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REVIEW

A review on the bio-functional roles of phospholipids from marine resources

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Abstract

Marine phospholipids (PLs) rich in ω-3 polyunsaturated fatty acids (ω-3 PUFAs) have drawn keen interest recently among researchers and consumers and could be assumed as a "miracle drug". Substantial amount of EPA and DHA, amazing and unique chemical properties and super bio-functional activities of marine PLs make it superior compared to terrestrial PLs, which lack long chain ω-3 PUFAs. Many comparative studies revealed that marine PLs showed higher health beneficial activities compared to PLs obtained from land sources. Marine PLs are not only beneficial in containing a high amount of ω-3 PUFAs but also in absorbing and assimilating ω-3 PUFAs in different tissues. Synergistic effects of PL compounds and ω-3 PUFAs in marine PLs showed super bio-functional performances like anti-atherosis and cardioprotective, anti-inflammatory, neuroprotective, immunological, and liver functions. A number of *in vivo* and *in vitro* studies on the administration of marine PLs extracted from fishes, mollusks, crustaceans, echinoderms reduced triacylglycerol (TAG) level and enhanced cardioprotective functions, demonstrated anti-inflammatory activity, reduced cell proliferation and tumor, increased cognitive functions and memory, and prevented hepatic damages. Therefore, this review paper provides detailed accounts on the present research status of critical biological and nutritional functions of marine ω-3 PUFAs rich phospholipids focusing on the origin, animal models, treatment, and roles.

1. Introduction

Phospholipids (PLs) are a group of amphiphilic lipids where a glycerol unit is attached with two fatty acids and a phosphate group is esterified to an organic molecule such as choline, serine, ethanolamine and inositol. Thus, the major PLs develop their names as phosphatidylcholine (PC), phosphatidylserine (PS) phosphatidylethanolamine (PE), and phosphatidylinositol (PI). PLs derive an amphiphile nature by containing a negatively charged phosphate group and glycerol at the head part which acts as hydrophilic and containing 2 long-chain fatty acids at the tail part that are hydrophobic and avoid water interactions. Marine PLs are defined as PLs derived from marine organisms and characterized by the presence of ω-3 long chain PUFAs. Marine PLs are unique and different from PLs derived from plants and vegetables because of their long chain ω-3 PUFAs. Compositions of PLs vary from one source to another in terms of PLs type or fatty acids nature (short, medium or long chain, saturated or unsaturated), both of them induce different properties and bio functions (Küllenberg *et al.,* 2012). They are important biomolecules that constitute structural building blocks, support cell and organelle membranes, and play a vital role in cell biochemistry and physiology. Additionally, exogenous PLs provided as a dietary source that is characterized by high nutritional value and various beneficial health effects, which are proved by many epidemiological studies (Küllenberg de Gaudry *et al.,* 2014; Zhang, Tao, Wang *et al.,* 2018; Tsoupras *et al.,* 2019). Long-chain ω-3 PUFAs, particularly eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid have drawn public attention as the human body is unable to synthesize these compounds and exert crucial physiological functions (Lee *et al.,* 2017; Saini and Keum, 2018; Haq *et al.,* 2018; Drouin *et al.,* 2019; Haq *et al.,* 2020).

Some health beneficial activities such as anti-

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inflammatory, anti-thrombosis, and anti-oxidative properties of marine PLs were reported (Küllenberg *et al.,* 2012; Burri *et al.,* 2012; Murru *et al.,* 2013; Lordan *et al.,* 2017). Additionally, marine PLs demonstrate superior combination into plasma lipoproteins and cell membranes, including lipoprotein. Marine PLs exhibit strong *in vitro* and *in vivo* antithrombotic, anti-atherogenic, and cardioprotective properties (Nasopoulou *et al.,* 2010; Nasopoulou *et al.,* 2011; Nasopoulou *et al.,* 2013; Tsoupras, Lordan and Zabetakis*et al.,* 2018). It is currently known that PLs perform pivotal roles to prevent metabolism-related and neurological diseases and to regulate basic biological processes as signalling compounds. Only PS carries a net negative charge, whereas the three rest groups available in the mammalian body such as PC are electrically neutral at physiological pH with one positive and one negative charge. In recent investigations, marine PLs have shown positive effects in patients with tumor associated weight loss. Approximately one-third ω-3 PUFAs are bound to PLs and two-thirds are bound to triglycerides. Some reports also showed that the uptake and utilization of ω -3 PUFAs bound to PLs were more efficient than those bound to general lipids (Burri *et al.,* 2012).

Many studies have documented that marine PLs not only carry a higher amount of ω -3 PUFAs than normal lipids from the same source but also exhibit better absorption in different tissues (Wijendran *et al.,* 2002; Gbogouri *et al.,* 2006). This might be due to the amphiphilic natures of PLs resulting in better water dispersal ability and higher reactivity with phospholipase than glycerolysis of general lipids. The supplementation of foods with ω-3 PUFAs rich PLs has recently emerged as a food supplement and pharmaceutical application. In this regard, the demands of marine PLs enriched with ω-3 PUFAs are increasing due to emerging health benefits (Wen *et al.,* 2016; Haq and Chun, 2018; Wang, Wang, Xu *et al.,* 2018). Therefore, the present review presents a detailed account of different biological and bio-functional roles of marine-derived phospholipids to provide useful references for academia, industrial processor, and consumers as well.

2. Biological functions of marine PLs

The review of recent reports on bio-functional properties of ω-3 PUFAs rich marine PLs was summarized as anti-atherosis and cardioprotective, anti-inflammatory, neuroprotective, immunological, and liver functions (Figure 1).

2.1 Anti-atherogenic and cardioprotective functions

Atherosclerosis disease occurs due to the deposition of fatty tissues inside the arteries' wall, forming an unusual structure known as plaque. Those plaque grow until they burst, rupturing the walls, and clotting blood within the artery. These clots also develop until they block blood flow; and in the case of the coronary artery, this causes a heart attack. This heart disease is the leading cause of mortality worldwide, and platelet is condemned to induce the heart attack and stroke by forming blood clots, and possibly more intriguingly their role as inflammatory cells. In recent years, the oral supplementation of dietary PLs has been investigated widely to reduce blood lipid profiles and cardiovascular problems. Fish roe PLs rich in phosphatidylcholine (PC)

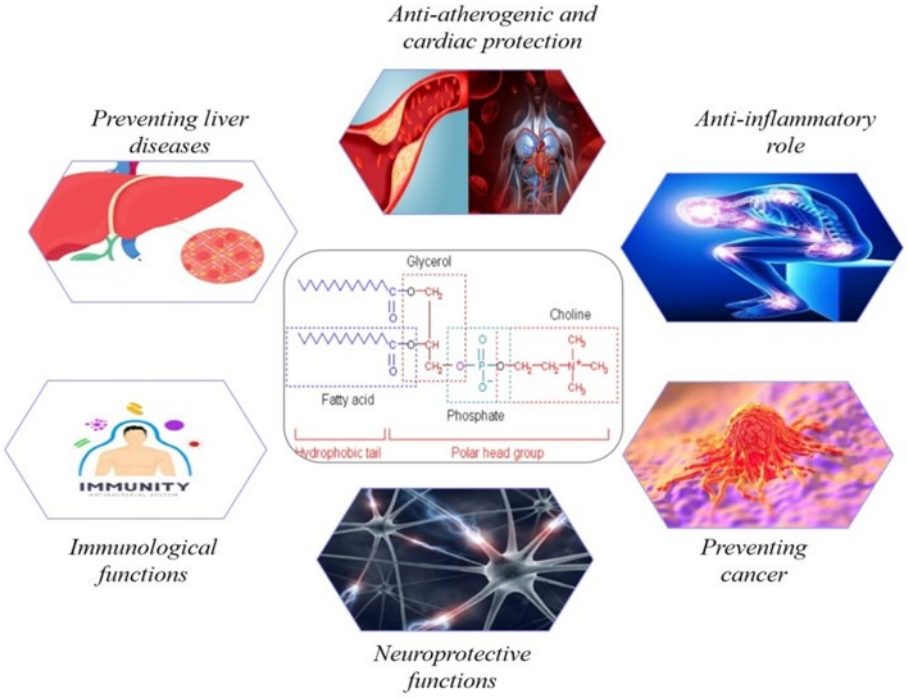

Figure 1. Bio-functional roles of marine phospholipids

and containing a high amount of ω-3 PUFAs have been shown to reduce blood plasma lipids. PLs not only reduce total cholesterol, LDL cholesterol, and triglycerides but also increase HDL cholesterol. Coronary artery disease and hypercholesterolemic patients are treated with Lovastatin to achieve reduced total cholesterol, LDL levels, and TG but simultaneously displayed to increase platelet activity, which ultimately is a risk factor for coronary heart disease. In this case, application of PLs in patients with cardiovascular disease not only reduces blood cholesterol level but also prevent platelet aggregation. Marine PLs are shown to have remarkable effects on blood lipid reduction in patients suffering from hyperlipidemia (Bunea *et al.,* 2004). Many researchers proved that supplementation of traditional fish oil lowers only blood TG levels, but has no effect on LDL and HDL levels whereas marine PLs reduce LDL, total cholesterol level, and TG level simultaneously increase HDL level. The anti-atherogenic and cardioprotective functions of ω-3 PUFAs studied in recent years are presented in Table 1. Ding *et al.* (2018) administered EPA and DHA rich PLs to male apolipoprotein E-deficient male mice with a high-fat diet and found a reduction in the atherosclerotic lesion and serum TAG level. PLs from marine organisms was effective in reducing hepatic and serum lipid content and expressing glucose and cholesterol metabolism (Beppu *et al.,* 2017; Runblad *et al.,* 2018). Zhang, Chi, Wu *et al*. (2018) fed 2% EPA-PL containing diet to mice for the duration of 4 weeks and reported reduction of not only body TAG level but also hepatic lipogenic genes. They also noticed enhanced hepatic fatty acid β-oxidation enzyme activity.

2.2 Anti-inflammatory role

Inflammation is a necessary biological protective response of the innate immune system to harmful stimuli or physiological triggers such as a pathogen or damaged cells, whereby the tissue is repaired or the pathogenic insult is eliminated. Chronic inflammation is associated with many complications in different diseases, its diagnosis, as well as treatment, creates an enormous challenge for medical practitioners. Additionally, applications of therapeutic treatments up to date were unsuccessful to obtain the desired effect, as a permissive immune environment is a prerequisite for their appropriate activity. It is evident that chronic inflammation and related immunosuppression pose a serious obstacle in the diagnostic and therapeutic area and those develop no chronic inflammation. Immunosuppression poses a serious obstacle in the prognostic and therapeutic areas as they both develop with no tangible clinical signs including unanticipated complications and possible impassiveness to various treatments (Meirow and Baniyash, 2017). Rather than therapeutic interventions, long-standing lifestyles such as maintaining healthy nutrition and exercise may ensure preventive outcomes towards inflammatory expressions. Presently, there is a growing logical rationale for the application of dietary PLs for the treatment of inflammatory problems to control inflammatory reactions. PLs supplementation in chemically induced arthritis rats reduced the level of arthritis most likely due to hindering the neutrophil leukocyte-mediated inflammatory reaction. Marine PLs have demonstrated anti-inflammatory and antithrombotic activities by hindering the platelet-activating factor or platelet-activating factor-receptor related pathways (Lordan *et al.,* 2017; Tsoupras, Lordan and Zabetakis, 2018; Tsoupras *et al.,* 2018). Marine PLs rich in ω-3 PUFAs have demonstrated to decrease inflammatory response by the inhibition of prostaglandins series-2. Krill oil rich in PLs was investigated for its anti-inflammatory activities in patients with rheumatoid arthritis and elevated C-reactive protein (CRP). The CRP levels and arthritic symptoms such as joint pains, stiffness, and functional impairment were reduced significantly (Table 2). Eicosanoids and PAF are mostly known lipid pro-inflammatory mediators responsible for inflammatory responses that are promisingly targeted by dietary interventions, especially to those food containing bioactive PLs (Burri *et al.,* 2012; Zabetakis, 2013). There is another therapeutic application of marine PLs is the treatment of the premenstrual syndrome. It is supposed that menstrual pain and cramps are caused by ω-6 fatty acids mediated inflammation, whereas supplementation of the ω-3 fatty acids could alleviate the mentioned symptoms. Krill oil rich in PLs was revealed to reduce not only abdominal pain, swelling, and joint pain but also improve emotional symptoms since brain PLs rich in docosahexaenoic acids are involved in brain functions. Marine PLs modulate neurotransmitters and thereby, positively affect the psychological and emotional symptoms in premenstrual women (Küllenberg *et al.,* 2012). Menstrual pain and cramps in women are caused by omega-6 fatty acids mediated inflammation and the supplementation of PUFAs rich PLs could alleviate the above-mentioned problems.

2.3 Marine PLs in preventing cancer

Cancer is an assemblage of diseases involved with abnormal cell growth with the capability to invade or spread to other parts of the body. Cancer cell membranes derive some unusual properties, for example changing the ability to adhesive characteristics that are observed in normal cells. This enables cancer cells to migrate from their surrounding tissue to other tissues or organs, causing tumour metastases. For example, the membranes

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Table 1. Anti-atherogenic and cardioprotective functions of phospholipids obtained from different marine species

Phospholipid source	Administration	Findings	References
Sea bass and gilthead sea bream	PLs was tested for their biological activity to rabbit platelets	Showed strong anti-PAF activity Anti-atherogenic properties in rabbits	Nasopoulou *et al.* (2007)
Sea bass (*Dicentrarchus labrax*) PLs	Polar lipids were administered to rabbit's platelets	Showed strong anti-PAF activity Showed strong cardioprotective functions	Nasopoulou *et al.* (2014)
DHA-PL and EPA-PL of sea cucumber and squid roe	Male apolipoprotein E-deficient male mice were administered with high-fat diet containing 1% of EPA-PL or DHA-PL	Reduced atherosclerotic lesion and serum TAG, LDL-c, hepatic TAG, TC and CeE level Enhanced cholesterol and bile acid synthesis and cholesterol efflux	Ding *et al.* (2018)
Antarctic krill oil	Apolipoprotein E-deficient female mice were supplemented with 4.86% krill oil	Reduced atherosclerotic lesion and serum VLDL, TAG, LDL level Reduced liver weight and hepatic TAG and TC Enhanced cholesterol metabolism	Parolini *et al.* (2017); Rundblad *et al.* (2018)
EPA rich PLs obtained from sea cucumber (*Cucumaria frondosa*) body wall	Mice fed with 2% EPA-PL containing diet for 4 weeks	Reduced serum and hepatic TAG, TC Reduced hepatic lipogenic gene Enhanced hepatic fatty acid β-oxidation enzyme activity	Zhang, Chi, Qu *et al.* (2018)
PLs from sea cucumber body wall and squid roe	Male rats who developed severe NAFLD was provided with 1 % DHA-PL and EPA-PL	Reduced hepatic TAG, lipogenesis, serum ALT and AST, and cholesterol synthesis Enhanced bile acid formation and hepatic lipolysis	Chang *et al.* (2018)
PC and PS from squid roe	Male SAMP8 mice fed with 1% DHA-PS/ DHA-PC for 8 weeks	Enhanced hepatic DHA level and reduced hepatic lipogenesis	Ding *et al.* (2018)
Marine fish PLs containing DHA (17-20%) and EPA (5-8%)	Mice induced with high-fat diet was supplemented with DHA/EPA – PLs (10/ 30 g DHA/EPA per kg diet) for 9 weeks	Reduced weight gain, white adipose tissue Reduced hepatic and plasma TAG Enhance glucose tolerance and reduce plasma insulin	Rossmeisl *et al.* (2012)
DHA/EPA-PC from herring fish and krill oil.	Healthy male and female subjects aged 18–70 years fed with fish meal and krill oil	Expression of genes involved with glucose and cholesterol metabolism and β-oxidation. Down regulated inflammation-related genes	Rundblad *et al.* (2018)
EPA/DHA-PLs from starfish	High-fat diet containing EPA/DHA-PL (2%/ 5%) for 8 weeks	Reduce hepatic and serum lipid content Significantly increase ω-3 PUFA content in liver Increased fatty acid β-oxidation activity	Beppu *et al.* (2017)
Marine fish PLs	Hyperlipidaemic rabbits	Reduce plasma TAGs, total cholesterol, and LDL	Lordan *et al.* (2017)
EPA-PL from cucumber (*Cucumaria frondosa*)	Male C57BL/6J mice supplemented with high fat/ high-fructose containing EPA PL (1%)	Reduced fasting serum glucose and insulin Increased insulin sensitivity	Liu *et al.* (2013)
EPA/DHA-PC from herring roe	Male C57BL/6J mice supplemented with high-fat diet containing 2% DHA-PL for 7 weeks	Reduced abdominal fat and plasma TAG Decreased hepatic and plasma cholesterol Inhibited lipid and cholesterol biosynthesis	Rossmeisl *et al.* (2014)
DHA-PL from cuttlefish (*Sthenoteuthis oualaniensis*) spawn	Male C57BL/6J mice provided with high-fat diet containing 2% DHA-PL for 7 weeks	Reduced epididymal adipose tissue weight, blood pressure and hepatic TAG level Reduced perirenal adipose tissue weight, serum glucose and TAG level Reduced obesity-related metabolic disorders, specially lipid metabolism	Liu *et al.* (2016)
Antarctic krill (*Euphausia superba*) oil	-	Cardiovascular disease protection	Sun *et al.* (2017)

of prostate and breast cancer cells were shown to have a higher concentration of lipid-containing cholesterol which is associated with higher apoptotic sensitivity. Regulation and alternation of the composition of lipid rafts can potentially alter cancer cell viability and metastatic behaviour (Table 3). Many studies have described the beneficial effects of PLs in cancer and metastasis inhibition (Zhang *et al.,* 2019). Sakakima *et al.* (2007) conducted an *in vitro* study with hepatic cancer cell lines and reported that PLs and menaquinone-4 restrained the growth of cancer cells in a dose-dependent manner. Supplementation with PC and menaquinone-4 in rats showed a distinct suppression of nodule formation and pre-neoplastic liver lesions in tested rats. Administering PC with menaquinone-4 showed more significant effects on the reduction of cancer cells due to synergistic effects. Marine PLs extracted from starfish and squid meal containing ω-3 PUFAs were observed to prevent the growth of chemically induced colon cancer in rats which was explained by an enhanced lipid peroxidation as a consequence of structural and functional shifts in the cellular membrane. Additionally, to prove the preventive effects of colon cancer in a mouse model, sphingomyelin was administered and drastic preventive effects on colon cancer formation. A high intake of marine PLs rich in ω-3 PUFAs recovered from fish has shown to reduce the metastatic progression of prostate cancer (Küllenberg de Gaudry *et al.,* 2014). Marine PLs rich in ω-3 PUFAs supplemented in patients who suffered from severe weight reduction due to pancreatic cancer aided in weight stabilization and improved life span (Werner *et al.,* 2017).

2.4 Neuroprotective functions

Neurological diseases primarily affect the structure or functions of neurons in the human brain. Neurons are the building blocks of the nervous system which include the brain and spinal cord. Many neurological diseases include Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Huntington's disease, Motor neuron disease, etc. These diseases are incurable, resulting in gradual degeneration and/or death of neuron cells. The lipid composition of brain cells changes with ageing; more clearly, the amount of ω-3 PUFAs in the brain cell tends to reduce with age, resulting in membrane fluidity reduction and cholinergic activities via retarded Na+- and Ca+- channels in the membrane are reduced. In these circumstances, they require PC and PUFAs for their excitability and neurotransmitter release (Table 4). It can be assumed that memory decline and the diminished learning capacity found in elderly people are consequences of a decrease of PC and/or PUFAs in the brain tissue. Marine PLs are a potential and effective carrier of essential ω-3 PUFAs such as DHA to the brain. Some researchers have proven that the preferential incorporation of DHA bound to PC into young rat brain (Table 4). Oral supplementation of marine PLs may play an important role not only in the elderly but also during pregnancy and infancy for neurological development. Supplementation of PLs rich in DHA may improve learning capability and visual function in age-related impairment and ω-3 PUFAs deficiency.

2.5 Immunological functions

PLs include a large group of lipids in cells and organelles which form membrane structures. In conjunction with their metabolic products, they control a range of aspects of innate immune cell biology including aggregation, shape change, blood clotting, and degranulation. The plasma membrane lipids such as glycerophospholipids, sterols, and sphingolipids play essential roles in regulating T cell (a cell system plays a key role in the immune response) differentiating, signalling, and effector functions. PLs hydrolysis provides a substrate for cell-cell communication; enable regulations of immunity, hemostasis, thrombosis, and vascular inflammation (O'Donnell *et al.,* 2018). PLs are also recognized by T cells, which are essential for the recognition of infection or cancer, as well as antigens. PLs, sphingomyelin and cholesterol are enriched at the contact zone between T cells and antigen-presenting cells during peptide/ major histocompatibility complexes recognition where a platform of lipid domains is necessary for optimal T cell signalling (Tuosto and Xu, 2018). The cholesterol and PL ratio in the cell membrane increases with age which has consequences in their functions and properties. For example, an increase in the cholesterol and PL ratio in lymphocytes reduces their immunological functions (Küllenberg *et al.,* 2012). The membrane viscosity of lymphocytes can be modified by altering optimal cholesterol and PL ratio, therefore, it is anticipated that an increase in PL concentration in lymphocyte cell membrane could regain the immunological function in elderly people. This effect was not found in the lymphocyte of young mice, supporting the theory those external PLs restores the optimal cholesterol and PL ratio in the affected lymphocyte membrane and all other cells, too maintaining their usual cell functions. The number of lymphocytes and macrophage phagocytic capacity was significantly improved with PLs supplementation indicating a modulatory positive effect of PLs on the immune function. PLs showed significant improvement of polymorphonuclear leukocyte phagocytic and killing activity and an increase in amino acid release in individuals feed with PLs. The amino acid release indicated the capability to change the membrane

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Table 2. Anti-inflammatory roles of phospholipids obtained from different marine species

Phospholipid source	Administration	Findings	References
Lipid extract rich PLs from *Mytilus coruscus*	Dextran sulfate sodium-induced colitis mice were supplemented with PLs extract at the rate of 150, 300, and 450 mg/kg for 33 days	Anti-inflammatory activity in mice Did not change liver index and thymus index Colon infiltration and significantly reduced histopathological scores	Wang, Wang, Xu *et al.* (2018)
Antarctic krill (*Euphausia superba*) extract	Treatment of pro-inflammatory activated human macrophages with krill oil (12.5, 50	Lipopolysaccharides inactivating properties Anti-inflammatory activity	Bonaterra *et al.* (2017); Costanzo *et al.* (2016);
EPA and DHA rich Krill oil (PLs : 51%, DHA-7%, EPA-12%, astaxanthin: 400 ppm)	Administered to mouse leukemic monocyte-macrophage cell line and inflammation human colorectal adenocarcinoma cell lines (250 mg/L in DMEM)	Improved intestinal barrier integrity and epithelial restitution Control bacterial adhesion and invasion in epithelial cells	Costanzo et al. (2016)
Krill oil provided by Akter BioMarine	Administered to LPS-treated peritoneal macrophages from obese Zucker rats	The TNF- α release was significantly inhibited in LPS-treated peritoneal macrophages	Vigerust *et al.* (2013)
Krill oil provided by Akter BioMarine; composition unreported	Collagen-induced arthritis-susceptible mice were supplemented with krill oil .44g/ 100 g diet for 2 months	Reduced the score of arthritis Hinder paw swelling in the arthritic mice	Ierna *et al.* (2010)
Krill oil provided by Akter BioMarine; composition unreported	DSS-induced ulcerative colitis rats were supplemented with 5 g krill oil/ 100 g diet for 4 weeks	Preserve colon length Changed the level of ILs, PGs, and Pparg expression beneficially	Grimstad *et al.* (2012)
Krill oil provided by Akter BioMarine; composition unreported	TNF- α transgenic mice fed with high-fat diet was supplemented with 5.8 g krill oil/ 100 g diet for 4 weeks	Reduced inflammatory conditions Decrease the MCP-1	Vigerust *et al.* (2013)
Krill oil (EPA, 17%; DHA, 10%;) from Neptune Technologies and Bioresources	Patients with chronic inflammation were administered a daily dose of 300 mg krill oil	Inhibited inflammation within 7-14 days	Deutsch (2007)
Krill oil from Erbozeta S.r.l provided as pill.	Mildly overweight hypertriglyceridemic subjects supplemented with 1 g krill oil/day	Reduced hs-CRP levels in plasma	Cicero *et al.* (2016)

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Table 3. Bio-functional activities of phospholipids from different marine species in protecting cancer

Phospholipid source	Administration	Findings	References
EPA-PC and DHA-PC and EPA-DHA bound lyso PLs from	Applied to rat main artery and human umbilical cord vein endothelial cell	Showed strong antiangiogenic performance on the rat main artery tissue	Tsushima *et al.* (2012)
DHA-PC of cuttlefish spawn (*Symplectoteuthis oualaniensis*)	Administered to mice bearing ascitic tumor	Reduce cell proliferation and cell cycle Inhibit the growth of tumor in mice	Yang *et al.* (2011)
DHA/EPA-PC of squid	Applied to colon cancer cell line at a dose of 100 µM for 24 h/ 48 h	Reduce cell viability Increase lipid peroxidation	Hossain *et al.* (2008)
EPA-PL from starfish (*Asterias amurensis*)	Supplemented to mice bearing ascites tumor	Increased total white adipose tissue mass and carcass weight Reduced serum non-esterified fatty acids and serum TNF-α and IL-6 Reduced TNF-α-stimulated lipolysis in adipocytes	Du *et al.* (2015)
Fish PLs	Supplemented to the pancreatic patient with cachexia	Improve pancreatic cancer and cachexia	Werner *et al.* (2017)
Antarctic krill (*Euphausia superba*) oil	Administered to osteosarcoma cell in a neoplastic condition	Reduced cell proliferation similar pattern to doxorubicin, a commercially used drug for osteosarcoma treatment	Su *et al.* (2018); Zheng *et al.* (2017)
PC contained (29%) salmon roe extract	Supplemented to prostate cancer patient	Reduce metastatic progression of prostate cancer	Küllenberg de Gaudry *et al.* (2014)
PLs from salmon (*Salmo salar*) fillet	Human platelet-rich plasma	Antithrombotic bioactivities against platelet-activating factor (PAF) and thrombin	Tsoupras *et al.* (2019)

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Table 4. Neuroprotective functions of phospholipids obtained from different marine species

Phospholipid source	Administration	Findings	References
PC (89 mg/g), PI (53 mg/g) and PE (40 mg/g) extracted from pacific saury (*Cololabis saira*)	Administered to Chinese hamster ovary cells	Neuroprotective activity	Zhang *et al.* (2018a)
DHA-PC extracted from squid roe (*Sthenoteuthis Oualaniensis*)	Omega-3 PUFA deficient mice supplemented with DHA-PC	Increased DHA level in liver, erythrocytes, cortex and testis	Wu *et al. (2017);* Wang, Wang, Zhang *et al.* (2018)
PL rich in DHA extracted from squid roe	Omega-3 PUFA deficient mice supplemented with diet containing 11.11 g/ kg DHA-PL for 3 weeks	Increased DHA level of infant cerebral cortex and in erythrocytes	Wang, Wang, Zhang *et al.* (2018)
Purchased DHA-PC, Avanti Polar Lipids, Alabaster, AL, USA.	Male Long-Evans rats were supplemented with a diet containing 12.8 g/kg DHA-PC	Increased DHA level in the brain	Kitson *et al.* (2016)
EPA-DHA rich Antarctic Krill oil	SAMP8 mice were administered with 1% Antarctic Krill oil	Increased cognitive function proved by Morris water maze method Reduced anxiety in open field test Reduced oxidative damage	Li *et al.* (2018)
PLs extracted from sea cucumber *(Calceolaria frondosa*)	Mice administered to 150 mg/kg body weight/ day with feed	Increased memory and cognitive in Morris water maze test Reduce oxidative damage and apoptosis	Le Guen *et al.* (2016).
PC and PS rich DHA extracted from squid roe	MPTP induced PD model mice were supplemented with high-fat diet containing 1% DHA-PC	Increased motor coordination in rotarod test Increased locomotors activity and explanatory behavior in open field test Enhanced dopaminergic neurons damage	Wang, Wang, Xu *et al.* (2018)
DHA-glycero phosphatidylethanolamine from ascidian	Aβ-induced rats were supplemented with oral administration for 4 weeks	Increased learning ability in 8-arm radial maze	Yamashita *et al.* (2017)
Krill oil containing PLs	Elderly 61-72n years aged subjects we supplemented with krill oil in a diet for 12 weeks	Enhanced cognitive and brain function	Konagai *et al.* (2013)
PLs extracted from squid (*Sthenoteuthis oualaniensis*) roe	PLs was supplemented to senescence-accelerated prone 8 (SAMP8) mice	Prevented Alzheimer disease Reduced neurodegenerative diseases	Wen *et al.* (2016).
PLs extract from sea cucumber (*Cucumaria frondosa*) PL	PLs was supplemented to senescence-accelerated prone 8 (SAMP8) mice	Reduced the loss of dopaminergic neurons in mice Reduced oxidative stress Reduced Parkinson's Disease	Wang, Wu, Xen *et al.* (2018)
EPA-PC/PE/PS extracted from sea cucumber (*Calceolaria frondosa*)	EPA-PC/PE or EPA-PS (2%) were administered to SAMP8 mice with a diet for 8 weeks	Increased memory and cognitive in Morris water maze Reduce oxidative damage and apoptosis	Zhou *et al.* (2018).
DHA-PC from squid roe (*Sthenoteuthis oualaniensis*); PC rich in EPA obtained from sea cucumber	SAMP8 mice were supplemented with high-fat diet containing 1% DHA-PC or EPA-PC for 2 months; 20-40 µg/mL DHA-PC or EPA-PC in CHO-APP/PSI cells for 48 h	Enhanced memory and learning capacities in Morris water maze test Enhanced anti-oxidative activity	Milte *et al.* (2009)
Phosphatidylserine in krill	Aged mouse (12 months) was supplemented with 20 and 50 mg/kg feed for 7 days	Enhanced cerimide level in the hippocampus. Reduce latency.	Mansour *et al.* (2017)
Antarctic krill (*Euphausia superba*) oil provided by Aker Biomarine Antarctic, Norway)	Male and female rats were orally administered at 0.2 g/rat/ day for6 weeks	Enhanced cognitive effects assessed by Aversive Light Stimulus Avoidance Test Enhanced anti-depression effect	Wibrand *et al.* (2013).
EPA and DHA rich Antarctic krill (*Euphausia superba*) oil	Administered to D-galactose induced aging mice at 100, 200, 600 mg/kg/day	Enhanced cognitive function assayed by Morris water maze test Reduced oxidative damage	Cheong *et al.* (2017).

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Table 5. Bio-functional activities of marine phospholipids in preventing liver diseases

Phospholipid source	Administration	Findings	References
PLs from sea cucumber and squid *roe*	Male apoE deficient mice were supplemented with high fat containing 1% PLs for 8 weeks	Reduced serum TAG, TC, LDL cholesterol level Reduced hepatic TAG and TC level Increased bile acid synthesis and cholesterol efflux	Ding *et al.* (2016)
Antarctic krill (*Euphausia superba*) oil	Female apoE deficient mice were supplemented with western diet containing 4.86% krill oil for 12weeks	Reduced atherosclerotic lesion and serum TAG, LDL level Reduced hepatic TAG and TC level and liver weight Reduced cholesterol synthesis	Rundblad *et al.* (2018)
EPA-PL from sea cucumber (*Cucumaria frondosa*)	Male C57BL/6J mice were administered with a diet containing 2% EPA-PL for 14 days	Reduced epididymal adipose tissue and serum TC, hepatic TAG level Enhanced hepatic DHA, HDL cholesterol Reduced fatty acid synthesis in epididymal adipose tissue	Zhang *et al.* (2017)
EPA and DHA rich Antarctic krill (*Euphausia superba*) oil	Healthy subjects of the 18-36 age group were supplemented with 832.5 mg krill oil for 28 days	Reduced plasma TAG and large VLDL and chylomicrol particle Increased HDL level, plasma and RBC ω-3 PUFAs Increased plasma antioxidant level	Berge *et al.* (2015)
EPA_PL from sea cucumber (*Cucumaria frondosa*)	Female C57BL/6J mice were administered with high-fat diet containing 1% EPA-PL for 4 weeks	Reduced hepatic and serum TAG, TC level Reduced hepatic lipogenic genes and enzymes Enhanced hepatic fatty acid oxidation enzyme activity and mRNA gene expression	Liu *et al.* (2014)
PLs of sea cucumber and squid roe.	Rat treated with orotic acid to develop severe non-alcoholic fatty liver disease	Reduced epididymal and perirenal adipose tissue Reduced hepatic TAG and serum ALT level Reduced hepatic lipogenesis and cholesterol synthesis	Chang *et al.* (2018)
PC and PS from squid roe.	SAM8 mice were supplemented with 1% PC or 1% PS containing diet for 8 weeks	Reduced serum and hepatic TAG and TC level Increased hepatic DHA level Reduced hepatic lipogenesis	Ding *et al.* (2018)
Marine fish PLs (DHA: 17-20%; EPA: 5-8%)	High-fat diet-induced C57BL/6J mice supplemented with high-fat diet with PLs (10-30 g/ kg diet) for 9 weeks	Reduced weight gain and white adipose tissue Reduced hepatic and plasma TAG level Increased glucose tolerance levels while reduced adipose tissue hypertrophy	Rossmeisl *et al.* (2012)
Antarctic krill oil	Zucker rats supplemented with 0.5 g oil/ 100g diet for 4 weeks	Reduced hepatic TAG and serum LDL cholesterol	Batetta *et al.* (2009)
PLs from sea cucumber (*Cucumaria frondosa*)	SAMP8 mice supplemented with diet containing 2% PLs for 8 weeks	Reduced hepatic and serum TAG, TC and saturated fatty acids levels. Increased hepatic lipolysis while reduced hepatic lipogenesis	Ding *et al.* (2016)
Antarctic krill oil (EPA: 12%; DHA: 8%)	Sprague Dawley rats induced with high-fat diet supplemented with 2.5% krill oil for up to 12 weeks	Reduced body weight Reduced serum and hepatic TAG, TC and cholesterol content Reduced hepatic lipogenesis and enhanced fat oxidation Enhanced hepatic oxidative phosphorylation	Ferramosca *et al.* (2012).
Antarctic krill (*Euphausia superba*) oil	High-fat diet-induced C57BL/6 mice supplemented with krill oil (1.25, 2.5, and 5% wt) for 8 weeks	Reduced liver fat and liver weight Reduced hepatic TAG, cholesterol level Reduced serum cholesterol and glucose level Reduced fatty acid synthesis and uptake	Zheng *et al.* (2018)

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Table 5 (Cont.). Bio-functional activities of marine phospholipids in preventing liver diseases

Phospholipid source	Administration	Findings	References
Antarctic krill (*Euphausia superba*) oil	Male C57BL/6 mice fed high-fat diet was supplemented with krill oil	Reduced metabolic disturbances Anti-obesity and anti-diabetic effects Promote therapeutic benefits by reducing endocannabinoid precursor availability	Piscitelli *et al.* (2011); Batetta *et al.* (2009)
PL obtained from squid roe	C57BL/6 mice low fat diet and a high-fat diet containing 0.7% DHA-PL	Reduced hepatic TAG level and increased hepatic DHA level Increased hepatic PL concentrations in mice Increased hepatic and cerebral DHA levels	Ding et al. (2013).
EPA/DHA–PL from starfish	C57BL/6 mice supplemented with high-fat diet containing 2-5% EPA/DHA-PL for 8 weeks	Reduced hepatic and serum lipid contents Increased fatty acid β-oxidation activity	Beppu *et al.* (2017).
PC obtained from sea cucumber	Hyperglycemic rats administered with 25/ 75 mg/ kg bodyweight for 60 days	Reduced fasting serum glucose whether increased serum insulin and glycogen	Hu *et al.* (2014)
DHA-PL from squid roe EPA-PL from sea cucumber	Male C57BL/6J mice supplemented with 2% EPA-PL or DHA-PL for 8 weeks	Increased glucose homeostasis and insulin sensitivity	Liu *et al.* (2014)

composition of polymorphonuclear leukocytes, resulting in an improvement of immunological properties.

2.6 Preventing liver diseases

Fatty liver disease is a health problem caused by obesity, alcohol drinking, sedentary lifestyle, and diabetes mellitus for which an established treatment is not yet available. Intake of PLs has been widely recommended for the treatment of liver disorders including fatty liver problems and viral hepatitis. A recent review showed that the application of PLs was indeed beneficial for hepatic disorders (Gundermann *et al.,* 2011). Due to excess alcohol consumption, the membrane PLs level of hepatic cells is reduced or altered which ultimately affects the membrane fluidity that leads to damaged membrane associated with enzyme carrier and receptor activities. Under prolonged conditions, these can lead to a change in collagen metabolism resulting in the formation of fibrosis and cirrhosis. Moreover, the liver is a vital organ for lipid metabolism. Due to dyslipidemia, various pathomechanisms such as lipid peroxidation, modification of lipoprotein structure, reduction in lipase enzyme, and lipid functions interact which trigger an increase in serum cholesterol and triglyceride levels. This ultimately results in a low level of high-density lipoprotein (HDL) secretion into the blood system that leads to reduced take-up and transportation of cholesterol from the periphery to the liver for metabolism (Gundermann *et al.,* 2011). Supplementation of PLs directly incorporated into the PLs deficient hepatic cells, which normalize the activity of membrane-bound enzymes and reduce alcohol-induced liver injury. The mechanisms were discussed as the ability of PLs' to prevent acetaldehyde mediated hepatic collagen accumulation by stimulating collagenase enzyme activity. In a human trial, this effect was investigated in a placebo-controlled randomized clinical trial continued for around 20 years, showing that PLs improved liver problems in drinkers. Moreover, the hepatocyte apoptosis, as well as the formation of TNF-a by Kupper cells and lipid peroxidation, was reduced (Table 5). The PLs supplementation was prevented not only the development of alcohol-induced liver cirrhosis but also early liver changes induced by excess alcohol consumption (e.g. hyperlipidemia and fatty liver). Actually, alcohol intake enhances plasma lipids, which is transported to and deposited in the liver as TG and cholesterol ester form which causes alcohol-induced liver damage. The mechanisms of liver lipid deposition prevention by PLs were explained that PLs reactivate the alcohol-induced inhibition of mitochondrial fatty acid oxidation and thus reduced liver damage.

All the hepatic protective activities were attributed to the PLs since the functionalities were not found during supplementing TG or head group alone. PLs provided much better results in reducing liver TG levels in rats compared to a TG supplementation with almost similar fatty acids composition. Patients with chronic alcohol-induced liver damage treated with PC were shown to be effective in improving liver-related symptoms such as cholestasis and icterus. Moreover, PLs supplementation was shown to be effective not only in alcohol-related liver disease but also in hepatic damage caused by viral infections or toxins. Improvement of liver functions was reported with PLs supplementation to patients suffering from non-alcoholic liver damage (Varganova *et al.,* 2019). The primary site for PLs synthesis and metabolism is hepatic tissue. The fatty acids profile of liver PLs and TG is known to be influenced by several factors including dietary intake, endogenous metabolism, gender, and age. FAs are important in maintaining the modulation of membrane fluidity, interacting intracellular signalling pathways, and performing as a substrate for the production of signalling molecules.

3. Conclusion

Significant progress has been made on the studies of bio-functional roles of ω-3 PUFAs rich marine PLs. A considerable extent of suggestion indicated that ω-3 PUFAs rich marine PLs are more beneficial for health aspects compared to ω-3 PUFAs in TAG/ EE forms, and even from terrestrial PLs. An important source of marine PLs might be fish by-products, which can reduce the competition to use terrestrial resources for the extractions and utilization of PLs. Thus, the full health advantages of ω-3 PUFAs rich marine PLs could be maximized in our daily applications.

Conflicts of interest

The authors declare no conflicts of interest.

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