In mice fed with HFD treated with COil and exenatide, a reduced intra-abdominal fat deposition was found than in HFD mice, which were not administered the supplementation (Jansen et al. 2019). The study concluded that COil was successful in preventing atherosclerosis and can be used as a dietary supplement to prevent the chances of cardiovascular disorders (Eilertsen et al. 2012).

The cost of the brain and mental disorders has been rising sharply and, in some countries, currently exceeds the budget of other ailments, including cardiovascular or metabolic diseases (Cole et al. 2005; Kidd 2007). In recent years, cognitive decline, especially in Alzheimer's patients, has become an important challenge for health care systems since it affects the quality of older people's lives and the socio-economic environment of patients and their families. Prevalence of various mood ailments, including depression, schizophrenia, Huntington's disease, rapidly increases simultaneously as the life expectancy does.

The brain tropism of ω3-PUFAs can be highlighted by showing the ability of these compounds to even preventing neurodegenerative disorders. Many systematic reviews, surveys, Cochrane reviews, and meta-analyses confirmed the beneficial action of ω-3 dietary supplementation on many brain functions, cognitive activity, and prevention of dementia in the elderly and mature adults, including in Alzheimer's disease and other cognitive disorders (Dangour et al. 2010; Jiao et al. 2014; Mazereeuw et al. 2012; Yurko-Mauro et al. 2015). However, in general, many reports did not assess a clear association between ω3. PUFAs intake and the prevention of cognitive impairments in healthy adults and Alzheimer's disease affected subjects. People with mild cognitive deficits may improve their condition with ω3-PUFA nutritional supplementation, as shown by their amelioration in attention, immediate recall, and processing speed (Mazereeuw et al. 2012). A meta-analysis performed in 2016 with 26 different studies reported a 17% lower risk of depression with increasing fish intake (Li et al. 2016). Yet, a Cochrane review in 2015 with 26 studies reported insufficient evidence to assess whether ω-3s (1000–6600 mg/day EPA, DHA, and/or other ω-3 PUFAs) were beneficial for major depressive disorder in recruited adults (Appleton et al. 2015). In this case, it had not found effects on depressive symptoms that were small-to-modest beneficial. However, the researchers concluded that the effect was not clinically significant. Finally, another systematic review and meta-analysis of ten studies of ADHD children or related neurodevelopmental disorders, such as developmental coordination disorder, found no factual improvement by introducing ω-3-PUFAs in the diet on behavioral measures such as aggression, emotional lability, conduct problems, and oppositional behavior (Cooper et al. 2016).

Notwithstanding, in subgroup analyses of the simple higher-quality studies, including those with stringent inclusion criteria, ω-3 PUFAs supplementation (60 to 1296 mg/day EPA and/or DHA) improved significantly parent-rated emotional lability and oppositional behavior. Many of these findings need to be confirmed from more additional clinical trials.

Diet, as one of lifestyle modifiable factors, may contribute to the prevention or enhancement of chronic neurodegenerative processes. The ω-3 fatty acid DHA, which is of marine origin, is a significant nutrient for optimal functioning of the central nervous system (CNS) (Cole et al. 2005; Valenzuela and Valenzuela 2013). CNS tissues contain high quantities of the following PUFA: arachidonic acid (20:4, ω-6) and DHA. The concentration of both acids can be regulated by dietary consumption. DHA is of great importance for brain phospholipids, which count 25% of the total fatty acids of the gray matter.

Dosage and use modalities

The use of COil has been suggested as an alternative to EPA and DHA due to a highly rich source of wax esters (Tande et al. 2016). A study by Tande et al. (2016) evaluated the clinical safety of COil in a randomized, double-blind, placebo-controlled clinical trial. The study was conducted for 1 year, and capsules of 2 g COil were given to the 64 participants. A placebo group acted as a control for the study. Several biochemical and hematological parameters were monitored to understand if long-term supplementation of COil has any adverse reactions (Tande et al. 2016). It was concluded that COil supplementation did not have any adverse effects on the body, as reflected by normal biochemical and hematological parameters of the participants (Tande et al. 2016). However, COil-supplemented groups displayed a slight increase in the incidence of eczema, which was minor and could be due to other factors (Tande et al. 2016). In another study, 18 subjects were given COil capsules to evaluate the bioavailability of EPA and DHA from wax esters present in COil. It was observed that plasma levels of EPA increased significantly in COil-given group in comparison with EPA ethyl ester-given group. This indicated that ω-3-fatty acids available in COil are bioavailable, and it can be used as a potential source for EPA and DHA (Cook et al. 2016). It has been reported that wax esters are not efficiently digested by terrestrial organisms due to the absence of specific lipases required to digest complex wax esters. For example, fishes and birds efficiently digest wax esters due to evolutionary adaptations developed by them. In contrast, dogs and rats incorporate the free fatty acids released after wax ester digestion with only 25% and 50% efficiency (Place 1992).

Conclusions

The COil is extracted from marine zooplankton *C. finmarchicus* found in the North Atlantic Ocean. COil extracted from *C. finmarchicus* is rich in wax esters, carotenoid and has been projected as the best alternative to fish oil. The presence of ω3-PUFAs makes COil particularly suited for generating lipid signaling to tune metabolism and the adipose tissue/muscle relationship. Figure 4 summarizes this fundamental task exerted by

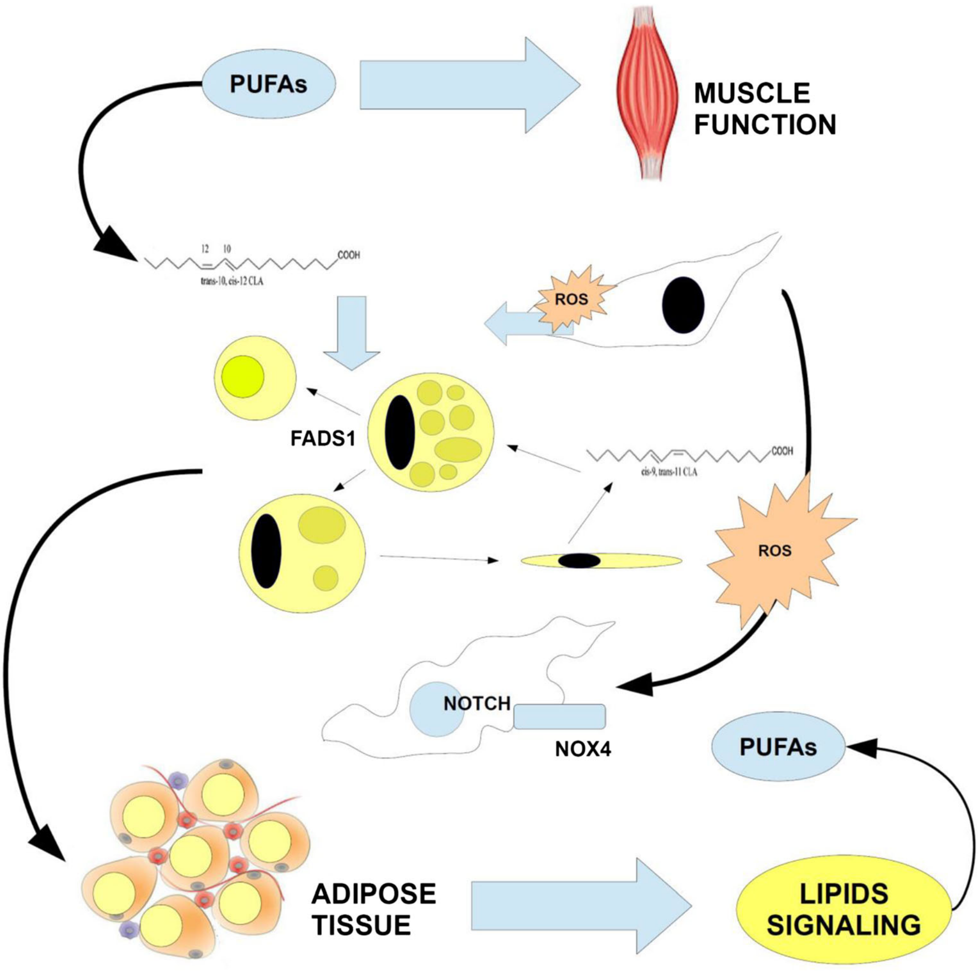

Fig. 4 Polyunsaturated fatty acids (PUFAs) from the diet are important regulators of the muscular activity and adipocyte biology. They participate in the active tuning signaling, mediated by reactive oxygen species (ROS) and lipids, in supporting the major role of the adipose tissue to maintain tissue homeostasis and tissue immunity. Low ROS levels from fibroblasts, activated by linoleic acid, induce fatty acid desaturase (FADS1) in adipocytes and their cycle regulation via conjugated linoleic acid isomers (CLAs), which leads to adipocyte turnover. High ROS levels can induce NADPH oxidase 4 in adipocytes (NOX4) and activate dedifferentiating genes such as Notch, which leads to changes in tissue homeostasis and the onset of tissue stability. In this mechanism, PUFAs are major actors of the complex energy modulation and the maintenance of organ and tissue renewal

PUFAs. The beneficial activity of PUFAs might be highlighted as major signaling molecules, particularly with conjugated linoleic acids (CLA), of the role exerted by adipose tissue in metabolic, immune, and tissue homeostasis.

Recent decades have seen an unprecedented rise in the use of PUFA-rich oil in the aquaculture industry. A simultaneous rise in the demand of PUFAs is also observed in the health care industry, where PUFAs are suggested preventing various disorders related to lifestyles such as obesity, diabetes mellitus, chronic low-grade inflammation, atherosclerosis, and brain and cardiovascular disorders (CVDs). Apart from PUFAs, COil is also a rich source of antioxidants, such as ASX and SDA. Several studies have demonstrated that COil supplementation can be a very effective dietary intervention to manage body weight, reduce the chances of cardiovascular disorders, heal the damaged arteries due to atherosclerosis, and to prevent the oxidative damage caused by free radicals.

However, further scientific research is warranted in understanding the molecular mechanism that contributes to the beneficial effects of COil. The demand for COil is rising, and highly efficient technologies to recover the COil from the zooplankton are required to improve the yield and recovery of the oil. The use of small zooplanktons in the extraction of lipid-rich oil has gained momentum, and small crustaceans like *C. finmarchicus* have been suggested as one of the best sources to obtain PUFA-rich oils. Thus, COil appears to be a promising new area of research that may lead to new insights into the health benefits of its different components.

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Compliance with ethical standards

Conflict of interest Adrien Ongenae and Salva Piscopo work for Nutrilogics SA, a company producing natural dietary supplements. No one of the other authors has any conflict of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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