

Antarctic Krill (*Euphausia superba*) Oil: A Comprehensive Review of Chemical Composition, Extraction Technologies, Health Benefits, and Current Applications

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Abstract: Antarctic krill (*Euphausia superba*) oil has been receiving increasing attention due to its nutritional and functional potentials. However, its application as a novel food ingredient has not yet been fully explored. This review summarizes the chemical composition, extraction technologies, potential health benefits, and current applications of krill oil, with the aim of providing suggestions for its exploitation. Krill oil is a unique lipid consisting of diverse lipid classes and is characterized by a high concentration (39.29% to 80.69%) of phospholipids (PLs) associated with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It also contains considerable amounts of bioactive minor components such as astaxanthin, sterols, tocopherols, vitamin A, flavonoids, and minerals. The current technologies used in krill oil production are solvent extraction, nonsolvent extraction, super/subcritical fluid extraction, and enzyme-assisted pretreatment extraction, which all greatly influence the yield and quality of the end-product. In addition, krill oil has been documented to have various health benefits, including anti-inflammatory effects, cardiovascular disease (CVD) prevention, women's health, neuroprotection, and anticancer activities. Although krill oil products used for dietary supplements have been commercially available, few studies have attempted to explore the underlying molecular mechanisms to elucidate how exactly the krill oil exerts different biological activities. Further studies should focus on this to improve the development of krill oil products for human consumption.

Keywords: applications, chemical composition, extraction technologies, health benefits, krill oil

Introduction

Antarctic krill (*Euphausia superba*) is an important marine crustacean organism that lives in the Antarctic Ocean and has attracted strong research interest worldwide. It plays a fundamental role in the Antarctic food web, as most of the larger marine organisms living there feed on the shrimp-like krill (Nicol & Endo, 1999). The biomass of Antarctic krill has been estimated at approximately 379 million metric tons, with the annual post-larval production of 342 to 536 million metric tons (Atkinson, Siegel, Pakhomov, Jessopp, & Loeb, 2009). To ensure the sustainability of krill fishery activity, the Commission for the Conservation of Antarctic Marine Living Resources (CCAMLR) has set a catch limit of 620,000 tons per year (CCAMLR, 2018). However, the actual annual catch is only around 250,000 tons, indicating that krill remains underutilized.

Recently, fish stocks have fallen considerably due to overfishing and environmental pollution. Krill is therefore expected to be an alternative marine resource with potential applications. Presently, krill is mainly used in the aquaculture industry and the sport-fishing market. Great efforts have also been made to develop krill products for human consumption. Krill oil is gaining attention as a source of health-beneficial lipids due to its abundant nutrients, such as n-3 polyunsaturated fatty acids (n-3 PUFAs), phospholipids (PLs), astaxanthin, vitamins, flavonoids, and minerals. The lipid content of krill is 0.5% to 3.6% (Grantham, 1977); thus, based on the current catches, about 1,250 to 9,000 tons of krill oil could be extracted with proper processing. In 2008, krill oil was authorized as GRAS (Generally Recognized as Safe) by the U.S. Food and Drug Administration (FDA). In 2009, it was approved to be placed on the market as a novel food ingredient in the European Community, and in 2014 also by China. More recently, the European Community has decided to extend the authorized uses of krill oil to pregnant and lactating women. It is anticipated that krill oil will have an expanding future market.

Some published reviews have discussed the nutritional value and health benefits of krill, as well as its potential utilization as human food (Burri & Johnsen, 2015; Suzuki & Shibata, 1990; Tou,

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Jaczynski, & Chen, 2007). However, there has been less focus on krill oil. This review provides a detailed summary of the chemical composition, extraction technologies, health benefits, and current applications of krill oil, with the aim to provide detailed information for krill oil production and to provide ideas for developing new types of krill oil products.

Chemical Composition of Krill Oil

Lipid classes

Common edible oils consist mainly of triacylglycerols (TAGs) (>95%) (Shahadi, 2005a), but krill oil shows a more diverse profile of lipid classes: PLs, TAGs, diacylglycerols (DAGs), monoacylglycerols (MAGs), free fatty acids (FFAs), and others (Phleger, Nelson, Mooney, & Nichols, 2002). The contents of the different lipid classes in krill oil are influenced by many factors, such as seasonal variation, interannual environmental changes, capture stations, and sexual maturity of krill samples (Fricke, Gercken, Schreiber, & Oehlenschläger, 1984; Kolakowska, 1991; Phleger et al., 2002). In addition, the storage conditions, transportation process, and pretreatment method of raw material also have influences on the lipid composition of krill oil extracted (Sun et al., 2017a; Tilseth & Høstmark, 2015; Yin et al., 2015). For example, dehydration of krill with hot air would result in a higher FFA content compared to freeze-drying due to the lipid hydrolysis at high temperature (Sun et al., 2017a).

Table 1 summarizes the contents of lipid classes in various krill samples published in some studies. Krill oil is characterized by a high PL content ranging from 39.89% to 80.69% depending on sample variety and analysis method. The differences in lipid composition found between years and regions may have been caused by changes in feeding behavior (Bottino, 1975; Fricke et al., 1984; Phleger et al., 2002). Similar to fish (Takama, Suzuki, Yoshida, Arai, & Anma, 1994), the oil extracted from the ovarian tissues of krill showed a higher PL level than that from muscle tissues (Clarke, 1980). Due to the developing ovaries, gravid females contained more PLs than males (Kolakowska, 1991). In addition, extraction solvents play an important role in the PL contents of extracted krill oil. Krill oils extracted with ethanol and isopropanol contain higher PL levels than when using other solvents, such as hexane and acetone (Gigliotti, Davenport, Beamer, Tou, & Jaczynski, 2011; Xie et al., 2017).

Phosphatidylcholine (PC) (44.58% to 99.80% of total PLs) and phosphatidylethanolamine (PE) (0.20% to 24.74% of total PLs) are the major PL types in krill oil (Table 2). As reported by Araujo, Zhu, Breivik, Hjelle, and Zeng (2014, 2016), lysophosphatidylcholine (LPC) also represents a considerable percentage, which might be attributable to the hydrolysis of PC caused by improper storage or pretreatment of krill material. In addition, phosphatidylserine, phosphatidylinositol, lysophosphatidylethanolamine, sphingomyelin, phosphatidylglycerol, phosphatidic acid, and cardiolipin have been detected in small quantities (not more than 10%) in some other studies (Bottino, 1975; Clarke, 1980). PLs, especially PC, have already been in use as food additive and nutritional complement for a long time. Currently, most of the commercial PLs are derived from egg yolk, vegetable oils, and milk and dairy products (Ali et al., 2017). The abundant presence of PC in krill oil makes this oil a potential marine resource for providing natural PLs.

Fatty acid (FA) composition

The main FAs present in krill oil are C14:0, C16:0, C16:1, C18:1, C20:1, C20:5 (EPA), and C22:6 (DHA) (Fricke et al.,

1984; Phleger et al., 2002; Xie et al., 2017). It is widely known that the n-3 PUFAs derived from dietary lipids, mainly EPA and DHA, play a significant role in human health (Connor, 2000; Heinze & Actis, 2012; Young, 2009). Fish oils are uniquely rich in EPA and DHA, and they have been traditionally consumed as dietary supplements of n-3 PUFAs. Table 3 lists the typical FA composition of krill oil, in comparison with some common marine fish oils (Codex Standard 329–2017, 2017). The table shows that the EPA and DHA levels in krill oil are comparable to those in other listed fish oils. However, most of the EPA and DHA in krill oil is associated with PLs as opposed to TAGs in fish oil. According to Clarke (1980), the PL fraction separated from the krill lipid had much higher percentages of PUFA and n-3 PUFA and lower percentages of saturated fatty acid (SFA) and monounsaturated fatty acid (MUFA) than TAG, as shown in Figure 1. In particular, 31.13% of EPA and 14.87% of DHA were found in the PL fraction, while only 3.17% of EPA and 1.5% of DHA were present in the TAG fraction. These results are confirmed by other studies (Castro-Gómez, Holgado, Rodríguez-Alcalá, Montero, & Fontecha, 2015; Gigliotti et al., 2011; Xie et al., 2017), indicating that krill oil with high PL level contains high concentrations of EPA and DHA (Xie et al., 2018). Recent studies have found that the n-3 PUFAs in the form of PLs contribute to a significantly higher bioavailability than those in the form of TAGs (Amate, Gil, & Ramírez, 2001; Mathews et al., 2002). In this regard, krill oil may be superior to fish oil as a source of EPA and DHA.

Structure of TAG and PL in krill oil

In addition to FA composition, the positional distributions of FA on the backbone of TAG and PL are also vital for the nutrition, absorption, and metabolism of lipids (Aoyama et al., 1996; Croset, Brossard, Polette, & Lagarde, 2000; Decker, 1996; Lagarde & Bernoud-Hubac, 2012).

Castro-Gómez et al. (2015) identified 65 TAG molecular species from carbon number (CN) 42 to CN 60 within 1 to 11 double bonds in krill oil. The most abundant TAG species are 14:0/16:0/18:1, 16:0/16:1/16:1, 16:0/18:1/18:1, and 16:0/16:0/18:1, with relative proportions of 8%, 6%, 5.5%, and 4.8% in the total detected TAG species, respectively. This is in agreement with the large presence of 14:0, 16:0, 16:1, and 18:1 in the FA profile of TAG (as discussed in the Section Fatty Acid Composition). Although the TAG fraction is low in EPA and DHA, the EPA residues are predominantly in *sn*-1,3 while the DHA residues are preferentially in *sn*-2 (Akanbi & Barrow, 2018). This is similar to the distribution of n-3 PUFAs in fish oils (Akanbi, Adcock, & Barrow, 2013; Sacchi, Medina, Aubourg, Giudicianni, & Addeo, 1993; Standal, Axelsson, & Aursand, 2009). In addition, Araujo et al. (2014) reported that 21% of n-3 PUFAs were located in the *sn*-2 positions of TAGs in krill oil.

Choline-containing PLs are the major PLs in krill oil. Winther, Hoem, Berge, and Reubsæet (2011) detected a total of 69 choline-head group PL species in krill oil by high-performance liquid chromatography-electrospray ionization-mass spectrometry (HPLC-ESI-MS), among which 60 were identified as PC species and 9 as LPC species. Based on the relative intensity, PC (16:0/18:1), PC (16:0/20:5), and PC (16:0/22:6) were the most abundant species, which is in agreement with the studies conducted by Le Grandois et al. (2009) and Castro-Gómez et al. (2015), although they reported different numbers of PC and LPC species identified. Furthermore, it was found that 7 PC species contained n-3 PUFA groups in both *sn*-1 and *sn*-2 positions, which were PC (18:4/20:5), (18:4/22:6), (20:5/20:5), (20:5/22:6), (20:5/23:5),

Table 1–Lipid classes in Antarctic krill (% of total lipids).

Sample information	PLs	MAGs	DAGs	Sterols	FFAs	TAGs	Sterol esters	Waxes	Analysis methods	References
<i>Euphausia superba</i> collected in different stations of the Ross Ice Shelf, 1972	54	ND	17	ND	ND	8	ND	ND	TLC quantitated by gravimetry	Bottino, 1975
<i>Euphausia superba</i> collected in South Georgia, 1978	Station 11 Mature males Gravid females Ovary Muscle	58 41.25 39.29 40.27 39.89 45.7	ND 1.4 0.43 0.64 0.63 ND–2.0 1.3	ND 16.17 16.89 16.35 21.21 1.7	ND 14.36 11.41 3.79 10.13 16.1	36 21.50 29.21 30.99 26.68 33.3	ND ND 2.84 ND–2.0 2.68 ND–2.0 ND	ND 1.9 ND–2.0 2.7 ND–2.0 ND	TLC detected by densitometer TLC quantified by an enzymatic test for esterified glycerol	Clarke, 1980 Fricke et al., 1984
<i>Euphausia superba</i> collected from the Scotia Sea on December 16, 1977										
<i>Euphausia superba</i> collected from the Gerlache Strait on March 12, 1981	44.0	0.9	3.6	1.4	8.5	40.4	ND	ND		
<i>Euphausia superba</i> caught in the Admiralty Bay on December 12, 1986	Immature males Mature males Gravid females Spent females	59.0 62.6 64.0 52.9 66.6–72.0	ND ND ND ND	7.7 8.2 4.3 8.6 4.0–6.1	3.6 4.0 3.2 5.5 1.1–1.8	25.9 20.4 25.2 26.8 22.1–38.4	ND ND ND ND ND	3.9 4.3 3.6 6.2 ND	TLC detected by densitometer TLC-FID	Kotakowska, 1991 Phleger et al., 2002
<i>Euphausia superba</i> caught in the US AMLR Elephant Island in 1998	69.80	ND	ND	1.09	28.53	0.59	ND	ND	TLC-FID	Li et al., 2013
Krill oil extracted from krill meal with ethanol	48.37	ND	ND	0.66	13.54	37.63	ND	ND		
Krill oil extracted from krill meal with hexane	80.69	ND	0.93	2.80	3.46	11.85	ND	ND	HPTLC quantitated by densitometer	Araujo et al., 2014
Krill oil capsules obtained from Aker Biomarine	49.0	ND–0.1	6.2	1.0		43.7	ND	ND	HPLC-ELSD	Castro-Gómez et al., 2015

Notes: ND, not detected.
Abbreviations: TAGs, triacylglycerols; PLs, phospholipids; DAGs, diacylglycerols; MAGs, monoacylglycerols; FFAs, free fatty acids; TLC, thin-layer chromatography; TLC-FID, thin-layer chromatography flame-ionization detection; HPTLC, high-performance thin-layer chromatography; HPLC, high-performance liquid chromatography; ELSD, evaporative light scattering detector.

Table 2–Phospholipids (PLs) composition in krill oil (% of total PLs).

PC	PE	PI	PS	SM	PA	DPG	PG	LPC	LPE	Analysis methods	References
82.76	13.79	ND	ND	ND	ND	ND	1.72	1.72	ND	TLC quantitated by gravimetry	Bottino, 1975
76.18–86.97	7.51–16.23	0.20–1.86	0.67–1.21	ND–0.70	0.23–0.56	1.14–2.42	ND	0.51–5.20	0.14–1.56	TLC quantitated by phosphate estimation	Clarke, 1980
77.90	13.35	1.97	ND	ND	1.31	2.19	ND	3.28	ND	TLC quantitated by phosphate estimation	Fricke et al., 1984
75.68	12.05	2.50	ND	ND	3.64	ND	ND	6.36	ND	TLC quantitated by densitometer	Kořakowska, 1991
62.54	24.74	7.56	ND	ND	ND	ND	ND	ND	5.15	HPTLC quantitated by densitometer	Araujo et al., 2014
50.99	3.30	ND	1.33	ND	ND	ND	ND	44.39	ND	HPLC-ELSD	Castro-Gómez et al., 2015
99.80	ND–0.2	ND	ND	0.2	ND	ND	ND	ND	ND	HPTLC determined by densitometer	Araujo et al., 2016
44.58	7.00	ND	5.10	ND	ND	ND	ND	43.31	ND	HPLC-ELSD	Xie et al., 2017
87.93–95.16	4.84–12.07	ND	ND	ND	ND	ND	ND	ND	ND		

Notes: ND, not detected.

Abbreviations: PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin; PA, phosphatidic acid; DPG, cardiolipin; PG, phosphatidylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; TLC, thin-layer chromatography; HPTLC, high-performance thin-layer chromatography; HPLC, high-performance liquid chromatography; ELSD, evaporative light scattering detector.

Table 3–Typical fatty acid compositions of krill oil and some fish oils (Standard for fish oils Codex Stan 329–2017, 2017).

Fatty acid	Krill	Anchovy	Tuna	Menhaden	Salmon
C14:0	5.0–13.0	2.7–11.5	ND–5.0	8.0–11.0	1.5–5.5
C15:0	NA	ND–1.5	ND–2.0	ND–1.0	ND–1.0
C16:0	17.0–24.6	13.0–22.0	14.0–24.0	18.0–20.0	6.5–16.0
C16:1 (n-7)	2.5–9.0	4.0–12.6	ND–12.5	9.0–13.0	2.0–6.0
C17:0	NA	ND–2.0	ND–3.0	ND–1.0	ND–1.0
C18:0	NA	1.0–7.0	ND–7.5	2.5–4.0	2.0–5.0
C18:1 (n-7)	4.7–8.1	1.7–3.7	ND–7.0	2.5–3.5	NA–2.5
C18:1 (n-9)	6.0–14.5	3.6–17.0	10.0–25.0	5.5–8.5	8.0–47.0
C18:2 (n-6)	ND–3.0	ND–3.5	ND–3.0	2.0–3.5	1.5–15.0
C18:3 (n-3)	0.1–4.7	ND–7.0	ND–2.0	ND–2.0	ND–6.0
C18:3 (n-6)	NA	ND–5.0	ND–4.0	ND–2.5	ND–1.0
C18:4 (n-3)	1.0–8.1	ND–5.0	ND–2.0	1.5–3.0	0.5–4.0
C20:0	NA	ND–1.8	ND–2.5	0.1–0.5	ND–0.5
C20:1 (n-9)	NA	ND–4.0	ND–2.5	ND–0.5	1.5–10.0
C20:1 (n-11)	NA	ND–4.0	ND–3.0	0.5–2.0	NA
C20:4 (n-6)	NA	ND–2.5	ND–3.0	ND–2.0	ND–2.5
C20:4 (n-3)	NA	ND–2.0	ND–1.0	NA	0.5–3.0
C20:5 (n-3)	14.3–28.0	5.0–26.0	2.5–9.0	12.5–19.0	2.0–11.5
C21:5 (n-3)	NA	ND–4.0	ND–1.0	0.5–1.0	NA–4.0
C22:1 (n-9)	ND–1.5	ND–2.3	ND–2.0	0.1–0.5	ND–7.0
C22:1 (n-11)	NA	ND–5.6	ND–1.0	ND–0.1	NA–1.5
C22:5 (n-3)	ND–0.07	ND–4.0	ND–3.0	2.0–3.0	1.0–3.0
C22:6 (n-3)	7.1–15.7	4.0–26.5	21.0–42.5	5.0–11.5	3.0–14

Abbreviations: ND, not detected; NA, not applicable or available.

(22:6/22:6), and (20:5/22:5) (Winther et al., 2011), reflecting the abundance of n-3 PUFAs present in the PC molecular. In addition, nuclear magnetic resonance (NMR) analysis demonstrated that n-3 PUFAs in the krill PLs were more likely to be distributed at the *sn*-2 positions compared to *sn*-1 positions (Hupfeld, 2018).

Minor components

Astaxanthin. Astaxanthin is the main carotenoid found in some marine animals and algae. It possesses strong antioxidant ability and biological benefits (Ambati, Phang, Ravi, & Aswathanarayana, 2014). According to Miki (1991), astaxanthin is 10 times more potent as an antioxidant than other carotenoids such as zeaxanthin, lutein, canthaxanthin, and β -carotene, and 100 times more potent than α -tocopherol. The characteristic dark red color of krill oil is due to the presence of astaxanthin. Studies have revealed that the amount of astaxanthin in krill oil ranges from 40 to 5000 mg/kg, depending on krill material, extraction method,

and analysis method (Ali-Nehari, Kim, Lee, Lee, & Chun, 2012; Lambertsen & Braekkan, 1971; Sun et al., 2017a; Tandy et al., 2009; Xie et al., 2017). The use of acetone as an extraction solvent is helpful to achieve krill oil with a high astaxanthin content (Beaudoin & Martin, 2004; Xie et al., 2017).

The astaxanthin in krill oil is mainly present as fatty acid esters. Lambertsen and Braekkan (1971) reported that the relative percentages of astaxanthin diesters, monoesters, and free astaxanthin were 51%, 43%, and 6%, respectively, which is in agreement with some other studies (Foss, Renström, & Liaaen-Jensen, 1987; Yamaguchi et al., 1983). Further studies showed that C14:0, C16:0, C16:1, C18:1, C20:0, C20:5, and C22:6 were the main FAs found in astaxanthin esters (Grynbaum et al., 2005). Grynbaum et al. (2005) also identified three types of astaxanthin isomers in krill oil, (all-*trans*) astaxanthin, (13-*cis*) astaxanthin, and (9-*cis*) astaxanthin, and the (all-*trans*) isomer accounted for the largest percentage. Based on the stereoisomer analysis, (3*R*,

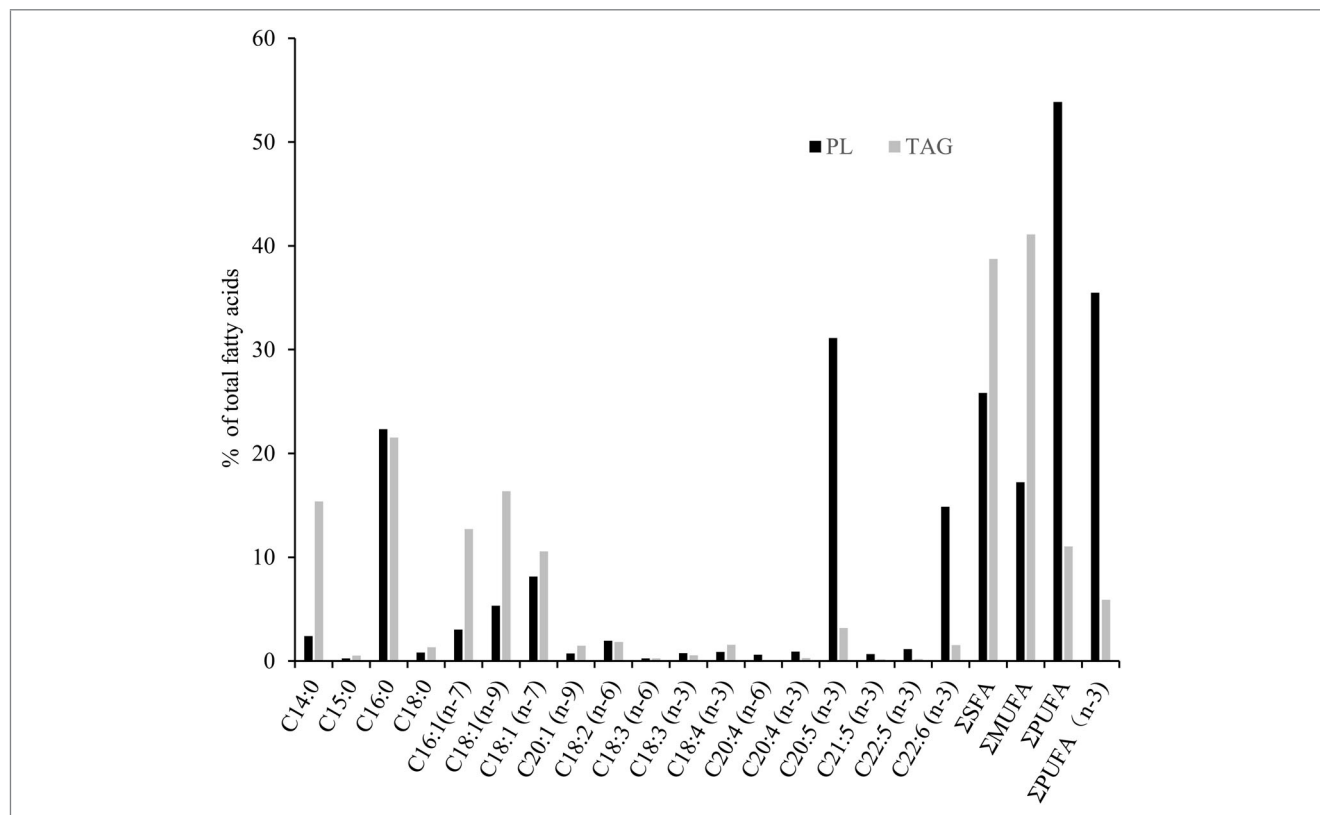


Figure 1—Comparison of fatty acids associated with PL and TAG in krill oil. Recreated based on the published data from Clarke (1980).

Abbreviations are: PL, phospholipid; TAG, triacylglycerol; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

3'R)-astaxanthin was the primary optical stereoisomer found in the krill oil (Foss et al., 1987).

Sterols. Krill oil contains a substantial amount of sterols (2.3% to 3.9% of total lipids) and is mainly composed of cholesterol and desmosterol (Fricke et al., 1984; Xie et al., 2017). Cholesterol accounts for 81.33% to 82.34% of total sterols, with a concentration of 18.95 to 31.96 mg/g of oil (Xie et al., 2017). This is much higher than the concentrations in some fish oils, such as tuna oil (2.04 mg/g of oil) and hoki oil (5.15 mg/g of oil) (Tengku-Rozaina & Birch, 2013), and is even higher than that in egg yolk (11.81 mg/g of oil) (Fenton & Sim, 1991). Dietary cholesterol is associated with cardiovascular disease (CVD) (Nissinen, Gylling, & Miettinen, 2008). The cholesterol present in krill oil may be a matter of concern if the oil is consumed as a food supplement. Bruheim and Cameron (2017) pointed out that pure ethanol extraction could result in a lower level of cholesterol in krill oil compared to the ethanol mixed with water extraction. However, much more effort should be devoted to exploring new extraction or purification techniques to decrease the cholesterol level in krill oil.

Desmosterol, which is the immediate precursor of cholesterol (Barrett, Volkman, Dunstan, & LeRo, 1995), represents a small percentage of 1.70% to 18.63% of total sterols (Fricke et al., 1984; Phleger et al., 2002; Xie et al., 2017). Phleger et al. (2002) also found some other sterols in krill samples captured in 1977, including 24-nordehydrocholesterol (0.1% to 1.7%), *trans*-dehydrocholesterol (1.1% to 1.5%), brassicasterol (0.5% to 1.7%), 24-methylenecholesterol (0.1% to 0.4%), and two stanols (0.1% to 0.2%). The minor differences may be attributable to variation in

the food sources of krill between years as the crustaceans cannot *de novo* synthesize sterols, which must be obtained from the diet or phytosterol dealkylation (Goad, 1978).

Vitamins. Vitamin E is the general term for all tocopherols and tocotrienols. There are four homologue pairs (α -, β -, γ -, δ -) of tocopherols and tocotrienols. All of them have antioxidant abilities and biological benefits, among which α -tocopherol is the most active (Valk & Hornstra, 2000). Like with most of the marine animals (Ackman & Cormier, 1967), α -tocopherol is the principal tocopherol in krill, with a level of 14.74 to 63.0 mg/100 g of oil (Tilseth, 2010; Xie et al., 2017). Traces of γ (0.25 to 3.67 mg/100 g of oil) and δ -tocopherol (0 to 0.65 mg/100 g of oil) were also detected in some studies (Sun et al., 2018; Xie et al., 2017). Generally, more than 90% of tocopherols in krill oil is in the α -tocopherol form. The presence of tocopherols may provide krill oil with additional antioxidant ability and exhibit synergistic effects with other bioactive components.

Vitamin A is an essential nutrient for humans and is closely related to the immune function and some infectious diseases (Mayo-Wilson, Imdad, Herzer, Yakoob, & Bhutta, 2011). Frozen krill contains 0.11 mg/100 g of vitamin A based on wet weight (Suzuki & Shibata, 1990). This fat-soluble vitamin could be concentrated into the oil during lipid extraction. According to our previous study, vitamin A concentrations ranged from 16.40 to 28.55 mg per 100 g krill oil, depending on the extraction solvents used (Xie et al., 2017). A similar result was also found by Tilseth (2010), who reported a vitamin A level of approximately 18 mg/100 g in the oil produced from cooked krill by centrifugation. Compared with some other marine fish oils, krill oil shows a

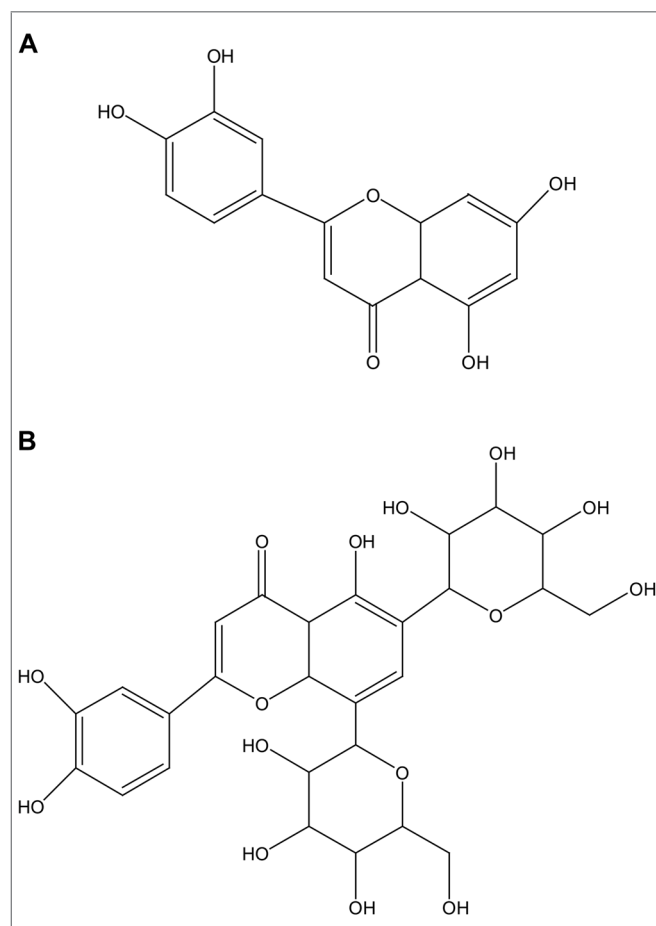


Figure 2—Structure of (A) luteolin and (B) flavonoid compound derived from krill oil. Modified from Sampalis (2013) and Xiao (2017).

higher vitamin A content than tuna oil (11.09 mg/100 g of oil) and menhaden oil (0.1 to 0.6 mg/100 g of oil), but lower than hoki oil (99.76 mg/100 g of oil) (Scott & Latshaw, 1991; Tengku-Rozaina & Birch, 2013).

Flavonoids. Flavonoids are composed of a group of diverse polyphenols with similar backbone structures (Xiao, 2017), and they have been shown to possess a wide range of biological activities, such as with anti-oxidant, antibacterial, immunomodulatory, anticancer, anti-inflammatory, and antithrombotic benefits (Xiao, 2017; Yang, Liu, Yang, Gupta, & Jiang, 2018). Traditionally, flavonoids can be categorized into six subclasses, including flavonols, flavones, isoflavonoids, flavanols, flavanones, and anthocyanins (Yang et al., 2018). By far, most of the flavonoids have been reportedly found in fruits, vegetables, and grains (Merken & Beecher, 2000). Interestingly, a novel flavonoid compound was characterized in krill oil, which has a structure similar to 6, 8-di-C-glucosyl luteolin, as shown in Figure 2. Sampalis (2013) patented a krill extract with a combination of $\geq 40\%$ PLs and ≥ 7 mg/100 mL flavonoids, and proved its effects on the protection of skin against the harmful effects of ultraviolet B (UVB) radiation, and improvement of dyslexia and abnormal motor function. Some studies indicated that the C-glycosylation in certain positions of flavonoids improved their antioxidant abilities (Cai, Mei, Jie, Luo, & Corke, 2006; Huber, Vasantha Rupasinghe, & Shahidi, 2009; Omar, Mullen, & Crozier, 2011) and anti-diabetic activities (Matsuda, Wang, Managi, & Yoshikawa, 2003). However, there is

a lack of direct data on the properties of the flavonoids present in krill oil.

Minerals. Whole krill have considerable contents of minerals important for bone health, such as calcium (1322 mg/100 g), phosphorus (1140 mg/100 g), and magnesium (360 mg/100 g), which meet the recommended dietary allowances (RDAs) of these minerals for adults (Tou et al., 2007). Although krill processing results in losses in these minerals to different degrees, a krill lipid extract containing diverse minerals (>0.1 mg/100 g of zinc, >0.1 mg/100 g of selenium, >0.1 mg/100 g of calcium, >50 mg/100 g of potassium) could be obtained by the method patented by Sampalis (2011).

In addition, krill is an exceptional marine organism which contains a high level of fluoride (2,400 mg/kg dry matter) (Soevik & Braekkan, 1979). Fluoride was considered an essential element in the past, but an increased fluoride intake may result in skeletal fluorosis which is now known to be a global health problem (Barbier, Arreola-Mendoza, & Del Razo, 2010). Although the fluoride in krill is mainly concentrated in the exoskeleton (Soevik & Braekkan, 1979), free fluoride or loosely bound fluoride may diffuse from the exoskeleton into the meat, especially in dead krill. Therefore, the transfer of fluoride should be taken into account during the krill oil extraction process to avoid a high fluoride amount in the oil. Generally, removal of the exoskeleton from krill material before oil extraction could result in a krill oil with low fluoride level (<0.5 ppm), while the oils extracted from whole krill have higher fluoride contents (3 to 5 ppm) (Bruheim et al., 2016; Jansson, Ervik, & Grimsmo, 2018).

Krill Oil Extraction Technologies

Currently, krill oil is extracted from different krill biomasses including fresh krill (Beaudoin & Martin, 2004; Katevas, Toro Guerra, & Chiong Lay, 2014) and dried krill (Gigliotti et al., 2011; Jansson et al., 2018; Ronen, Ran, & Ben-Dror, 2017; Xie et al., 2017). Krill contains extremely high levels of active proteolytic enzymes, which would result in rapid autolysis of krill after catching. Thus, the processing of krill oil from fresh krill must take place on board immediately after capture (Beaudoin & Martin, 2004; Katevas et al., 2014). In contrast, krill meal, a dried product obtained from fresh krill (Yoshitomi & Shigematsu, 2003), is a more appropriate material for the extraction of krill oil on-shore, especially in countries that do not possess ocean-going ships or off-shore processing techniques. There are a few well-documented procedures for extracting krill oil, including solvent extraction, nonsolvent extraction, super/subcritical fluid extraction, and enzyme-assisted extraction (Table 4). Different extraction methods have their individual benefits and drawbacks, which are discussed below.

Solvent extraction

As a traditional method of oil production (Shahadi, 2005b), solvent extraction is the most common method for krill oil extraction. A similar polarity is significant for the efficient extraction of target compounds from biomass (Gong & Bassi, 2016). It is therefore impossible to use a single solvent to extract all of the lipids from krill due to its diverse lipid classes with different polarities. According to our previous study (Xie et al., 2017), alcohols such as isopropanol and ethanol can extract large amounts of PLs from krill meal, but they can produce krill oil with low levels of minor components. In contrast, acetone is effective for extracting minor components, but it cannot extract PLs. Hexane is widely accepted as the most common solvent used in vegetable oil

Table 4–Summary of krill oil extraction technologies.

Technology	Details of procedures	Advantages	Disadvantages	References
Solvent extraction	Single solvent (ethanol, isopropanol, acetone, ethyl acetate, isohexane, n-hexane) extraction from krill meal	Simple method	Ineffective to extract all of the lipids from krill; varied composition of products depend on the solvent used	Xie et al., 2017
	Folch method using a mixture of chloroform:methanol (2:1; v:v) as extraction solvent	Most efficient in the published studies	Use of large amount of toxic solvents	Gigliotti et al., 2011; Bruheim et al., 2016; Xie et al., 2017
	Two-step successive acetone and alcohol extraction	High lipid yield	Time-consuming; multi-step operation; use of large amount of solvents	Beaudoin & Martin, 2004
	Mixed solvents extraction, e.g. acetone:ethanol (1:1; v:v); hexane:ethanol (9:1; v:v)	High lipid yield; comparably simpler with the two-step extraction	Use of large amount of solvents	Gigliotti et al., 2011; Ronen et al., 2017
	Extrusion of krill meal and then extraction with n-hexane	More effective than the extraction without extrusion pretreatment	Low PLs content in the extracted oil	Yin et al., 2015
Nonsolvent extraction	Cooking and grinding; centrifuging	Solvent-free	Easily emulsified in process; large investment of equipment; inefficient	Larsen et al., 2007
	Cooking; centrifuging; membrane filtration	Solvent-free	Possibly emulsified in process; large investment of equipment; inefficient	Tilseth & Høstmark, 2015
	Cooking at high temperature; decanting; pressing; centrifuging	Solvent-free; simultaneously obtaining both PLs-enriched krill oil and neutral lipid-enriched krill oil	High temperature; large investment of equipment; oxidation risk of products	Katevas et al., 2014
Super/subcritical fluid extraction	SC-CO ₂ extraction	Solvent-free extract; mild conditions; environmental friendliness; higher quality and higher thermally stable functional proteins	Inefficient extraction of PLs; expensive; hard to scale up	Yamaguchi et al., 1986
	SC-CO ₂ extraction with added co-solvent ethanol	Mild conditions; environmental friendliness; efficient extraction of PLs	Expensive; hard to scale up; difficulties in removing ethanol	Bruheim et al., 2018
	Subcritical butane extraction	Solvent-free; low temperature	Expensive; hard to scale up	Sun et al., 2018; Xie et al., 2017
Enzyme-assisted extraction	Pulverizing krill; protease pretreatment in ultra-high-pressure reactor; filtration; centrifugation; extraction with ethanol	Mild conditions; simultaneously obtaining both the oil and meal with higher quality; high lipid yield; obtaining a valuable by-product krill peptides	Expensive; long hydrolysis time; hard to scale up; need to be assisted by other extraction methods	Lee, 2014
	Disintegrating; adding water; hydrolysis with heat and enzymes; deactivating enzymes; centrifuging to remove solids; separating and drying the PLs-protein complex; solvent extraction	Low fluoride in the products; simultaneously obtaining both the oil and protein hydrolysates; high lipid yield	Expensive; longer hydrolysis time; hard to scale up; need to be assisted by other extraction methods	Bruheim et al., 2016

Abbreviations: SC-CO₂, supercritical carbon dioxide; PLs, phospholipids.

production due to its relatively low cost, high extraction efficiency, and low amount of residue in the meal (Johnson & Lusas, 1983). However, it exerts moderate abilities in extracting both the PLs and minor components from krill (Li et al., 2013; Xie et al., 2017). A combination of polar solvent and nonpolar solvent could balance the extraction efficiencies of PLs and minor components (Ronen et al., 2017). The Folch method is a popular method for total lipid extraction from animal tissue, and it could give high lipid yields (Bruheim et al., 2016; Gigliotti et al., 2011; Xie et al., 2017). However, it is not commercially feasible because of the toxicity of the solvents (methanol and chloroform) involved.

Currently, a two-step extraction approach with acetone and ethanol is the most common method (Beaudoin & Martin, 2004).

The successive extraction treatments provide a better lipid yield than single solvent extraction. A similarly high lipid yield can be obtained by a one-step strategy with a mixture of acetone and ethanol (1:1, *v/v*) (Gigliotti et al., 2011), and the procedure is simpler than that of the two-step extraction. In addition, solvent extraction combined with the extrusion pretreatment of krill meal can improve the lipid extraction efficiency (Yin et al., 2015). The defatted krill material or krill meal still can be used as a good resource of also recovering proteins using isoelectric solubilization/precipitation (Chen, Tou, & Jaczynski, 2009), or producing peptides or target amino acids by enzymatic hydrolysis (Wang et al., 2016; Zhao, Yin, Liu, & Cao, 2013) or fermentation technology (Sun & Mao, 2016) for human consumption.

Solvent extraction is economical and easy to scale up, but it requires large amounts of solvents that might cause environmental problems. The technique is also labor-intensive and time-consuming due to the multiple uses of extraction and evaporation steps.

Nonsolvent extraction

Nonsolvent extraction does not utilize organic solvents to extract oil from krill. Mechanical pressing is the traditional nonsolvent extraction method, and it is commonly applied to oilseeds with high oil contents, such as sunflower oil (40 to 42% of lipid in the seed) and sesame oil (50 to 57% of lipid in the seed) (Khan & Hanna, 1983). It is a relatively inefficient method compared with solvent extraction, and thus it is used to extract most of the oil before solvent extraction of the rest. Theoretically, krill material is not suitable for traditional mechanical pressing as its lipid content is not high: only 0.5 to 3.6% of lipid in fresh krill (Grantham, 1977) and 17.42% in krill meal (Yin et al., 2015). To obtain krill oil by this technique, fresh or defrosted krill must be ground into a slurry in an aqueous medium; this facilitates the release of lipids in the following mechanical disruption procedure, and then part of the oil is recovered by centrifugation (Larsen, Fey, Breuning, & Ludvigsen, 2007). However, the slurry formed in the grinding process might be emulsified due to the amphipathic nature of PLs, resulting in further unsuccessful separation of the oil from the mixture. Katevas et al. (2014) developed another nonsolvent process that includes cooking, decanting, pressing, and centrifuging. The detailed procedures are shown in Figure 3. This method can simultaneously obtain both PLs-enriched krill oil and neutral lipid-enriched krill oil. Notably, the first cooking procedure is conducted at a high temperature (approximately 90 °C) without agitation and grinding to avoid emulsification. In addition, the krill material is preferably processed in a fresh state because the ice crystals formed during freezing can destroy krill tissues, which in turn cause emulsification during processing and results in poor-quality products.

The advantage of nonsolvent extraction is the lack of solvent, which makes it inherently safer and more eco-friendly than solvent extraction. However, the high investment in equipment and high energy requirement for this process still represent significant shortcomings. In addition, the high operation temperature may increase the oxidation risk of products. More importantly, nonsolvent extraction is not an efficient approach to extract all of the available oil from krill. According to Katevas et al. (2014), the method only gave a total lipid yield of 2.2%. Thus, some krill manufacturers make this mechanical separation as an initial treatment to extract part of oil from krill and simultaneously produce krill meal which will be subsequently extracted by other techniques, such as solvent extraction and supercritical fluid extraction (Tilseth & Høstmark, 2015).

Super/subcritical fluid extraction

Supercritical fluid extraction has gained sufficient attention in lipid extraction because it offers the advantages of solvent-free extract, mild conditions, and environmental friendliness. The most widely used supercritical solvent is supercritical carbon dioxide (SC-CO₂) due to its safety, nontoxicity, chemical inertness, and modest critical properties (Friedrich & Pryde, 1984). However, it is not an ideal solvent to extract all of the krill lipids as it fails to extract PLs (Yamaguchi et al., 1986). Even so, higher quality and higher thermally stable functional proteins can be obtained from the krill residues deoiled by this extraction method than those

deoiled by traditional solvent extractions (Ali-Nehari, Kim, Lee, & Chun, 2012). The addition of 5 to 20% ethanol in the SC-CO₂ extraction can increase the solute solubility for PLs and thus improve lipid recovery (Bruheim, Tilseth, & Mancinelli, 2018). However, this may not be attractive in terms of desolvation due to the liquid state of ethanol at room temperature. In addition, the commercial application of supercritical fluid extraction is still limited due to the expensive high-pressure equipment and limited processing capacity.

Subcritical fluid extraction has similar advantages to supercritical extraction but is performed at a lower pressure and temperature. Compressed propane and butane are the most commonly used subcritical fluids in oil extraction because they are colorless and easily removed from the extracted products (Liu, Wang, Li, Wang, & Qin, 2015). The extraction of krill oil with subcritical butane under the conditions of 30 °C and 0.3 to 0.8 MPa led to the yield and oil quality similar to hexane, but it was faster and used less solvent (Xie et al., 2017). Sun et al. (2018) demonstrated that krill oil extracted by subcritical butane had higher astaxanthin and tocopherol contents but lower oxidation degree compared with traditional solvent extraction. Like supercritical fluid extraction, subcritical fluid extraction is hard to industrialize and is not quite affordable for routine purposes.

Enzyme-assisted extraction

Pre-treatment with enzymes is a novel and an effective way to release bound compounds and to increase the lipid yield in the oil extracted (Domínguez, Núñez, & Lema, 1994). The addition of specific enzymes (for example, amylase, glucanase, protease, cellulase, or pectinase) can enhance the extractability of oil by breaking the cell wall, hydrolyzing the structural polysaccharides, and destroying the lipid bodies. The mild conditions of the process also promise a higher quality of oil and meal. These benefits make this technique appealing for krill oil extraction.

Proteases have been used to assist the production of krill oil from fresh krill (Bruheim et al., 2016; Lee, 2014). A typical enzyme-assisted extraction process is comprised of disintegrating the krill into small particles, adding water and heating, adding enzymes to hydrolyze the disintegrated material, deactivating the enzymes, removing solids (mainly the exoskeleton) from the processed material, separating and drying the PL-protein complex, and extracting the krill oil from the obtained complex (Bruheim et al., 2016). Notably, removal of exoskeleton from krill material can reduce fluoride contents in the products. Lee et al. (2014) patented another enzyme-assisted extraction process, in which an ultra-high-pressure (10 to 300 MPa) reactor was applied to make the krill easily liquefiable and ensure full contact with the proteases. After enzymatic reaction for 4 to 24 hr, the liquefied krill was filtered to separate the filtrate and sludge. The PLs-enriched oil was extracted by centrifugation from the filtrate, and the astaxanthin-enriched oil was extracted from the sludge with ethanol.

The greatest advantage of this approach is the mild conditions, which enable oil and protein with good quality to be obtained simultaneously from krill. Due to the enzymatic hydrolysis, krill peptides, a valuable by-product, can be recovered from this process. The low-molecular-weight peptides derived from krill have been attracting increasing attention and are generally considered as bioactive substances in functional food and nutraceuticals for health promotion and disease prevention (Chen et al., 2009; Zhao et al., 2013). However, the application of enzymes increases the cost compared with the traditional extraction approaches, and the

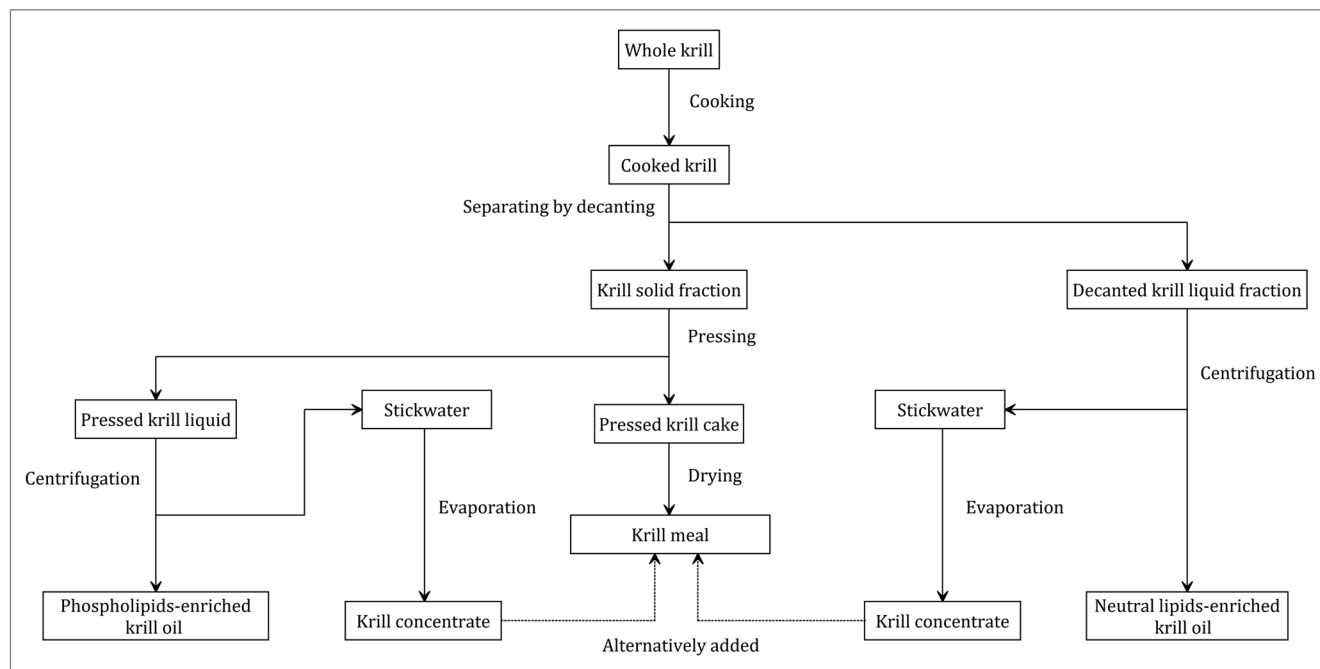


Figure 3—Schematic view of a typical nonsolvent extraction method. Modified from Katevas et al. (2014).

longer hydrolysis time reduces the potential for its large-scale industrial applications.

Health Benefits of Krill Oil

Krill oil is abundant in nutrients, such as EPA, DHA, PLs, tocopherols, vitamin A, and astaxanthin, which help to support human health. Numerous studies have been performed to evaluate the health benefits of krill oil, including anti-inflammatory effects, CVD prevention, anti-obesity and anti-diabetic effects, women's health, neuroprotection, and anti-cancer activities, which are summarized in Table 5.

Anti-inflammatory effects

Chronic inflammation is closely associated with diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease, and psoriasis (Barnes & Karin, 1997). Furthermore, systemic inflammation may also be related to the pathogenesis of some disorders, including obesity, atherosclerosis, cachexia, anorexia, and osteoporosis (Gan, 2004; Monteiro & Azevedo, 2010). Therefore, for better health, sufficient attention should be paid to the control of inflammation. The anti-inflammatory effects of krill oil have been confirmed both *in vivo* and *in vitro* models as shown in Table 5.

In vitro experiment has proven that krill oil could significantly attenuate the release of pro-inflammatory cytokine tumor necrosis factor α (TNF- α) by inhibiting the binding of lipopolysaccharide (LPS) to toll-like receptor 4 (TLR4) in LPS-induced inflammatory human acute monocytic leukemia cell line THP-1 in a dose-dependent manner. Krill oil at the concentration of 50 $\mu\text{g/mL}$ in medium completely abolished the LPS binding to TLR4 and inhibited the production of TNF- α by 75% (Bonaterra, Driscoll, Schwarzbach, & Kinscherf, 2017). Batetta et al. (2009) also found a decreased TNF- α release in LPS-treated peritoneal macrophages from obese Zucker rats supplemented with krill oil in diets compared with the control group. The authors ascribed the anti-inflammatory effects to the alteration of the endocannabinoid

(EC) system modified by n-3 PUFAs. The ECs derived from n-3 PUFAs were demonstrated to have anti-inflammatory properties (Calder, 2009). Moreover, krill oil potently down-regulated the mRNA expression levels of pro-inflammatory cytokines TNF- α and interleukin-8 (IL-8) in inflammatory cells infected with LF82 bacteria or exposed to cytomix (a combination of TNF- α and interferon- γ). Treatment with krill oil at a concentration of 250 mg/L in medium also improved wound healing, inhibited bacterial adhesion/invasion in epithelial cells and survival within macrophages. These results supported the health benefit claims of krill oil in reducing intestinal inflammation by improving intestinal barrier integrity and epithelial restitution (Costanzo et al., 2016).

In vivo studies have been focused on the anti-inflammatory activities on arthritis or colitis in mice or human (Table 5). Ierna, Kerr, Scales, Berge, and Griinari (2010) evaluated the anti-inflammatory property of krill oil in an experimental model of collagen-induced arthritis-susceptible DBA/1 mice. They demonstrated that consumption of krill oil at a daily dosage approximately equivalent to 0.44 g EPA+DHA per 100 g diet for 2 months improved the pathology in the arthritic mice by reducing the magnitude of cell influx, thickening of synovial membrane, erosion of cartilage, and infiltration of inflammatory cells into the joint. Krill oil also showed the potential to attenuate inflammation in a rat model of dextran sulfate sodium-induced ulcerative colitis. Supplementation with krill oil at a dosage of 5% in diet for 4 weeks significantly preserved the colon length in the rats and beneficially changed the levels of interleukins (ILs) and prostaglandins (PGs) which are associated with inflammation. Further investigations indicated that krill oil resulted in the inhibition of peroxisome proliferator-activated receptor gamma (Pparg) mRNA expression, thus reducing nuclear factor-kappa B (NF- κB) transcriptional activity and cytokine production (Grimstad et al., 2012). The level of C-reactive protein (CRP) in plasma shows a marked elevation under inflammatory conditions, and it has been used to monitor various types of inflammation (Young, Gleeson, & Cripps, 1991).

Table 5—Health benefits of krill oil.

Benefit	Study type	Krill oil information	Findings	References
Anti-inflammatory effects	<i>In vitro</i> studies on inflammatory human acute monocytic leukemia cell line (THP-1)	Krill oil prepared in the laboratory; unreported composition	Treatment with krill oil (12.5, 50 μ g/mL in RPMI-1640 medium) attenuated the release of TNF- α by inhibiting the binding of LPS to TLR4	Bonaterrea et al., 2017
	<i>In vitro</i> studies on inflammatory human colorectal adenocarcinoma cell lines (Caco2, HT29) and mouse leukemic monocyte macrophage cell line (RAW 264.7)	Krill oil provided by Gieliepi SPA; PLs, 51%; DHA, 7%; EPA, 12%; n-3 PUFAs, 21%; astaxanthin, 400 ppm	Treatment of Caco2 and HT29 cells (250 mg/L in DMEM), and RAW 264.7 (250 mg/L in RPMI 1640 medium) with krill oil down-regulated inflammation by improving intestinal barrier integrity and epithelial restitution, controlling bacterial adhesion and invasion to epithelial cells, and reducing the mRNA expression levels of TNF- α and IL-8	Costanzo et al., 2016
	<i>In vitro</i> studies on LPS-treated peritoneal macrophages from obese Zucker rats	Krill oil provided by Aker BioMarine; unreported composition	The TNF- α release was significantly inhibited in LPS-treated peritoneal macrophages from obese Zucker rats supplemented with krill oil (0.44 g EPA+DHA from krill oil per 100 g diet) for 4 weeks	Vigerust et al., 2013
	Animal experiment in the model of collagen-induced arthritis-susceptible DBA/1 mice	Superba® krill oil provided by Aker BioMarine; unreported composition	Supplementation with 0.44 g EPA+DHA from krill oil per 100 g diet for 2 months reduced the arthritis scores and hind paw swelling in the arthritic mice	Ierna et al., 2010
	Animal experiment in the model of DSS-induced ulcerative colitis rats	Krill oil provided by Aker BioMarine; unreported composition	Supplementation with 5 g krill oil per 100 g diet for 4 weeks preserved the colon length and beneficially changed the levels of ILs, PGs, and expression of Pparg mRNA	Grimstad et al., 2012
	Animal experiment in mice transgenic for TNF- α fed with high-fat diet	Krill oil provided by Aker BioMarine; unreported composition	Supplementation with 5.8 g krill oil per 100 g diet for 4 weeks decreased the MCP-1, but did not substantially change the levels of other pro-inflammatory cytokines	Vigerust et al., 2013
	Randomized double-blind clinical in patients with chronic inflammation	NKO® krill oil provided by Neptune Technologies & Bioresources; EPA, 17%; DHA, 10%; n-3/n-6, 15/1	A daily dose of 300 mg krill oil reduced CRP levels and inhibited inflammation within 7–14 days	Deutsch, 2007
	Randomized crossover clinical trial in mildly overweight hypertriglyceridemic subjects	Krill oil provided by Erbozeta S.r.l.; EPA, 75 mg per pill; DHA, 45 mg per pill	Supplementation with 1 g krill oil per day for 4 weeks significantly reduced hs-CRP levels in plasma from 2.15 to 0.43 mg/L	Cicero et al., 2016
	Animal experiment in obese Zucker rats	Krill oil provided by Aker BioMarine; unreported composition	Supplementation with 0.44 g EPA+DHA from krill oil per 100 g diet for 4 weeks decreased levels of LDL-C and TAG in liver and heart	Batetta et al., 2009
	Animal experiment in hyperlipidemia rats model	Krill oil purchased from local market; unreported composition	Supplementation with krill oil for 4 weeks reduced serum TC, LDL-C in all dosage groups (16.65, 50, 100 mg krill oil /100 g body weight; decreased serum TAG levels in the low and middle dosage groups (16.65, 50 mg krill oil per 100 g body weight)	Zhu et al., 2008
CVD prevention	Animal experiment in high-fat-fed C57BL/6 mice	Krill oil provided by Aker BioMarine; EPA, 12.5%; DHA, 7%; TAGs, 23%; FFAs, 6%; PLs, 58%; astaxanthin, 201 mg/100 g	Consumption of krill oil with 1.25%, 2.5%, or 5.0% in diet decreased levels of TC in liver and serum, TAG in liver; increased serum adiponectin	Tandy et al., 2009
	Animal experiment in dyslipidemic nonhuman primates suffering from naturally occurring diabetes type-2	98% pure krill PLs extracted from krill oil obtained from Aker BioMarine; EPA, 157 mg/g; DHA, 92 mg/g	Supplementation with krill PLs for 4 weeks increased blood HDL-C and apolipoprotein A1 at a dosage of 50 mg/kg/day; decreased TC, LDL-C, apolipoprotein B100 and TAG and increased HDL-C and apolipoprotein A1 at the dosages of 150 and 450 mg/kg/day	Hals et al., 2017
	Animal experiment in C57BL/6J mice fed with high-fat diet	Krill oil extracted from frozen Antarctic krill by a subcritical extraction system; EPA, 16.3%; DHA, 9.6%; TAGs, 62.30%; PLs, 28.68%; astaxanthin, 248.4 ppm; tocopherols, 67.7 ppm	Dietary intake of 5 g krill oil per 100 g diet for 12 weeks reduced the serum TC and LDL-C contents and improved the glucose tolerance and fast blood glucose	Sun et al., 2017b
	Muti-center, randomized study in patients with hyperlipidemia	NKO® krill oil provided by Neptune Technologies & Bioresources; unreported composition	Dietary intake of 1–3 g krill oil daily effectively reduced levels of blood glucose, TC, TAG, LDL-C, and increased HDL-C	Bunea et al., 2004
	Randomized, double-blind, multi-center study in adults with borderline high or high fasting serum TG levels (150 to 499 mg/dL)	Krill oil capsules provided by Aker BioMarine; EPA, 13.1%; DHA, 6.5%; TAGs, 30%; FFAs, 3.8%; PLs, 45%	Supplementation with krill oil at the dosages of 0.5, 1, 2, 4 g krill oil/day for 12 weeks reduced serum TAG levels, and did not increase LDL-C and total cholesterol	Berge et al., 2014

(Continued)

Table 5–Continued..

Benefit	Study type	Krill oil information	Findings	References
Anti-obesity and anti-diabetic effects	Randomized, double-blind, multi-center study in healthy adults with fasting serum TAGs between 1.3 and 4.0 mmol/L	Krill oil capsules provided by Rimfrost AS; n-3 PUFAs, 166 mg/g	Supplementation with krill oil for 8 weeks (4 g/day) significantly increased the level of total lipids, PLs, cholesterol, cholesteryl esters and nonesterified cholesterol in the smallest VLDL subclass and decreased blood glucose	Rundblad et al., 2017
	Randomized, cross-over, clinical trial in mildly overweight hypertriglyceridemic subjects	Krill oil provided by Erbozeta S.r.l.; EPA, 75 mg per pill; DHA, 45 mg per pill	Supplementation with 1 g krill oil per day for 4 weeks significantly improved TG, HDL-C and apolipoprotein A1 levels in plasma	Cicero et al., 2016
	Animal experiment in high-fat-fed C57BL/6 mice	Superba® krill oil provided by Aker BioMarine; EPA, 12.5%; DHA, 7%; TAGs, 23%; FFAs, 6%; PLs, 58%; and LPC, 6%	Supplementation with krill oil (1.25%, 2.5%, or 5.0% in diet) for 8 weeks significantly reduced AEA and 2-AG levels in heart, kidneys, gastrocnemius muscle, inguinal and epididymal adipose tissue	Piscitelli et al., 2011
	Animal experiment in obese Zucker rats	Krill oil provided by Aker BioMarine; unreported composition	Supplementation with 0.44 g EPA+DHA from krill oil per 100 g diet for 4 weeks decreased levels of AEA and 2-AG in visceral adipose tissue, AEA in liver and heart, and 2-AG levels in brain	Batetta et al., 2009; Di Marzo et al., 2010
	Animal experiment in hyperlipidemia rats model	Krill oil purchased from local market; unreported composition	Supplementation with krill oil for 4 weeks reduced body weights in the low and middle dosage groups (16.65, 50 mg krill oil per 100 g body weight)	Zhu et al., 2008
	Animal experiment in C57BL/6J mice fed with high-fat diet	Krill oil extracted from frozen Antarctic krill by enzyme-assisted extraction; EPA, 16.3%; DHA, 9.6%; TAGs, 62.30%; PLs, 28.68%; astaxanthin, 248.4 ppm; tocopherols, 67.7 ppm	Dietary intake of 5 g krill oil per 100 g diet for 12 weeks reduced body weight gain; improved the glucose tolerance and fast blood glucose; resulted in less fat accumulation in tissue such as adipose and liver	Sun et al., 2017b
	Animal experiment in male C57BL/6N mice fed with high-fat diet	Krill oil extracted from frozen Antarctic krill by a subcritical extraction system; PLs, 42.3%; TGs, 30.6%; FFAs, 12.2%; sterol esters, 6.2%; cholesterol/sterols, 5.8%; unknown neutral lipids, 2.9%; EPA, 19.40%; DHA, 14.10%; astaxanthin, 191 ppm	Krill oil supplementation with 5.0% in diet for 10 weeks resulted in a 15% lower body weight gain and a dramatic suppression of hepatic steatosis by modifying gene expressions of AMPK	Yang et al., 2016
	Animal experiment in obese New Zealand white rabbits	Krill oil capsules provided by Aker BioMarine; unreported composition	Consumption of the krill oil diet at a dose of 600 mg n-3 PUFAs daily for 60 days reduced the fasting blood glucose and improved glucose tolerance by decreasing Acaca expression in liver and increasing Hmgcs2 and Cd36 in skeletal muscle	Ivanova et al., 2015
Women's health	A randomized controlled parallel study in healthy adults	RIMFROST Sublime® krill oil; astaxanthin, 982ppm	Supplementation with 4 g krill oil per day for 8 weeks increased plasma levels of n-3 PUFAs; reduced fasting glucose; down-regulated the mRNA expression of thirteen genes including genes involved in glucose and cholesterol metabolism and β -oxidation	Rundblad et al., 2017; Rundblad, Holven, Bruheim, Myhrstad, & Ulven, 2018
	Animal study in ovariectomized rats	Krill PLs obtained from Nippon Suisan Co. Ltd.; unreported composition	Supplementation with 182 mg EPA + 118 mg DHA obtained from krill PLs for 2 weeks improved the cerebral blood circulation in ovariectomized rats by regulating NCX1 mRNA expression, K_{ATP} channels, K_{Ca} channels in basilar artery	Sakai et al., 2014
	Double-blind, randomized clinical trial in patients of reproductive age diagnosed with premenstrual syndrome	NKO® Krill Oil provided by Neptune Technologies & Bioresources; unreported composition	One gram krill oil daily for three months reduced dysmenorrhea and the emotional and physical symptoms of PMS	Sampalis et al., 2003
Neuroprotective effects	Animal study in Wistar-Unilever rats	Krill oil obtained from Aker Biomarine; unreported composition	Rats supplemented with 1.25 g krill oil per 100 g diet for 7 weeks had better performance in ALSAT, UALST and FST, as well as up-regulated mRNA for Bdnf in the hippocampus	Wibrand et al., 2013

(Continued)

Table 5–Continued..

Benefit	Study type	Krill oil information	Findings	References
	Animal experiment in D-galactose-induced aging mice	Krill oil provided by Ningbo Today Food Co., Ltd; PLs, 56.8%; EPA, 12.5%; DHA, 7.5%; astaxanthin, 375ppm	Supplementation with krill oil at the dosages of 100, 200, 600 mg/kg/d for 40 days decreased the escape latency and led to a better performance in the Morris water maze test; improved the oxidative stress biomarkers (increasing serum SOD and GSH-Px; up-regulating the expression of Celsr3 and Ppp1r1b	Cheong et al., 2017
	Animal experiment in model of ovariectomized rats	Krill oil was obtained from Aker BioMarine; unreported composition	Supplementation with krill oil of 200 mg/kg/d for 2 months decreased levels of the gene expression of Bdnf, SELADIN-1, MDA, APP, GSK-3 β , AChE and NE	Mansour et al., 2017
	Animal experiment in SAMP8 mice	Krill oil extracted by 95% ethanol; EPA, 15.7%; DHA, 9.78%	Treatment with krill oil (1% in diet) for 12 weeks improved learning and memory abilities and relieved nervousness by Morris water maze, Barnes maze test and open-field test; reduced A β accumulation in hippocampus; ameliorated oxidative stress in brain by decreasing MDA and 8-oxo-G levels and increasing SOD and GSH-Px activities	Li et al., 2018
	Animal experiment in aged rats	Krill oil produced by pressurized liquid extraction; unreported composition	Supplementation with krill oil of 70 mg/d for 3 months improved peripheral and central insulin resistance; increased Bdnf levels; facilitated both mitochondrial and protein synthesis which are necessary for synaptic plasticity	Tomé-Carneiro et al., 2018
	Randomized, double-blind, clinical study in healthy elderly volunteers	Krill oil provided by Nippon Suisan Kaisha Ltd.; unreported composition	Supplementation with krill oil of 0.25 g/d for 12 weeks resulted in a great change in oxyhemoglobin concentrations during the working memory task and a lower differential value for P300 latency during the calculation task than the control group	Konagai et al., 2013
Anti-cancer effects	<i>In vitro</i> studies on human colon cancer cells (SW480)	Krill oil purchased from local market; unreported composition	Treatment of SW480 cells with krill oil (2.5–20 μ g/mL in DMEM) for 48 hr resulted in time-dependent inhibition of cell growth	Zhu et al., 2008
	<i>In vitro</i> studies on human cancer cell lines (U937, K562, SMMC-7721, PC-3, MDA-MB-231, HL60 and MCF-7)	Krill oil extracted from freezing Antarctic krill by the mixed organic solvents of n-hexane and ethanol (10:1)	Treatment of the cell lines with EPA and DHA obtained from krill oil (10–400 μ g/mL in DMEM) acted inhibition effects on cell growth	Zheng et al., 2017
	<i>In vitro</i> studies on human colon adenocarcinoma cell lines (HCT-15, SW-480 and Caco-2 cells)	Krill oil purchased from Swisse Wellness Pty Ltd.; unreported composition	Treatment o with FFA extract obtained from krill oil at 0.12 μ L/100 μ L in medium) for 48 hr resulted in significantly high apoptosis in all three colorectal cancer cell lines	Jayathilake et al., 2016
	<i>In vitro</i> studies on human osteosarcoma cells (143B)	Krill oil (no information about its source); EPA, 24.6%; DHA, 14.7%	Treatment of the cell line with EPA and DHA obtained from krill oil (1.89 μ M in DMEM) inhibited 23%, 50% and 64% of cell proliferation at 24, 48 and 72 hr, respectively	Su et al., 2018

Abbreviations: A β , β -amyloid; Acaca, acetyl-CoA carboxylase alpha; AChE, acetylcholinesterase; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; ALSAT, the Aversive Light Stimulus Avoidance Test; AMPK, adenosine monophosphate-activated protein kinase; APP, amyloid precursor protein; Bdnf, brain-derived neurotrophic factor; Cd36, CD36 molecule/fatty acid translocase; CRP, C-reactive protein; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DMEM, Dulbecco's modified Eagle's medium; DSS, dextran sulfate sodium; EPA, eicosapentaenoic acid; FFAs, free fatty acids; FST, the Forced Swimming Test; GSH-Px, glutathione peroxidase; GSK-3 β , glycogen synthase kinase-3beta; HDL-C, high-density lipoprotein cholesterol; Hmgcs2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; hs-CRP, high-sensitivity CRP; IL-8, interleukin-8; ILs, interleukins; LDL-C, low-density lipoprotein cholesterol; LPC, lysophosphatidylcholine; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; NCX1, Na⁺/Ca²⁺ exchanger 1; NE, norepinephrine; n-3 PUFA, n-3 polyunsaturated fatty acids; 8-oxo-G, 7,8-dihydro-8-oxoguanine; PGs, prostaglandins; PLs, phospholipids; PMS, premenstrual syndrome; Pparg, proliferator-activated receptor gamma; SAMP8, senescence-accelerated prone mouse strain 8; SELADIN-1, selective AD indicator-1; SOD, superoxide dismutase; TAG, triacylglycerols; TC, total cholesterol; TLR4, toll-like receptor 4; TNF- α , tumor necrosis factor α ; UALST, the Unavoidable Aversive Light Stimulus Test; VLDL, very low-density lipoprotein.

A daily dose of 300 mg krill oil within a short treatment period (7 to 14 days) resulted in a significant decline in the CRP concentration and alleviation of arthritic symptoms in patients suffering from chronic inflammatory conditions (Deutsch, 2007). Cicero et al. (2016) also found that supplementation with 500 mg krill oil twice a day for 4 weeks was able to significantly reduce high-sensitivity CRP (hs-CRP) level in plasma from 2.15 to 0.43 mg/L in mildly overweight hypertriglyceridemic subjects.

CVD prevention

CVD is well known as a global health problem that is an important cause of death in adults and the elderly people (Sans, Kesteloot, & Kromhout, 1997; Yusuf, Reddy, Ôunpuu, & Anand,

2001), which can be prevented by consuming n-3 PUFAs-rich food as supported by many reports (Harris, Connor, Alam, & Illingworth, 1988; Rizos, Ntzani, Bika, Kostapanos, & Elisaf, 2012; von Schacky, Angerer, Kothny, Theisen, & Mudra, 1999). Fish oil consumption has been accepted to exert a beneficial effect on CVD mainly due to the presence of n-3 PUFAs. Currently, many studies have also been conducted to investigate the relation between krill oil and CVD prevention, which are discussed below.

Abnormal levels of TAG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) potentially increase the risks of CVD, and they have often been regarded as CVD risk factors (Papakonstantinou, Lambadiari, Dimitriadis, & Zampelas, 2013).

Some studies were conducted in animal models to evaluate the effects of krill oil on these CVD risk factors in blood and tissues (Batetta et al., 2009; Hals, Wang, & Xiao, 2017; Sun et al., 2017b; Tandy et al., 2009; Zhu, Shi, Qian, Cai, & Li, 2008). An 8-week feeding trial supplemented with 1.25%, 2.50%, or 5.00% krill oil in diet showed that the krill oil-containing diet significantly reduced hepatic TG and TC levels, as well as decreased the serum TG in high-fat-fed mice (Tandy et al., 2009). At the highest dosage of 5% in diet, an increased serum adiponectin was also observed in krill oil-fed mice, supporting the anti-atherogenic properties of krill oil (Kadowaki et al., 2006; Lu et al., 2008; Tandy et al., 2009). Sun et al. (2017b) also found that krill oil supplementation (5% in diet) for 12 weeks significantly reduced the serum TC and LDL-C contents (2.50 mol/L and 0.45 mol/L, respectively) in high-fat-fed mice compared with the control group (3.70 mol/L and 0.65 mol/L, respectively). In addition, Batetta et al. (2009) and Zhu et al. (2008) demonstrated that krill oil could decrease the TAG, TC, and LDL-C levels in high-fat-fed mice with related metabolic dysfunction. Similar results were also reported in a different animal model of cynomolgus monkeys by Hals et al. (2017). They suggested that krill oil was effective in improving CVD risk factors including TC, LDL-C, HDL-C, TAG, apolipoprotein B100, and apolipoprotein A1 in dyslipidemic nonhuman primates suffering from naturally occurring diabetes type-2.

More evidence for the protective role of krill oil against CVD has been reported in human clinic trials (Berge, Musa-Veloso, Harwood, Hoem, & Burri, 2014; Bunea, El Farrah, & Deutsch, 2004; Cicero et al., 2016; Rundblad et al., 2017). Bunea et al. (2004) investigated the correlations between commercial krill oil intake and the blood lipid profiles in 120 patients with hyperlipidemia who were diagnosed with mildly high to very high levels of blood TC (193.9 to 347.9 mg/dL) and TAG (203.8–354.4 mg/dL). The patients who were given krill oil 1 to 3 g/day for 12 weeks had significantly higher HDL levels and lower blood glucose, TC, TAG, and LDL levels than those who were given placebo. Similarly, Berge et al. (2014) reported that krill oil capsules consumption was associated with the reduced CVD risk factors in 300 adults who had borderline high or high fasting serum TG levels (150–499 mg/dL). A reduction of 10% (relative to placebo group) in serum TAG was found in the subjects after administering krill oil at the dosage of 0.5 to 4.0 g/day for 12 weeks. This improvement of lipid profile after krill oil treatment was also observed in mildly overweight hypertriglyceridemic subjects (Cicero et al., 2016) and in healthy adults with fasting serum TAG between 1.3 and 4.0 mmol/L (Rundblad et al., 2017).

Anti-obesity and anti-diabetic effects

Unbalanced energy intake can disturb the EC system, and this dysregulation of EC system can in turn result in excessive visceral fat accumulation and reduced adiponectin release from these tissues, thereby increasing the risks of obesity and type 2 diabetes. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the most widely studied ECs, and they have been suggested to be involved in the control of lipid and glucose metabolism (Di Marzo, 2008). Elevated levels of AEA and 2-AG were observed in the tissues of obese subjects (Batetta et al., 2009; Di Marzo et al., 2010). Diets containing krill oil were shown to be effective in lowering the concentrations of AEA and 2-AG in heart, kidneys, gastrocnemius muscle, inguinal and epididymal adipose tissue in the high-fat-fed C57BL/6 mice (Batetta et al., 2009; Piscitelli et al., 2011), as well as decreasing body weight gains in hyperlipidemic rats (Zhu et al., 2008) and obese mice (Sun et al., 2017b; Yang et al., 2016).

The n-3 PUFAs have been widely demonstrated to decrease the biosynthesis of arachidonic acid (ARA) and its incorporation into PLs, thus potentially reducing the amounts of biosynthetic precursors for AEA and 2-AG (Matias et al., 2008). The anti-obesity effects of krill oil might be attributable to the presence of n-3 PUFAs. This was confirmed by Maki et al. (2009), who found that 4 weeks of krill oil supplementation at a dosage of 2 g/day increased plasma EPA and DHA in overweight and obese men and women.

Fat-induced insulin resistance is a common problem. Ivanova et al. (2015) showed that consumption of the krill oil diet at a dose of 600 mg n-3 PUFAs daily for 60 days reduced fasting blood glucose, and improved glucose tolerance in obese New Zealand white rabbits. A significant reduction of fasting blood glucose was also observed in healthy subjects after krill oil consumption (4 g/day) for 8 weeks, which indicated its potential anti-diabetic properties (Rundblad et al., 2017). Yang et al. (2016) ascribed these beneficial effects to the activation of adenosine monophosphate-activated protein kinase (AMPK) which participates in regulating glucose and lipid metabolism. It was also proposed that n-3 PUFAs from krill oil ameliorated insulin sensitivity and insulin secretion, and altered gene expression levels of key enzymes involved in β -oxidation and lipogenesis in liver and skeletal muscles (Ivanova et al., 2015).

Women's health

Premenstrual syndrome (PMS) is commonly observed in young and middle-aged women. It is a consistently cyclic disorder during the luteal phase of menstruation, characterized by emotional, behavioral, and psychological symptoms (Dickerson, Mazyck, & Hunter, 2003; Stevinson & Ernst, 2001). Although the etiology of PMS has not been clearly elucidated, approximately 75% of women are affected by some PMS symptoms during their reproductive years (Barnhart, Freeman, & Sondheimer, 1995). Many types of dietary supplements, including vitamins (A, E, and B₆), calcium, magnesium, and multivitamin/mineral supplements have been proposed for the alleviation of certain symptoms of PMS in women (Bendich, 2000; Dickerson et al., 2003). It has also been reported that n-3 PUFAs may reduce the psychiatric and the somatic symptoms of PMS (Sohrabi, Kashanian, Ghafoori, & Malakouti, 2013).

As a potential source of n-3 PUFAs and vitamins A and E, krill oil exerted positive effects on the management of the physical and emotional symptoms of PMS. Patients administering commercial krill oil soft gels as prescribed in three menstrual cycles used fewer pain relievers for menstrual pain, and they got lower scores than control group in the self-assessment questionnaire for PMS based on the American College of Obstetricians and Gynecologists diagnostic criteria for PMS ranging from 0 (no symptoms) to 10 (unbearable). In addition, the effectiveness of krill oil for the management of PMS and dysmenorrhea was much more successful than fish oil (Sampalis et al., 2003). The superior performance of krill oil has been speculated to be due to its unique biomolecular profile, with a combination of PLs, n-3 PUFAs, and diverse antioxidative substances. The n-3 PUFAs associated with PLs in krill oil also showed a higher bioavailability than that as TAGs in fish oil (Schuchardt et al., 2011), which might in turn play a more active role in the regulation of emotional symptoms (Sampalis et al., 2003). However, the underlying mechanisms still require further investigations.

In addition, postmenopausal women commonly experience cerebrovascular dysfunction due to estrogen deficiency (Serock, Wells, & Khalil, 2008). K_{ATP} channels, K_{Ca} channels, and

$\text{Na}^+/\text{Ca}^{2+}$ exchanger 1 (NCX1) play vital roles in the auto-regulation of cerebral blood flow, but they are easy to be affected when ovarian function is abnormal. Administration of krill oil (182 mg EPA + 118 mg DHA obtained from krill PLs daily) for 2 weeks beneficially regulated NCX1 mRNA expression, K_{ATP} channels, and K_{Ca} channels in the basilar artery, thus improving the cerebral blood circulation in ovariectomized rats. These findings indicated that krill oil would be a good nutritional supplement for postmenopausal women (Sakai et al., 2014).

Neuroprotective effects

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is commonly observed in elderly people (Francis, Palmer, Snape, & Wilcock, 1999). Patients show gradual cognitive decline during the development of the disease, often accompanied by behavioral disturbances such as aggression, depression, and wandering, which greatly reduce the quality of life for both patients and their caregivers. Several studies in animal or humans models have been carried out to investigate the neuroprotective effects of krill oil, as shown in Table 5.

Treatment with krill oil at the dosage of 1.25 g per 100 g diet for 7 weeks had a positive effect on learning and memory processes in a rat experiment using the Aversive Light Stimulus Avoidance Test, the Unavoidable Aversive Light Stimulus Test, and the Forced Swimming Test. Brain-derived neurotrophic factor (Bdnf) is a gene associated with neuronal growth and differentiation in the hippocampus, and an elevated expression level of mRNA for Bdnf was also observed in the rats supplemented with krill oil (Wibrand et al., 2013). These results are consistent with the study conducted by Tomé-Carneiro et al. (2018). Furthermore, Cheong et al. (2017) reported the association between krill oil consumption and proteomic changes in brain tissues of D-galactose induced aging mice. They found that dietary krill oil at the dosages ranging from 100 to 600 mg/kg/day for 40 days significantly changed the expression levels of 29 unique proteins in brain tissues of aging mice. In particular, the expression levels of *Celsr3* and *Ppp1r1b* mRNA, which are associated with brain development, learning acquisition, and working memory, were significantly up-regulated in the group receiving krill oil. Krill oil also improved the tested oxidative stress biomarkers in serum including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and malondialdehyde (MDA). In addition, Li et al. (2018) confirmed the protective effect of krill oil against AD in an animal model of senescence-accelerated prone mouse strain 8 (SAMP8) mice. Supplementation with krill oil (1% in diet) for 12 weeks could effectively improve the learning and memory abilities and relieve nervousness in SAMP8 mice based on the Morris water maze, Barnes maze test and open-field test. The accumulation of β -amyloid ($\text{A}\beta$) plays an important role in the cognitive decline and AD pathology. Krill oil was also shown to reduce the accumulation of $\text{A}\beta$ in hippocampus, as well as ameliorate oxidative stress in brain by decreasing MDA and 7,8-dihydro-8-oxoguanine (8-oxo-G) levels, and increasing SOD and GSH-Px activities in the brain of SAMP8 mice.

Estrogen loss in aging women may lead to an increased risk of AD (Janicki & Schupf, 2010). Studies in ovariectomized rats showed significantly decreased concentrations of estrogen, serotonin, dopamine, and insulin growth factor-1, as well as altered gene expression of amyloid precursor protein, glycogen synthase kinase-3 β (GSK-3 β), Bdnf, and selective AD indicator-1 (SELADIN-1), which are related to AD in rats. After supplementation with krill oil (200 mg/kg/d) for 2 months, all the parameters

in ovariectomized rats moved towards normalization, indicating the protective effects of krill oil against neurodegeneration and inhibition of the development of AD in elderly women (Mansour, Moustafa, Hassan, & Thabet, 2017).

Human studies also supported the beneficial effects of krill oil on cognitive function. Oxyhemoglobin is mainly associated with cerebral blood flow, and its concentration in blood might partially represent the level of activation of regional cerebral function when executing cognitive tasks (Hibino et al., 2013). The P300 event-related potential is one of the cognitive components that is used as an objective procedure to assess neuroelectrical activity-associated cognitive behaviors and activities (Alvarenga et al., 2005; Hansenne, 2000). By monitoring the variation in oxyhemoglobin contents and P300 event-related potential components in the cerebral cortex, Konagai et al. (2013) evaluated the effects of dietary krill oil on cognitive function in 45 healthy elderly males during memory and calculation tasks. After administration of krill oil (1.98 g/day for 12 weeks), the subjects showed a significant change in oxyhemoglobin concentrations when performing the working memory task, and a lower differential value of P300 latency during the calculation task than the control group, which revealed the positive effects of krill oil on improving the cognitive function in the elderly.

Anti-cancer activities

Cancer has recently become one of the major causes of death in both developed and developing countries (Jemal et al., 2011). The global incidence of cancer is still constantly increasing due to the aging and growth of the population alongside an increasing adoption of cancer-causing lifestyle choices, such as smoking, lack of exercises, and "westernized" diets (Torre et al., 2015). Chemotherapy and radiotherapy are important anti-cancer treatments by triggering apoptosis to block neoplastic inception or delay disease progression. However, they have numerous negative effects, such as myelosuppression, mucositis, dermatitis, and diarrhea (Jayatilake, Senior, & Su, 2016). The idea of using dietary nutrients that are capable of modulation of apoptosis has been raised as a potential anticancer therapy (Block, Patterson, & Subar, 1992). To date, the literature contains few experimental studies on the anti-cancer effects of krill oil *in vivo*. However, some *in vitro* studies have been carried out to investigate the effects of krill oil or krill oil extract on the growth of some cancer cell lines.

Colon cancer is the second leading cause of cancer-related death in the USA (Jemal et al., 2005). Krill oil showed time- and dosage-dependent antiproliferative effects on the growth of colon cancer cells (SW480). Treatment with krill oil at the concentration of 20 $\mu\text{g}/\text{mL}$ in Dulbecco's modified Eagle's medium (DMEM) for 48 hr resulted in a 29.9% inhibition of cell growth of SW480 (Zhu et al., 2008). Jayatilake et al. (2016) also focused on the effects of FFA extract obtained from krill oil on the cell proliferation and apoptosis in three cell lines of human colon adenocarcinoma (HCT-15, SW-480 and Caco-2 cells). Treatment with 0.12 μL FFA extract of krill oil in 100 μL DMEM for 48 hr resulted in inhibition effects on the proliferation of HCT-15 and SW-480 cells. In addition, the FFA extract induced significantly higher apoptosis in all the three colon cells compared with the control group. The anti-cancer activity of krill FFA extract was also confirmed in human osteosarcoma cells, and the inhibition effect of 1.89 μM of FFA extract from krill oil was comparable to 0.5 to 1.0 μM of doxorubicine, which is a commonly used anti-cancer drug (Su, Tanalgo, Bustos, & Dass, 2018). Zheng et al. (2017) separated and identified the E-configuration structures of

Table 6—Recent patent applications for krill oil.

Patent No.	Title	Purpose	References
US 20060078625	Compositions including krill extracts and conjugated linoleic acid and methods of using same	Treatment of joint ailment, PMS, CVD, bone disease, immune deficiency, diabetes, stress related disease, and hormonal disease	Rockway, 2006
US 20070098808	Krill and/or marine extracts for prevention and/or treatment of cardiovascular diseases arthritis, skin cancer diabetes, premenstrual syndrome and transdermal transport	Treatment or prevention of CVD, rheumatoid arthritis, skin cancer, PMS, diabetes and transdermal transport enhancement	Sampalis, 2007
US 20080166420	Krill oil compositions	Treatment and prevention of CVD, including the reduction of one or more significant risk factors involved with CVD	Sones, 2008
WO 2010035013	Krill oil powder and krill oil tablets	The treatment of prophylaxis or disorders related to the cardiovascular system, metabolic system, skin and bone	Klaveness, 2010
US 20120321720	Therapeutic application of parenteral krill oil	Parenteral treatment of endotoxemia during severe sepsis or patients with toxic blood concentrations of highly lipophilic drugs	Driscoll, 2012
WO 2013127727	Hormone containing emulsion comprising krill phospholipids	Treatment or prophylaxis of neurological damage after strokes or trauma; treatment or prophylaxis of neurological damage after concussion or traumatic injury to the central nervous system	Kaspar, Krüger, Röthlein, Schmitt, & Wolf, 2013
US 20130295171	Krill oil and reacted astaxanthin composition and associated method	A medicine delivery system; enhancing cardiovascular health	Minatelli, Hill, & Moerck, 2013
AU 2013205516	Natural marine source phospholipids comprising flavonoids, polyunsaturated fatty acids and their applications	Protection of skin against the harmful effects of UVB radiation including skin cancer; improving dyslexia and abnormal motor function	Sampalis, 2013
US 20130095142	Lipid emulsion having krill oil as an active ingredient and preparation method therefor	A nutritive intravenous lipid emulsion having krill oil	Shin, 2013
US 20140271907	Compositions comprising eicosapentaenoic acid and krill oil and methods of use thereof	Treatment or prevention of CVD	Zakrzewski, 2014
US 9220735	Methods of using krill oil to treat risk factors for cardiovascular, metabolic, and inflammatory disorders	Treatment of risk factors for metabolic, cardiovascular, and inflammatory disorders	Bruheim et al., 2015
US 9295699	Krill oil and carotenoid composition, associated method and delivery system	A medicine delivery system that delivering carotenoids	Minatelli, Hill, & Moerck, 2016
US 9730966	Method of reducing appetite in a human subject comprising administering krill oil composition	Reducing appetite in humans	Bruheim et al., 2017
US 20170354694	Krill oil preparations with optimal mineral and metal composition, low impurities and low and stable TMA levels	Reducing CVD risk factors; treating or preventing cognitive disease or disorder; preventing depression; treating or preventing inflammation or inflammatory disease; preventing PMS	Ronen et al., 2017
US 20170065645	Krill oil preparations and their uses	Treating or preventing of CVD, cognitive disease, inflammatory disease, obesity, abdominal obesity; reducing high blood pressure, heart rate, blood plasma concentrations of saturated fatty acids, blood plasma concentrations of palmitic acid; increasing blood plasma concentrations of α -linolenic acid, blood plasma concentrations of stearic acid	Zchut et al., 2017
US 9889163	Bioeffective krill oil compositions	Anti-inflammation; anti-oxidation; improving insulin resistances; improving blood lipid profile	Bruheim et al., 2018
US 20180084813	CO-Q10, krill oil and vitamin D	Used as dietary supplements to provide Co-Q10, krill oil, and vitamin D	Derohanes, Rayl, Siwek, & Williams, 2018
US 20180243345	Method for increasing muscle growth using krill extract	Increasing muscle mass mediated by activation of mTOR pathway	Peele, Jäger, & Purpura, 2018

Abbreviations: PMS, premenstrual syndrome; CVD, cardiovascular disease; UVB, ultraviolet B; mTOR, mechanistic target of rapamycin.

EPA and DHA in krill oil, and they found that they exerted much higher inhibitory activities on the growth of some cancer cell lines (U937, K562, SMMC-7721, PC-3, MDA-MB-231, HL60, and MCF-7) than EPA and DHA in some commercial fish oils. Actually, tocopherols and astaxanthin were also reported

to have anti-cancer activities (Constantinou, Papas, & Constantinou, 2008; Rao et al., 2013). It is possible that the synergistic effects of all the bioactive compounds present in krill oil made the contribution to the strong anti-cancer ability observed in these studies. However, more *in vivo* studies are required to confirm

the anti-cancer effects and to elucidate its underlying molecular mechanisms.

Comparison of krill oil and fish oil

Recently, many studies have compared the performances of krill oil and fish oil supplements as they are the different carriers of EPA and DHA. Krill oil has been reported to exert more profound effects on the management of hyperlipidemia (Bunea et al., 2004), PMS (Sampalis et al., 2003), and cognitive function (Konagai et al., 2013). Some studies ascribed the better performance of krill oil to the higher bioavailability of EPA and DHA in the form of PL (Laidlaw, Cockerline, & Rowe, 2014; Ramprasath, Eyal, Zchut, & Jones, 2013; Rossmeisl et al., 2012; Ulven et al., 2011). However, these studies are questionable as most of them did not use the identical doses of EPA and DHA of krill oil and fish oil when comparing their health outcomes, and ignored the discrepancies of other components present in the two kinds of marine oils (Salem & Kuratko, 2014). For example, although Ramprasath et al. (2013) reported that krill oil could more effectively increase the concentration of n-3 PUFA in plasma than fish oil, the amounts of EPA and DHA consumed daily by subjects were different (777 mg for the krill oil group and 664 mg for the fish oil group, respectively). In a similar study (Ulven et al., 2011), both the dosages of EPA and DHA (543 mg for the krill oil group and 864 mg for the fish oil group) and the ratio of EPA/DHA (1.74 in the krill oil and 1.12 in the fish oil) were different. Furthermore, the minor components present in the two oils were not considered in most studies (Bunea et al., 2004; Konagai et al., 2013; Sampalis et al., 2003). A particularly interesting study was reported by Köhler, Sarkkinen, Tapola, Niskanen, and Bruheim (2015), who observed that EPA and DHA in krill meal had a lower bioavailability than krill oil, while similar with fish oil. This implied that the EPA and DHA in PL form alone appeared not to be a satisfactory explanation for the better performances of krill oil because the EPA and DHA forms in krill oil and krill meal were identical but their bioavailabilities differed. By now, there is no direct evidence supporting the fact that the better properties of krill oil are dominated by the EPA and DHA in the form of PL. The exact mechanism may be multifactorial because krill oil contains high concentrations of other biologically active components in addition to EPA and DHA, such as astaxanthin, tocopherols, vitamin A, and flavonoids. It has been reported that krill oil and fish oil differentially regulated lipid catabolic and synthetic pathways in mice fed with a high-fat diet, although both of them reduced plasma lipids and modulated lipid homeostasis (Tillander et al., 2014), but the underlying mechanism needs to be intensively studied. In general, more carefully controlled human trials are needed to determine the efficacies and performances of krill oil and fish oil after chronic administration.

Commercial Applications of Krill Oil and Further Prospective

Production of krill oil has recently become one of the most attractive activities in the food industry. As a novel food ingredient, krill oil has great potential in food, nutraceutical and pharmaceutical applications due to its diverse health benefits. Currently, krill oil products are commonly available as dietary supplements in the forms of soft gels, capsules, gummies, and tablets in the market. Aker Biomarine, Neptune Technologies & Bioresources, Rimfrost AS, and Enzymotec are the best-known krill oil producers worldwide and their krill oil products are popular in the European and American health markets, such as Superba® Krill Oil, NKO® Krill Oil, RIMFROST Sublime® Krill Oil, K•REAL® Krill

Oil. Patent applications are available on krill oil for preventing CVD, inflammation, cognitive disease, PMS, and improving brain function (Table 6). Some of the krill oil products are made with a combination of other functional supplements, such as other carotenoids, Co-Q10, vitamin D, and conjugated linoleic acid to provide more attractive benefits (Derohanes et al., 2018; Rockway, 2006). For example, a mixture of krill oil, probiotic *Lactobacillus reuteri*, and vitamin D has been suggested to reduce gut inflammation by increasing epithelial restitution and modulating the gut microbiota (Costanzo et al., 2018); and intranasal krill oil plus cotinine shows potential in treatment of depressive symptoms derived from recurrent associative trauma memories in posttraumatic stress disorder (PTSD) patients (Alvarez-Ricartes et al., 2018).

Even though many functionalities and commercial applications of krill oil have been explored, few studies provided detailed underlying molecular mechanisms to elucidate how exactly krill oil exerts its different activities. We previously found that krill oils with different chemical compositions led to significant differences in their antioxidant abilities (Xie et al., 2018). This suggests that there is a close relationship between the chemical composition of krill oil and its functionalities. However, as shown in Table 5, most published studies associated with the health benefits of krill oil did not describe the composition of the krill oil used in animal and clinical experiments. Further studies should emphasize the association between composition and health benefits of krill oil to help develop more diversified functional krill oil products for targeted health benefits and to accelerate the future applications of krill oil.

Conclusions

Krill oil extracted from Antarctic krill (*Euphausia superba*) has attracted increasing attention due to its potential value. In this review, we discuss the chemical composition, extraction methods, health benefits, and current applications of krill oil. Krill oil is rich in nutritional compounds, including EPA, DHA, astaxanthin, tocopherols, vitamin A, flavonoids, and minerals, which are all beneficial to human health. Specifically, most of the EPA and DHA in krill oil is present as a unique chemical form of PLs, which has led to considerable research comparing the benefits of krill oil and fish oil. However, the high level of cholesterol should be considered if the oil is used as a dietary supplement. Solvent extraction, nonsolvent extraction, super/subcritical fluid extraction, and enzyme-assisted pretreatment extraction are the four main technologies applied in krill oil production, and each of which has its own benefits and drawbacks. The chemical composition of krill oil greatly depends on the extraction approach.

Currently, krill oil products used for dietary supplements are commercially available. Various studies, including *in vitro* and *in vivo* experiments, have demonstrated that krill oil could provide anti-inflammatory, CVD preventive, anti-obesity and anti-diabetic, women's health, neuroprotection, and anti-cancer benefits. However, the mechanism of action remains to be studied. It is widely recognized that the functionalities of a product are strongly associated with its chemical composition. Therefore, more research is needed to elucidate the underlying relationship between the chemical composition and functionalities of krill oil, which would be helpful to exploit more appropriate extraction methods and to develop various krill oil products with tailored functionalities targeting specific markets.

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Authors' Contributions

Dan Xie was responsible for the study design, searching and collating the data presented, and preparing the initial draft. Mengyue Gong and Wei Wei provided assistance in the concept of the work and also revised the manuscript. Jun Jin, Xiaosan Wang, Xingguo Wang, and Qingzhe Jin aided in revising the manuscript critically. All authors reviewed the final manuscript before submission.

Conflict of Interest Statement

The authors have declared no conflict of interest.

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