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REVIEW

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The potential of marine resources for retinal diseases: a systematic review of the molecular mechanisms

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ABSTRACT

We rely on vision more than on any other sense to obtain information about our environment. Hence, the loss or even impairment of vision profoundly affects our quality of life. Diet or food components have already demonstrated beneficial effects on the development of retinal diseases. Recently, there has been a growing interest in resources from marine animals and plants for the prevention of retinal diseases through nutrition. Especially fish intake and omega-3 fatty acids have already led to promising results, including associations with a reduced incidence of retinal diseases. However, the underlying molecular mechanisms are insufficiently explained. The aim of this review was to summarize the known mechanistic effects of marine resources on the pathophysiological processes in retinal diseases. We performed a systematic literature review following the PRISMA guidelines and identified 107 studies investigating marine resources in the context of retinal diseases. Of these, 46 studies described the underlying mechanisms including anti-inflammatory, antioxidant, antiangiogenic/vasoprotective, cytoprotective, metabolic, and retinal function effects, which we critically summarize. We further discuss perspectives on the use of marine resources for human nutrition to prevent retinal diseases with a particular focus on regulatory aspects, health claims, safety, and bioavailability.

KEYWORDS

Algae; fish; macular degeneration; omega-3 fatty acids; retina; retinopathy

Introduction

Vision is the most important sense for diurnal primates such as human beings. In contrast to most other mammals, we rely on vision more than on any other sense to gather information about the environment (Kaas 2008). It is, therefore, not surprising that for patients, the loss of vision profoundly affects their quality of life. Quality of life measurements and utility scores show that patients consider blindness as a condition worse than for example Acquired Immune Deficiency Syndrome (AIDS) or breast cancer (Chaudry, Brown, and Brown 2015). Apart from the mere loss of sight, severe visual impairment may result in the loss of independence, trauma, and depression (Javitt, Zhou, and Willke 2007) as well as an increased rate of suicide (Waern 2002). Indeed, patients with severe visual impairments would tradeoff up to 48% of their remaining life time to regain normal vision, with this lifetime pay-off reaching 60% in blind patients (Knauer and Pfeiffer 2008). This profound impact on the affected patients is often underestimated by the medical personal (Chaudry, Brown, and Brown 2015). Of note, even a mild visual impairment can lead to a significant reduction of the quality of life and emotional well-being of the affected patient (Finger et al. 2011). In addition to the effects on the individual, blindness, and diseases leading to blindness have an impact on many levels of society (Klettner and Lingelbach 2018).

The beneficial effect of diet or food components on the development of retinal diseases has already been shown in several studies (Broadhead et al. 2015; Dow et al. 2018; Eggersdorfer and Wyss 2018; Rinninella et al. 2018; Wong et al. 2018; Chapman, Jacobs, and Braakhuis 2019). In recent years, marine resources have become increasingly interesting for the treatment and prevention of retinal diseases. With over 70% of the surface of the earth covered with water, the greatest diversity of organisms can be found in the ocean and accounts for 90% of the world's living biomass (Arrieta, Arnaud-Haond, and Duarte 2010). This rich biodiversity, which is still far from being fully explored, offers a promising biotechnological potential. Currently, a total of around 238,000 eukaryotic marine species are described, which is estimated to represent only one-third to one-fourth of all existent marine species (Appeltans et al. 2012; WoRMS Editorial Board 2021). Bioactive substances from marine resources are widely used in medical, cosmetic,

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biotechnological, and nutritional products (Hosseini, Rezaei, and McClements 2020), with half of them comprising pharmacological and human health applications. The number of products is rapidly growing by 4% per year with approximately 18,000 natural products and 460 patents associated with genes isolated from marine organisms (Arrieta, Arnaud-Haond, and Duarte 2010).

In particular, the intake of fish, omega-3 fatty acids, and extracts obtained from algae are promising (Chong et al. 2008; Zhu et al. 2016). While the consumption of marine products has been associated with a reduced incidence of retinal diseases, the underlying molecular mechanisms are insufficiently explained. In this review, we summarize the mechanistic effects of marine resources on the pathophysiological processes in retinal diseases. Only marine resources which can be processed as food were considered in this study.

Retinal diseases

According to a recent meta-analysis, globally 36.0 million people are considered blind and 216.6 million suffer from moderate to severe vision impairment (Flaxman et al. 2017). The WHO even estimates that 2.2 billion people are vision-impaired or blind (WHO 2019). The prevalence and causes differ by the region and socio-economic status of the respective countries. Among the major causes of blindness are glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR), especially in the elderly population (Flaxman et al. 2017; Bourne et al. 2018).

As most diseases endangering vision are age-related and the population of the planet is increasing and aging, the number of affected people is estimated to increase profoundly, from 36 to 114.6 million blind and from 216.6 to 587.6 moderately or severely vision impaired by 2050 (Bourne et al. 2017). In addition, other diseases are also of high relevance concerning visual impairment, such as retinopathy of prematurity (ROP) which is the major avoidable cause for childhood blindness (Solebo, Teoh, and Rahi 2017), or retinitis pigmentosa (RP), the most common blinding genetic retinal dystrophy (Verbakel et al. 2018).

Age-related macular degeneration

AMD is a multifactorial disease with a strong contribution of genetics and life-style, but the main risk factor is age (Heesterbeek et al. 2020). In its early stages, AMD presents with so-called drusen (subretinal deposits) and pigmentary changes in the retinal pigment epithelium (RPE), a cell layer between the retina and the blood vessels of the choroid. In later forms, AMD can either present as an atrophic (dry) form, with extended areas of RPE and photoreceptor degeneration and a gradual loss of visual acuity, or as an exudative (wet) form, presenting with choroidal neovascularization, with vessels growing beneath or into the retina, and retinal edema (Klettner 2015b; Miller 2016). The wet form of AMD is accompanied by rapid and severe vision loss. On a cellular level, a number of processes are considered to contribute to AMD pathogenesis, such as oxidative stress, inflammation, lipid alterations, and angiogenic signaling (Ikeda et al. 2006; Curcio et al. 2011; Shaw et al. 2016; Guillonneau et al. 2017).

Diabetic retinopathy

DR is a complication of diabetes and one of the leading causes of severe vision impairment in the working population (Nentwich and Ulbig 2015). Diabetes is characterized by hyperglycemia caused by insulin deficiency or impaired insulin function. DR is a microangiopathic disease, which presents in the early state with microaneurysms, exudates, and hemorrhages (Antonetti, Klein, and Gardner 2012). In late stages, this can lead to the growth of new vessels and proliferative diabetic retinopathy, and, because of the breakdown of the blood-retinal barrier function, to macular edema (Stitt et al. 2016). The main factors contributing to the pathogenesis of DR are hyperglycemia, oxidative stress, inflammatory activation, ischemia, and angiogenic signaling (Rangasamy et al. 2014; Wan et al. 2015).

Retinopathy of prematurity

ROP is a vasoproliferative disease of prematurely born infants, leading to retinal detachment. It is a leading cause of blindness in children (Solebo, Teoh, and Rahi 2017). The disease is initiated because of the interference of the developmental retinal vascularization by premature birth. Developmental retinal vascularization is driven by hypoxia. In prematurely born children, high oxygen in the environment stops retinal vascularization, leading to an undersupply of oxygen and hypoxia as the retina matures. This hypoxia induces angiogenic factors and induces pathological retinal neovascularization with leaky vessels leading to scar formation and retinal detachment (Hellström, Smith, and Dammann 2013). The main risk factors are preterm birth with low gestational ages and uncontrolled oxygen delivery in neonatal care (Darlow et al. 2005; Hartnett and Lane 2013)

Glaucoma

Glaucoma is a neurodegenerative disease, the highest risk factor being high intraocular pressure. In glaucoma, retinal ganglion cells, responsible for delivering retinal information to the brain, degenerate, leading to a progressive and irreversible loss of the visual field (Casson et al. 2012). The main pathomechanisms are mechanical processes because of high ocular pressure, but also immunological processes, oxidative stress, and neurotoxic compounds are considered as possible contributors to glaucoma pathogenesis (Tezel et al. 2010; Bell et al. 2013; Evangelho et al. 2019).

Retinitis pigmentosa

RP is characterized by the primary degeneration of rods followed by the loss of cones. It is the most common inherited retinal dystrophy that generally manifests with night blindness in adolescence followed by concentric visual field loss

and the loss of central vision later in life. More than 80 different genes have been described that can cause RP, either associated with a vital function or the structure of the photoreceptors or the RPE, such as phototransduction, visual cycle, or the connecting cilium (Verbakel et al. 2018).

Marine resources

Marine animals

The world register of marine species currently counts 237,106 accepted marine species (Date: February 22, 2021), whereas roughly 200,000 marine animal species are described (WoRMS Editorial Board 2021). In comparison to this, a small percentage of species are globally harvested (1,800 different species) and even a smaller amount of 516 different species are farmed in marine and coastal aquaculture (FAO 2019). The production from capture fisheries and aquaculture was 170.9 megatons (Mt) in 2016, of which over 60% comes from marine origin with 108 Mt. Most of the production is used for human consumption as the demand for fish and fish products is growing and the production has been more than tripled since 1950. Fish consumption all over the world is increasing with an average of 3.2% per year (FAO 2019).

The supply of marine animals for human consumption derived from aquaculture production plays an increasingly important role, with around 80 Mt in 2016, of which aquaculture production from marine and coastal sides account for around 1/3 (28.7 Mt). Whereas the capture fishery has remained constant over the last 25 years with 90.9 Mt in 2016 of which nearly 90% come from marine capture (FAO 2019). Most of the world's total capture fishery and aquaculture production constitutes fish (131 Mt), far ahead of the production of molluskan (23 Mt), crustaceans (15 Mt) and other aquatic invertebrates (1 Mt). While the production of fish in aquaculture includes over 369 species (with 27 species accounting for more than 90% of the production), 109 molluskan species are used, mainly belonging to the class of bivalvia such as oysters, shells, mussels, and clams. The aquaculture of crustaceans includes 64 different species, of those mainly shrimps and only a small part is contributed by crawfish, crab, prawn, and krill (FAO 2019).

Fish provides a very good protein source, particularly in low-income countries. In Western societies, the demand for fish and fish products has also increased as fish is considered to be part of a healthy diet as they also contain a high amount of minerals, vitamins, and long-chain unsaturated fatty acids such as omega-3 and omega-6 fatty acids (Sidhu 2003).

Although the majority of total capture fishery and aquaculture production is used for human consumption, there is also a growing interest in processing and utilizing by-products from aquatic animals. These by-products are processed for fish oil and fishmeal and are used as feed or simply biodiesel and -gas. In addition, they can also be processed for high-value products such as the concentrated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (as nutraceuticals), collagen (for cosmetics), gelatin (for pharmaceuticals and as food ingredient), chitosan (used in food technology, medical, and cosmetic products), pigments and enzymes (food industry), and bioactive peptides (pharmaceuticals, nutraceuticals) (Olsen, Toppe, and Karunasagar 2014; FAO 2016).

Marine plants

The kingdom Plantae currently includes around 10,000 accepted marine species, with *Rhodophyta* (red algae) and *Chlorophyta* (green algae) contributing the largest proportion of species. The class brown algae belongs to the kingdom Chromista and includes around 4,000 accepted species (WoRMS Editorial Board 2021). Although the exact number of algal species is currently unknown, 70,000 algae species are currently estimated (Guiry 2012). This diversity in species offers the potential to discover new bioactive compounds for the use of seaweed for food and food supplements.

Seaweeds produce large amounts of biomass, without using arable land, fresh water, or fertilizer. They are a renewable marine resource and contribute substantially to the global carbon fixation (Krause-Jensen and Duarte 2016; Duarte et al. 2017). With an increasing human population and limited land available, the cultivation and use of seaweed for various applications provide a green alternative. Between 2005 and 2015, the world production of cultivated seaweed doubled to 29.4 Mt, in addition to wild harvest that remained constant over the years (1.1 Mt) (FAO 2019). Seaweeds are cultivated in about 50 countries, but around 95% are produced by just four countries: China (13.9 Mt), Indonesia (11.3 Mt), the Philippines (1.6 Mt), and the Republic of Korea (1.2 Mlt). Over 90% of the production is generated from only six algae species (*Eucheuma* seaweeds, *Japanese kelp*, *Gracilaria* seaweeds, *Wakame*, *Elkhorn* sea moss, *Nori*) (FAO 2019).

The diversity of macroalgae is a source for potential molecules with health-promoting effects for humans (Pangestuti and Kim 2011; Mayer et al. 2019). Dried macroalgae consist on average of 16% water, 33% ashes (such as xanthophylls and mineral nutrients), 14% proteins, 2% fat (e.g., omega-3 and -6 fatty acids), and 35% carbohydrates (including, e.g., starch, carrageen, and fucoidan) (Lorbeer, Tham, and Zhang 2013; Charoensiddhi et al. 2017).

Systematic literature review of the effects of marine resources on retinal diseases

We conducted a systematic review of the literature to identify the pathophysiological mechanisms underlying the effects of marine resources on retinal diseases according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009).

Search strategy

We searched for publications listed in PUBMED describing the effect of a marine resource on the pathophysiology of a

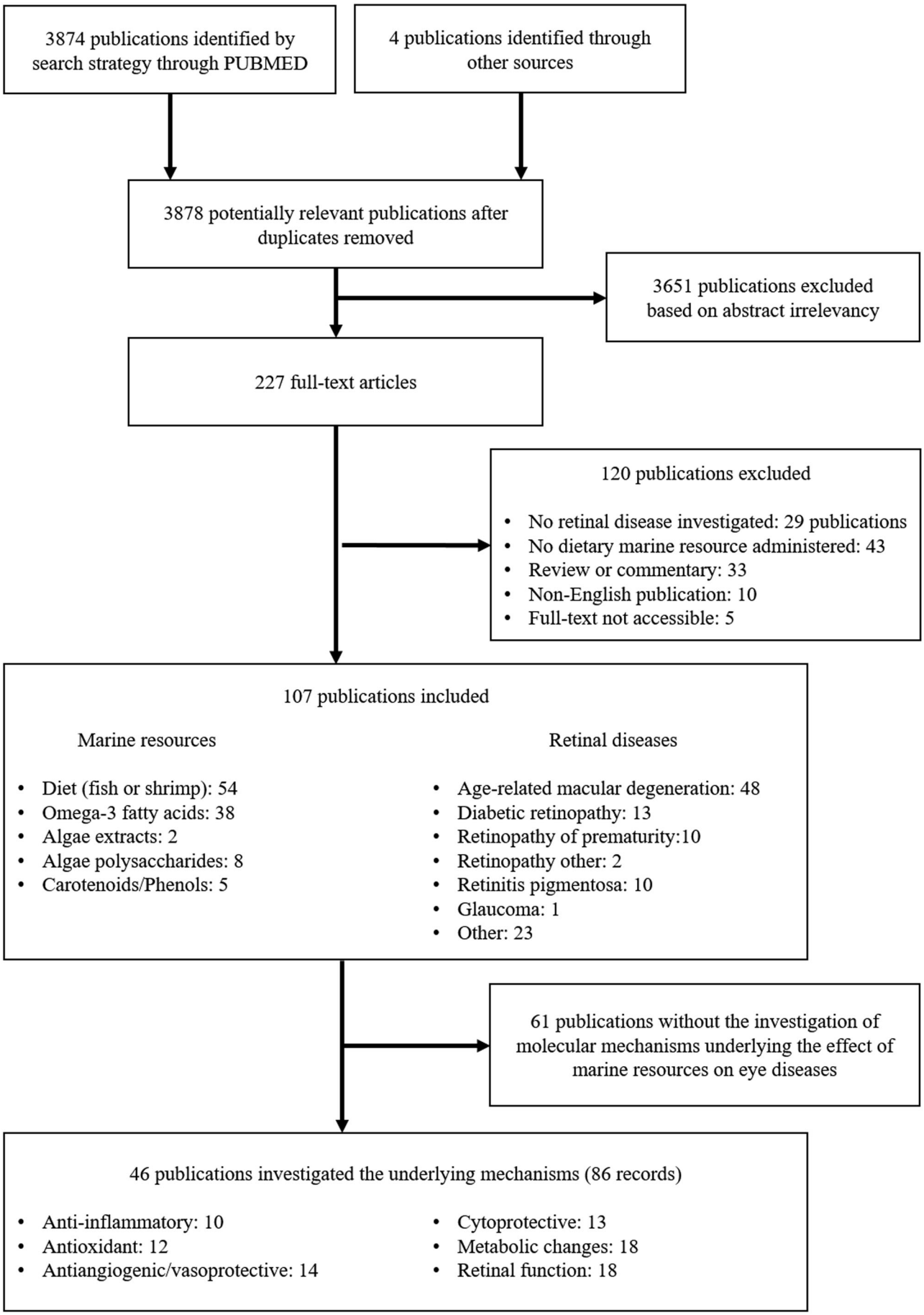

Figure 1. Flow diagram of the systematic search according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al. 2009). Of note, the number of "records" does not equal the number of publications because some studies investigated multiple pathophysiological mechanisms representing different "records."

retinal disease. Search Terms were as follows: (Algae OR algal OR alga OR seaweed OR kelp OR fish OR sponge OR mollusks OR mollusca OR bivalvia OR bivalves OR gastropoda OR gastropod OR cephalopoda OR cephalopod OR clam OR oyster OR shell OR mussel OR sea snail OR abalone OR escargot OR sepia OR squid OR octopus OR coleoidea OR crustacean OR crustacea OR shrimp OR crawfish OR lobster OR crab OR prawn OR sea cucumber OR sea urchin OR sea squirt OR jellyfish OR krill) AND (AMD OR (macular degeneration) OR retinopathy OR (diabetic macular edema) OR DME OR maculopathy OR blindness OR glaucoma OR retinitis OR cone dystrophy OR (RPE OR Retinal Pigment Epithelial) OR MU-PH1 OR R28 OR 661 W OR (Retinal ganglion) OR (Retinal Microvascular Endothelial) OR (Trabecular Meshwork)).

Publications until May 13, 2020 were included. We only included marine resources that are approved as food ingredients or extracts made from marine resources. We did not include endangered animal and plant species as well species that do not have potential as food. We did not consider review articles, articles without full-text accessibility, and non-English articles.

Selection of studies and data extraction

Three authors (K.K., E.B., M.Z.) screened the abstracts and two authors (K.K., M.Z.) subsequently reviewed the full-text versions of the potentially eligible studies. After screening 3878 publications, we identified 227 full-text articles, of which 107 publications were included (Figure 1 and Supporting Information Tables S1 and S2). In an additional selection step, we excluded all publications that did not assess the underlying pathophysiologic mechanisms, resulting in 46 included publications. The studies were categorized according to the underlying pathophysiological mechanisms investigated: (1) anti-inflammatory, (2) antioxidant, (3) antiangiogenic/vasoprotective, (4) cytoprotective, (5) metabolic changes, and (6) retinal function. An overview of the markers used to identify each pathophysiological mechanism can be found in Supporting Information Table S3. Disagreement between the authors (K.K., M.Z.) was resolved by discussion among them.

Risk of bias assessment

To assess the potential risk of bias in the included studies, we performed a risk of bias analysis according to the Cochrane guidelines (Higgins and Green 2011), with modifications for preclinical research (Office of Health Assessment and Translation (2015) 2019), considering the following: (i) randomization, (ii) sample size calculation, (iii) allocation concealment (all selection bias), (iv) blinding, (v) exposure classification (i.e., target engagement, verification of compound) (both performance/detection bias), (vi) complete outcome analysis (attrition bias), (vii) selective reporting (reporting bias), (viii) conflict of interest, and (ix) correct statistical analysis (both other bias). The assessment was performed with respect to the pathophysiological mechanisms assessed. According to the Cochrane guidelines, each study was judged as "low risk," "high risk," or as "unclear risk," with the last category indicating either lack of information or uncertainty over the potential for bias (Higgins and Green 2011).

The overall reporting of quality was mostly incomplete (Supporting Information Table S4). Only 16 out of 46 studies reported randomization, while five studies reported the lack of randomization and the remaining did not report about it at all. Eight studies reported a priori sample size calculation, eleven studies allocation concealment and three studies the lack thereof. Thirteen studies specified the blinding of researchers and two the lack thereof. Twenty-one studies provided data demonstrating exposure classification (i.e., target validation, compound verification), while one study was unable to demonstrate it. We were able to rule out bias for the reporting of complete data only for four studies, while one study was biased due to unexplained unequal numbers of biological replicates. Selective reporting was ruled out for eleven studies. Twenty-eight studies provided a conflict-of-interest statement without any conflict disclosed, while five studies reported a conflict of interest. Common statistical issues identified in 23 studies were the use of statistical tests that require normally distributed data (e.g., *t*-test or ANOVA) without reporting that normal distribution or the homogeneity of variance was tested or confirmed, a low sample size that was insufficient ($n = 3$–4 per group) to assume a normal distribution, or no adjustments for multiple comparisons.

Effects of marine resources on retinal disease prevalence and severity

Of the identified 107 studies that addressed the effect of marine resources on retinal diseases (Figure 1 and Supporting Information Table S1), many of the studies investigated dietary fish and shrimp (54 records) as well as omega-3 fatty acids (38), while only a few looked at algae extracts (2), algae polysaccharides (8), or carotenoids/phenols (5). Concerning retinal diseases, the majority of the studies investigated AMD (48), followed by DR (13), ROP (10), RP (10), and other retinopathies (2). Only one study addressed glaucoma.

A large number of epidemiological studies reported an association of higher dietary fish and omega-3 fatty acid consumption with a reduced risk of developing AMD and a lower prevalence of advanced AMD (Augood et al. 2008; Carresi et al. 2009; Wang et al. 2009; Montgomery et al. 2010; Jia et al. 2011; Amirul Islam et al. 2014; Ristau et al. 2014; Zerbib et al. 2014; Joachim et al. 2015; Merle, Silver, et al. 2015; Souied et al. 2015; Wu et al. 2017; de Koning-Backus et al. 2018; Gürbüz Yurtseven et al. 2018; Joachim et al. 2018; Zhang et al. 2018; Arslan, Kadayifçilar, and Samur 2019; Kang and Kim 2019; Merle et al. 2019; Keenan et al. 2020; Merle, Rosner, and Seddon 2020).

In patients with high genetic risk, weekly fish consumption was associated with a 40% lower risk of late AMD (Wang et al. 2014). In contrast, three studies demonstrated

Table 1. Number of mentioned underlying mechanisms for each marine resource.

Pathophysiological mechanisms	Fish or shrimp	Omega-3 fatty acids	Algae extracts	Algae polysaccharides	Carotenoids/ Phenols
Anti-inflammatory	2	8	–	–	–
Antioxidant	–	4	1	5	2
Antiangiogenic/ vasoprotective	5	2	1	5	1
Cytoprotective	–	6	1	5	1
Metabolic changes	2	17	–	–	–
Retinal function	–	14	–	–	4

Of note, the number of "records" does not equal the number of publications because some studies investigated multiple pathophysiological mechanisms representing different "records."

Table 2. Studies investigating anti-inflammatory effects of marine resources on retinal diseases.

Marine resource	Source, dose	Retinal disease/model	Species/cells	Anti-inflammatory effect	Reference
Fish	Diet, ≥1 serving/month	Age-related macular maculopathies	Human	Decrease in serum c-reactive protein levels	Seddon et al. (2006)
Fish	Diet, ≥2 servings/week	Retinopathy (vascular mortality)	Human	Decreased white cell and platelet count	Kaushik et al. (2008)
Fish oil	SMOFLipid emulsion, 20%, fish oil 30 g/dL	ROP	Human	No effect on leucocytes and platelets counts	Beken et al. (2014)
Fish oil	MaxEPA, 750 mg/day, containing 14% EPA and 10.6% DHA, equals 500 mg/day omega-3 fatty acid	DR	Rat	Reduced thromboxane B2 and leukotriene B4, increased thromboxane B3 and leukotriene B5 plasma levels	Hammes et al. (1996)
Fish oil	OmegaRx zone, 0.5 g/day DHA and 1 g/day EPA equals 400 mg EPA and 200 mg DHA/daily	Ischemic optic neuropathy	Rat	Decreased inflammatory macrophage recruitment, increased Arg1, CD206, and Fizz1 mRNA level (markers of M2 macrophages), decreased TNF, IL-1β, and iNos mRNA levels in the optic nerve	Georgiou et al. (2017)
Fish oil	21% menhaden oil, 2.5% omega-3 fatty acid	Herpetic chorioretinitis	Mouse	Reduced TNF, IL-2, IL-10, and IFNγ secretion in splenic cells and the retina	Berra et al. (2017)
Fish oil	10–250 μg/mL	DR	Monocytes/ macrophages U937 cells	Decreased TNF (10–25 μg/mL), IL-6 (250 μg/mL), monocytic chemotactic protein-1 secretion (50–250 μg/mL), no change in IL-8 secretion	Laubertová et al. (2017)
Fish oil	YS-2636, 36% EPA and 26% DHA and 3.6 mg/g mixed tocopherol	DR	ARPE-19 cells	Decreased TNF release	Dutot et al. (2011)
Algal oil	233 mg/kg/day, 33.34% DHA, 13.97% DPA	Visible-light-induced retinal damage	Rabbit	Decreased TNF, IL-1β, IL-8, and COX-2 protein expression and NF-κB mRNA levels in the retina	Deng et al. (2018)
Algae oil	*Schizochytrium* sp., 1.75 g/day DHA and 1 g/day EPA equals 350 mg/g DHA and 200 mg/g EPA	Anterior ischemic optic neuropathy	Rat	Reduced macrophage infiltration (ED1-positive cells) in the optic nerve, reduced TNF, IL-1, protein expression in the retina	Huang et al. (2020)

AA: arachidonic acid; ARPE-19: retinal pigment epithelium cell line; COX-2: cyclooxygenase-2; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; DR: diabetic retinopathy; EPA: eicosapentaenoic acid; IFNγ: interferon gamma; IL: interleukin; iNOS: inducible nitric oxide synthase; NF-κB: nuclear factor "kappa-light-chain-enhancer" of activated B-cells; ROP: retinopathy of prematurity; RPE: retinal pigment epithelium; TNF: tumor necrosis factor.

no effect of regular fish intake on the risk of AMD (Nano et al. 2013; Ersoy et al. 2014; McCarter et al. 2018). Another study observed that the consumption of fish was not different between patients with AMD and healthy controls (Gopinath et al. 2017). Two meta-analyses of prospective cohort studies concluded that fish consumption reduced the risk for early and late AMD with evidence for a linear relationship between the dose of fish consumption and AMD risk (Zhu et al. 2016; Dinu et al. 2018).

Furthermore, two prospective randomized clinical trials assessed the oral supplementation with omega-3 fatty acids. In the Age-Related Eye Disease Study 2 (AREDS2) trial in 4200 patients, the addition of the omega-3 fatty acids DHA and EPA to the AREDS formulation (antioxidant vitamins C and E, beta carotene, and zinc) did not further reduce the risk of progression to advanced AMD (Age-Related Eye Disease Study 2 Research Group 2013). In the Nutritional AMD Treatment 2 (NAT2) trial in 263 patients with early signs of AMD, the oral supplementation with DHA and EPA did not change the time to occurrence of choroidal neovascularization (Souied et al. 2013), while dietary oily fish and seafood consumption was significantly lower in patients with AMD and serum red blood cell DHA + EPA were associated with a substantial and significantly lower risk of neovascular AMD (Merle et al. 2014; Merle, Richard, et al. 2015). However, trial design, aims, and formulations were different and non-compliant patients remained in the data analysis of the AREDS2 study (Souied et al. 2015). Thus, further randomized trials are needed to explore which patient populations benefit from specific formulations.

Dietary fish intake was also related to a lower risk of DR (Sala-Vila et al. 2016; Chua et al. 2018) and glaucoma (Renard et al. 2013). Moreover, fish consumption reduced the prevalence of retinopathy in persons without diabetes, although only borderline statistically significant (Kaushik et al. 2008).

Table 3. Studies investigating antioxidants effects of marine resources on retinal diseases.

Marine resource	Source, dose	Retinal disease/model	Species/cells	Antioxidant effect	Reference
Fish oil	SMOFLipid emulsion, 20%, fish oil 30 g/dL	ROP	Human	Increased total antioxidant capacity, decreased total oxidant status, and oxidative stress index (not statistically significant) in the plasma	Unal et al. (2018)
Fish oil	10–250 μg/mL	DR	Monocytes/ macrophages U937 cells	Increased antioxidant capacity (10–250 μg/mL), no change in SOD activity, oxidative damage to DNA, protein oxidation, or lipid peroxidation	Laubertová et al. (2017)
Fish oil	YS-2636, 36% EPA and 26% DHA and 3.6 mg/g mixed tocopherol	DR	ARPE-19 cells	Decreased ROS production (DCFH-DA)	Dutot et al. (2011)
Algal oil	233 mg/kg/day, 33.34% DHA, 13.97% DPA	Visible-light-induced retinal damage	Rabbit	Increased catalase and SOD protein levels in the retina	Deng et al. (2018)
Macroalga, ethanol extract	*Eisenia bicyclis*, 0.1–50 μg/mL	Oxidative stress (BSO, H_2O_2, $OH^{\cdot}$, $O_2^{\cdot-}$)	RGC-5 cells	Increased cell viability (MTT, 50 μg/mL), decreased ROS production (DCFH-DA, 1–50 μg/mL), prevented GSH depletion (10–50 μg/mL), reduced levels of lipid peroxides (1.25–20 μg/mL)	Kim et al. (2012)
Algae-derived Diphlorethohydroxycarmalol	*Ishige okamurae*, 25–50 μg-mL	Oxidative stress (H_2O_2)	ARPE-19 cells	Protected from oxidative stress-induced death, decreased ROS production (DCF-DA)	Park et al. (2019)
Algae-derived polysaccharide compound	*Phaeophyceae*, 0.1–100 μg/mL	DR	ARPE-19 cells	Increased SOD (1–100 μg/mL) and GSH protein levels (10–100 μg/mL)	Xie et al. (2012)
Fucoidan	*Fucus vesiculosus, Fucus distichus* subsp. *evanescens, Fucus serratus, Laminaria digitata, Saccharina latissima*, high-molecular-weight, 1–100 μg/mL	Oxidative stress (H_2O_2, TBHP)	OMM-1, ARPE-19 cells	All fucoidans protected OMM-1 from oxidative stress-induced death, only fucoidan from *Saccharina latissima* was protective in ARPE-19 cells	Dörschmann, Saskia Bittkau, et al. (2019)
Fucoidan	*Fucus vesiculosus*, 100 μg/mL	DR	ARPE-19 cells	Decreased ROS production (DCFH-DA)	Li et al. (2015)
Fucoidan	*Fucus distichus* subsp. *evanescens*, containing 61.9% fucose, 26.2% uronic acids, 6.9% sulfate content, 1–250 μg/mL	Oxidative stress (TBHP)	ARPE-19 cells	Not protective against oxidative stress-induced death	Rohwer et al. (2019)
Fucan, sulfated	*Laminaria hyperborea*, high-molecular-weight, 1–100 μg/mL	Oxidative stress (H_2O_2, TBHP)	OMM-1, ARPE-19 cells	No change in cell viability in OMM-1 cells, further reduced in ARPE-19 cells (10–100 μg/mL)	Dörschmann, Kopplin, et al. (2019)
Fucoxanthin	*Laminaria japonica,* 5–50 μg/mL	Visible light-induced retinal damage	ARPE-19 cells	Decreased ROS production (DCFH-DA)	Liu et al. (2016)

8-OHdG: 8-hydroxy-2′-deoxyguanosine; ARPE-19: retinal pigment epithelium cell line; BSO: L-buthionine-(S,R)-sulfoximine; DCF-DA: dichlorohydrofluorescein diacetate; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; DR: diabetic retinopathy; EPA: eicosapentaenoic acid; GSH: glutathione; MDA: malondialdehyde; MnSOD: manganese-dependent superoxide dismutase; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; OMM-1: uveal melanoma cell line; RGC-5: retinal ganglion cell line 5; ROP: retinopathy of prematurity; RPE: retinal pigment epithelium; SOD: superoxide dismutase; TBHP: tert-butyl hydroperoxide.

Table 4. Studies investigating antiangiogenic and vasoprotective effects of marine resources on retinal diseases.

Marine resource	Source, dose	Retinal disease/model	Species/cells	Antioxidant effect	Reference
Fish	Diet, ≥2 servings/week	Retinopathy (vascular mortality)	Human	Increased arteriolar diameter and decreased venular diameter	Kaushik et al. (2008)
Fish	Diet, 1 OMM 7 servings/week	DR	Human	Wider retinal arteriolar and venular caliber	Chua et al. (2006)
Fish	Vegetable and fish avoidance	DR	Human	Associated with wider retinal venuler caliber	Keel et al. (2016)
Fish	69 species, *S. gracilis* 1.2 g/kg/day, *Decapterus tabl* 3°g/kg/day in mice	Oxygen-induced retinopathy	Mouse, 661 W, ARPE-19 cells	In vitro: *Selar crumenophthalmus, Spratelloides gracilis, Seriola dumerili,* and *Decapterus macarellus, Decapterus muroadsi, Decapterus tabl* inhibited HIF-1, mRNA of *Hif* and HIF target genes in hypoxia, HIF protein, in vivo: *D. tabl* but not *S. gracilis* reduced neovascularization (neovascular tufts, vaso-obliteration)	Shoda et al. (2020)
Fish oil	50 μL/day, containing 13 mg DHA and 22 mg EPA	Oxygen-induced retinopathy, intermittent hypoxia	Rat	Decreased VEGF and soluble VEGFR-1 protein levels in the retina, vitreous fluid, and choroid, reduced neovascularization, vessel size, capillary plexus, vascular network, vascular density, total vascular area, number of branching points and segments	Beharry et al. (2018)
Shrimp heparinoid, sulfated polysaccharide	4.5–450 ng single treatment	AMD	Rat	Suppresses choroidal neovascularization, reduces VEGF protein levels in the choroidal neovascularization area and VEGF and transforming growth factor β1 protein levels in the retina and choroid	Dreyfuss et al. (2010)
Algal oil	233 mg/kg/day, 33.34% DHA, 13.97% DPA	Visible-light-induced retinal damage	Rabbit	Decreased VEGF and HIF-1 in the retina	Deng et al. (2018)
Macroalga, ethanol extract and Ishophloroglucin A	*Ishige okamurae* ethanol extract 10 μg/mL, Ishophloroglucin A 0.015–0.5 μM	DR	Zebrafish	Decreased retinal vessel diameter and vessel formation	Fernando et al. (2019)
Fucoidan	*Laminaria japonica*, low-molecular-weight, 50–200 mg/kg/day in rats, 12.5–50 μg/mL in cells	DR	Rat, BMEC	In vivo: reduced diabetic retinal neovascularization, decreased retinal VEGF protein and mRNA expression, decreased retinal HIF-1 protein levels, in vitro: reduced cell proliferation and VEGF protein levels	Yang et al. (2013)
Fucoidan	*Fucus vesiculosus,* high-molecular-weight, 100 μg/mL	General retinal health, wound healing	Primary RPE, ARPE-19 cells	Decreased VEGF secretion and protein expression, reduced VEGF-induced angiogenesis of peripheral endothelial cells	Dithmer et al. (2014)
Fucoidan	*Fucus vesiculosus, Fucus distichus subsp. evanescens, Fucus serratus, Laminaria digitata, Saccharina latissima*, high-molecular-weight, 1–100 μg/mL	Oxidative stress (H_2O_2, TBHP)	OMM-1, ARPE-19 cells	Higher VEGF binding affinity than heparin, reduced VEGF secretion in ARPE-19, but no change or even an increase in primary RPE, except for fucoidan from *Saccharina latissima*, which reduced VEGF secretion also in RPE at 10 μg/mL	Dörschmann, Saskia Bittkau, et al. (2019)
Fucoidan	*Fucus distichus* subsp. *evanescens*, containing 61.9% fucose, 26.2% uronic acids, 6.9% sulfate content, 1–250 μg/mL	Healthy cells	ARPE-19 cells	Reduced VEGF secretion	Rohwer et al. (2019)
Fucan, sulfated	*Laminaria hyperborea*, high–molecular-weight, 1–100 μg/mL	Oxidative stress (H_2O_2, TBHP)	ARPE-19, primary porcine RPE cells	Reduced VEGF secretion (50–100 μg/mL)	Dörschmann, Kopplin, et al. (2019)
Fucoxanthin	*Laminaria japonica,* 5–50 μg/mL	Visible light-induced retinal damage	ARPE-19 cells	Reduced VEGF protein levels	Liu et al. (2016)

661 W: murine retinal cone cell; AMD: age-related macular degeneration; ARPE-19: retinal pigment epithelium cell line; BMEC: brain microvascular endothelial cells; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; DR: diabetic retinopathy; EPA: eicosapentaenoic acid; OMM-1: uveal melanoma cell line; RPE: retinal pigment epithelium; TBHP: tert-butyl hydroperoxide; VEGF: vascular endothelial growth factor; VEGFR-1: VEGF receptor-1.

Four studies demonstrated that preterm infants that received fish oil-based lipid emulsions developed ROP less frequently compared to lipid emulsions without fish oil (Beken et al. 2014; Torgalkar et al. 2019; Gharehbaghi et al. 2020; Tu et al. 2020), while two studies reported no difference (Najm et al. 2017; Unal et al. 2018). Further three studies from one research group reported that the overall occurrence of ROP was not reduced, but the risks of laser therapy and cholestasis were lower (Pawlik, Lauterbach, and Hurkała 2011a; Pawlik, Lauterbach, and Turyk 2011b; Pawlik et al. 2014).

Effects of marine resources on the pathophysiology of retinal diseases

From the 46 publications that investigated the underlying pathophysiological mechanisms of the beneficial effects of marine resources on retinal diseases, 10 records were on

anti-inflammatory, 12 on antioxidant, 14 on antiangiogenic/vasoprotective, 13 on cytoprotective effects, and 18 on metabolic changes as well as 18 reported beneficial effects on retinal function (Table 1 and Figure 1). In the following sections, we will explain the pathophysiological mechanisms in retinal diseases and the effects of marine resources on the processes identified in the systematic literature review.

Anti-inflammatory effects

Inflammation is a reaction of the tissue to the presence of danger signals that are to be eliminated to ensure tissue homeostasis. In general, a danger signal is detected by the cells of the immune system or other sentinel cells, which carry appropriate receptors. For example, toll-like receptor (TLR) 4, which is expressed by RPE or retinal microglia, detects lipopolysaccharides, a major cell-wall component of Gram-negative bacteria (Shen et al. 2014; De Nardo 2015). Of note, danger signals can be intrinsic to the host organism and do not have to come from a pathogen. Intrinsic danger signals, e.g., derived from stressed or necrotic cells, are usually called "danger-associated molecular patterns," pathogenic danger signals are designated as "pathogen-associated molecular patterns" (Zhang and Liang 2016; Patel 2018). The detection of the danger signal then may lead to the recruitment of inflammatory cells (e.g., neutrophils or macrophages) and to the secretion of inflammatory cytokines. These alter the tissue, e.g., blood vessels may become leaky to facilitate the migration of leukocytes into the inflamed tissue (Medzhitov 2008).

The goal of any inflammatory response is the removal of the danger signal and the return to the homeostatic state of the tissue (Freire and Van Dyke 2013). Inflammation is of high importance for the protection and survival of an organism. However, inflammatory responses often induce tissue injury. Moreover, if the cause of the inflammation cannot be removed (e.g., in persistent injury), inflammation can induce chronic tissue damage and a self-perpetuating situation (Chen and Xu 2015).

Most, if not all, retinal diseases are accompanied by inflammatory responses due to the very nature of the diseases, which are accompanied by some kind of tissue breakdown, exposing danger signals (Boehm, Oellers, and Thanos 2011).

To understand inflammatory processes in the retina, it is helpful to recognize the immune privilege of the retina. The retina is protected from the systemic immune surveillance by the blood-retina barrier, which excludes blood-borne lymphocytes from the retinal tissue. In addition to the barrier, the intraocular milieu is generally immunosuppressant (Forrester and Xu 2012). This is an evolutionary adaptation to the high vulnerability of the mammalian neuronal retinal tissue, its extremely limited ability to regenerate, and the profound importance of sight for the survival of the organism (Jiang, Streilein, and McKinney 1994). Furthermore, retinal tissue has its own macrophages, the microglia, which constantly surveil the retinal tissue (Rathnasamy et al. 2019). In addition, the RPE acts as a sentinel for danger signals and is involved in suppressing the immune system as well as in inflammatory processes (Klettner 2015a). Therefore, inflammation, if it cannot be avoided, is supposed to be an internal affair of the retina.

Monocytic recruitment

Microglia are the innate immune cells of the retina. In addition, invading macrophages have also been described for some diseases. The differentiation of these two cell types, however, is not easy, as they carry similar molecular markers.

In AMD, the contribution of monocytes (retinal microglia, systemic macrophages) is still controversially discussed, but it has been proposed that the chronic activation of microglia due to degenerative changes accumulating with age may contribute to AMD development (Copland et al. 2018). In addition, macrophages can be found in AMD tissue (Guillonneau et al. 2017). Activated monocytes secrete a variety of cytokines such as interleukin (IL)-6, IL-1ß, or tumor necrosis factor (TNF; see below).

In glaucoma, the elevation of intraocular pressure activates astroglia and microglia to secrete several cytokines in an attempt to protect retinal ganglion cells. Dying retinal ganglion cells present danger signals, activating several kinds of danger recognizing receptors that induce a profound inflammatory response (Križaj et al. 2014). The activation of TLR and TNF receptors induces the transcription factor nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF-κB) and inflammasomes. This may disrupt the blood-retina barrier and facilitate the additional infiltration of circulating immune cells (Križaj et al. 2014).

In DR, the main inducing factor is hyperglycemia. Hyperglycemia induces oxidative stress and the expression of TLR. Directly or indirectly through tissue damage, this leads to microglia activation and an NF-κB and extracellular-signal-regulated kinase (ERK)-mediated release of cytokines (Tang and Kern 2011; Su et al. 2014; Mesquida, Drawnel, and Fauser 2019). Inflammatory activation, such as increased iNOS expression, microglia activation or TNF secretion, may result in the loss of pericytes and the disruption the blood-retinal barrier (Leal et al. 2007; Mesquida, Drawnel, and Fauser 2019; Spencer et al. 2020).

In RP, activated microglia have been observed in degenerative regions in RP patients, phagocytosing degenerating rods (Milam, Li, and Fariss 1998), and in a variety of RP animal models (McMurtrey and Tso 2018). Here, oxidative damage has been suggested to be involved in microglial activation (Oka et al. 2008). Inhibiting microglia activation and phagocytosis protected photoreceptors in animal RP models (Lew, Mazzoni, and Finnemann 2020; Wang, Xue, and Cepko 2020). In addition, macrophage infiltration has been reported in a mouse model of retinal dystrophy (Hollingsworth and Gross 2020).

Fish oil and omega-3 fatty acids were reported to attenuate inflammatory macrophage infiltration and activation. For example, DHA-derived resolvin D1 (2 µg/kg body weight) reduced the number of F4/80-positive inflammatory macrophages in adipose tissue in obese-diabetic mice. Resolvin D1

also improved glucose tolerance and increased adiponectin production as well as protein kinase B (also known as AKT) phosphorylation, while reducing fasting blood glucose and IL-6 expression in adipose tissue (Hellmann et al. 2011). In a model of high fat diet-induced obese mice, DHA (4 µg/g body weight) did not change the total number of adipose tissue macrophage, but attenuated the pro-inflammatory shift in macrophage F4/80 expression and increased the number of anti-inflammatory low-expressing CD11b/F4/80 macrophages. DHA also decreased the expression of monocyte chemotactic protein-1 (MCP-1), while increase IL-10 expression and decreased serum glucose levels and hepatic steatosis (Titos et al. 2011). Of note, although DHA and resolvin D1 were not administered orally in these studies, the doses were based on the actual serum concentrations of non-esterified DHA that reflect the standard intake of omega-3 fatty acids supplements (Delorme et al. 1984; González-Périz et al. 2009).

The mechanisms underlying the effect of fish oil on inflammatory macrophage infiltration are still not completely understood. Fish oil-derived PUFAs have been demonstrated to decrease the expression of macrophage chemotactic mRNAs as well as mRNA and protein secretion of proinflammatory cytokines (Liddle et al. 2020). They also induce the AMPK/SIRT1 signaling pathway, which has been suggested to counteract endothelial hyperpermeability (Jing et al. 2014).

Similarly, algae and algae extracts can inhibit inflammatory macrophage infiltration into tissues. For example, the oral administration of the hydroquinone zonarol isolated from the brown algae *Dictyopteris undulata* inhibited the recruitment of Mac-2-positive macrophages into the mucosa in mice treated with dextran sulfate sodium, a model of ulcerative colitis. Zonarol also suppressed the gene expression of *Tnf*, *Il6*, and *iNos* and led to functional improvement, reduced cell death, and the normalization of colon length (Yamada et al. 2014). The authors further demonstrated that zonarol inhibited the hyperactivation of macrophages by reducing nitric oxide (NO) production and inflammatory gene expression. Brown algae-derived sulfated glycans, high-molecular-weight fucoidans, are also able to reduce inflammatory cell infiltration based on its anti-selectin activity, thereby reducing macrophage activation (for review see Pomin 2015). Concerning biological activity in general, the effect of fucoidan is dependent on its molecular structure, which in turns depends on several factors, such as species, harvest time, and location as well as extraction methods, and may differ profoundly in various studies (Pomin 2016; Ponce and Stortz 2020). When assessing the potential of fucoidan concerning the various biological activities, this should be kept in mind.

Our systematic search on the effects of marine resources on retinal diseases identified two studies from the same research group that demonstrated a beneficial effect on blocking the recruitment of macrophages into the eye (Table 2). They reported that the oral administration of fish oil rich in DHA and EPA reduced ED-1-positive macrophage infiltration (a marker of CD38, specific for extrinsic macrophages) at the optic nerve in a rat model of anterior ischemic optic neuropathy at four weeks post-injury. In the fish oil group, visual function was better preserved and the survival of retinal ganglion cells was increased (Georgiou et al. 2017). More recently, the authors demonstrated that algal oil derived from *Schizochytrium* similarly attenuated the number of ED1-positive cells in the optic nerve, while reducing the protein levels of iNOS, IL-1β, TNF, and phosphorylated ERK, and increasing the protein level of ciliary neurotrophic factor (Huang et al. 2020).

Cytokine responses

A major component of retinal inflammation is the release of inflammatory cytokines by microglia, astrocytes, Müller or RPE cells. In addition, infiltrating macrophages can contribute to cytokine secretion.

Cytokines are strongly associated with AMD development (Ambati, Atkinson, and Gelfand 2013). IL-6 was detected in ocular fluids of patients with exudative AMD and is connected with AMD progression (Seddon et al. 2005). It may also participate in neovascularization and correlate with edema. IL-1ß may be associated with photoreceptor degeneration (Wooff et al. 2019). TNF can be observed in neovascular tissue and may interfere with RPE function (Oh et al. 1999; Guillonneau et al. 2017). Drusen, hallmarks of AMD, have been demonstrated to activate inflammasomes (intracellular multiprotein complexes) (Klettner, Kauppinen, et al. 2013) with subsequent IL-1ß and IL-18 secretion (Doyle et al. 2012). In addition to cytokines, the complement system is important for the development of AMD, although its specific contribution has not been understood so far (Klein et al. 2005).

In glaucoma, activated microglia and astroglia secrete several cytokines, such as TNF, IL-18, or IL-1ß. These cytokines may originally protect retinal ganglion cells, but can also contribute to the disruption of the blood-retina barrier (Križaj et al. 2014). In DR, cytokines such as TNF, IL-1ß, IL-6, and IL-8 are released (Altmann and Schmidt 2018), with further increases in TNF and IL-8 with disease progression (Doganay et al. 2002). In RP patients, the levels of IL-2, IL-6, IL-23, MCP-1, and vascular endothelial growth factor (VEGF) are elevated in intraocular fluids (Ten Berge et al. 2019). In addition, in animal models of RP, TNF expression in photoreceptors or microglia was associated with photoreceptor death, while TNF deficiency conferred neuroprotection (Zhu et al. 2013; Rana et al. 2017).

Marine animal products from some fish, soft corals, sea snakes, sea hares, bryozoans, sponges, fungi, and starfish have been demonstrated to decrease the production of inflammatory cytokines (Ai et al. 2014; Fung et al. 2014; Mayer et al. 2019; Durand et al. 2020). Omega-3 fatty acids alter the activation of pro- and anti-inflammatory transcription factors and reduce the production of inflammatory cytokines and cyclooxygenase-2 (COX-2) metabolites (for review see Calder 2015; de Bus et al. 2019). This anti-inflammatory effect has been mainly attributed to the attenuation of the TLR4 signaling pathway (Rogero and Calder 2018).

Similarly, algae and algae extracts have been demonstrated to (i) decrease inflammatory cytokine production, including the release of interleukins and TNF from macrophages, (ii) inhibit intracellular mitogen-activated protein (MAP) kinase and NF-κB signaling, and (iii) suppress the activity of COX-2 and iNOS (for review see Fernando, Nah, and Jeon 2016; Mayer et al. 2019; Giannaccare et al. 2020). In particular, high-molecular-weight fucoidan has the ability to reduce inflammatory cytokine levels in different inflammatory models and organ systems as a consequence of its anti-selectin activity, preventing selectin-mediated leukocyte migration and infiltration (for review see Pomin 2015). In addition, the brown algae-derived xanthophyll fucoxanthin has been reported to decrease the production of inflammatory cytokines, NF-κB transactivation as well as the phosphorylation of MAP kinases in cell culture (Kim et al. 2010) and to decrease the antigen-induced degranulation of mast cells (Sakai et al. 2009). The oral administration of lycopene extracted from green algae *Chlorella marina* decreased the levels of COX and 15-lipoxygenase in monocytes of rats fed a high-cholesterol diet (Renju, Kurup, and Saritha Kumari 2014).

Our systematic search identified six studies investigating marine resources in the context of inflammatory cytokine release in retinal diseases (Table 2), including those mentioned already under monocytic activation (see above). In addition, Berra et al. reported that mice fed omega-3 fatty acid-rich menhaden oil showed diminished protein levels of TNF, IFNγ, IL-2, and IL-10 in the retina compared to omega-6 fatty acid-rich Safflower oil or corn oil in a model of herpetic chorioretinitis (Berra et al. 2017).

Systemic inflammation

The eye is considered a closed organ. Nevertheless, systemic influences also act on the inner environment of the eye, specifically the retina.

In AMD, systemic levels of cytokines may be of importance, as elevated systemic IL-6 has been associated with late stages of AMD (Nahavandipour et al. 2020) while certain AMD risk groups show elevated systemic TNF (Cao et al. 2013). The role of systemic inflammation in ROP has so far received little attention (J. C. Rivera et al. 2017). Infection may be a factor in the development of ROP, as an infection of the placenta or the infant and sepsis occurring in premature infants have been associated with ROP (Kim et al. 2018; Huang et al. 2019). High plasma levels of IL-6, IL-8, and TNF in the first days of life of the infant may be associated with a higher risk of ROP (Silveira, Fortes Filho, and Procianoy 2011). In models of ROP, IL-1ß was associated with retinal microvascular degeneration (Rivera et al. 2013). It has also been hypothesized that circulating cytokines may prime the pre-ROP retina, facilitating ROP in the later stages (Lee and Dammann 2012).

Higher omega-3 fatty acid intake has been associated with decreased levels of systemic inflammatory cytokines and endothelial activation in randomized clinical trials of cardiovascular disease, chronic renal diseases, sepsis, and acute pancreatitis (for review see Rangel-Huerta et al. 2012; Jiang et al. 2016). Similarly, high-molecular-weight fucoidan from *Fucus evanescens* administered either orally or subcutaneously attenuated the increases in protein levels of endothelin-1, TNF, and IFNγ induced by intraperitoneal injection of poloxamer 407 in mice, a model of dyslipidemia and atherosclerosis (Kuznetsova et al. 2019). Diet supplemented with laminarin, a brown algae polysaccharide, diminished the number of serum monocytes as well as the serum protein levels of prostaglandin E2 and TNF in a rat model of lipopolysaccharide challenge (Neyrinck, Mouson, and Delzenne 2007). Oral lycopene extracted from green algae *Chlorella marina* decreased the levels of systemic inflammatory markers including myeloperoxidase, c-reactive protein (CRP), and ceruloplasmin in a rat model of hyperlipidemia (Renju, Kurup, and Saritha Kumari 2014). A diet rich in astaxanthin from green algae *Haematococcus pluvialis* increased the number of monocytes and B cells, the concentration of immunoglobulins, the activity of natural killer cells and decreased the levels of serum CRP in female Beagle dogs (Chew et al. 2011).

With respect to retinal diseases, we identified four studies examining systemic inflammation in retinal diseases (Table 2). Fish consumption was associated with lower serum CRP in subjects with AMD (Seddon et al. 2006). In the Blue Mountains Eye Study, fish consumption was associated with a lower serum white cell and platelet count (Kaushik et al. 2008). In contrast, in infants with ROP, a fish oil-based lipid emulsion did not alter the serum leucocyte or platelet count compared to soybean oil (Beken et al. 2014). Furthermore, mice fed with omega-3 fatty acid-rich menhaden oil showed diminished TNF, IFNγ, IL-2, and IL-10 protein levels in the spleen in a model of herpetic chorioretinitis (Berra et al. 2017).

In summary, marine resources show vast potential for anti-inflammatory actions and should be further investigated in the context of retinal diseases. Especially considering retinal diseases with long-term low-grade chronic inflammation, marine resources could provide a remedy, ameliorating inflammatory alterations and prevention retinal degradation and loss of function

Antioxidant effects

Oxidative stress is the imbalance between oxidants and the ability of the biological system to remove them. This imbalance is a result of either an increased production of reactive oxygen species (ROS), reactive nitrogen species (RNS), lipid ROS, or a decreased expression of antioxidant defense enzymes, or – more likely – a combination of both.

There are a number of different ROS that are constantly produced in aerobic organisms due to oxidative phosphorylation, P450 metabolism, peroxisomes, and inflammatory cell activation (Poli et al. 2004). These include free radicals containing one or more unpaired electrons, oxygen species that have been elevated to a higher energy level, or strong oxidizing agents. Some examples of relevant ROS are hydrogen peroxide (H_2O_2), superoxide anion, hydroxyl radical, and singlet oxygen (Klettner 2012). Similarly, cells produce nitric

oxide (NO) which is a major messenger (Beckman and Crow 1993), but may also react with superoxide generating peroxynitrite. Peroxynitrite induces lipid peroxidation in cellular membranes (Radi et al. 1991), which are rich in polyunsaturated fatty acids making them vulnerable to peroxidation of unsaturated carbon–carbon bonds.

Cellular antioxidant defense enzymes counteract ROS production, including superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (Poli et al. 2004). SODs and GPXs are located in the cytosol and mitochondria where SOD reduces O_2^- to the more stable H_2O_2, which is further degraded to water by the selenoprotein GPX using reduced glutathione (GSH) as a substrate. GPX4 converts lipid hydroperoxides to lipid alcohols. Glutathione reductase is also located in the cytoplasm and mitochondria and converts oxidized glutathione to GSH. Catalase is located in peroxisomes where it removes H_2O_2. In addition, nonenzymatic antioxidants function to quench ROS, including GSH, vitamin E and C, β-carotene, and coenzyme Q (Clarkson and Thompson 2000).

While ROS have also been shown to be essential for intracellular signaling under physiologic conditions (for review, see Shadel and Horvath 2015), which should be considered when designing therapeutic strategies, oxidative stress is a pathological factor in aging and in many diseases including retinal diseases (Liguori et al. 2018). Oxidative stress mechanisms in retinal diseases may differ in the source of the oxidants, the cells affected, and the mechanisms activated.

Increased ROS production in retinal diseases

In AMD, extrinsic oxidative stress induction due to light exposure, smoking, high fat diet, and general aging are implicated to contribute to disease development (Chalam et al. 2011; Sohal and Orr 2012). The major pathological stimulus in DR, conversely, is chronic hyperglycemia. The excessive glucose flux causes, among others, a mitochondrial overproduction of ROS (Giacco and Brownlee 2010; Tangvarasittichai and Tangvarasittichai 2019). In ROP, the major source for ROS is hypoxia, which has been shown to be a potent inducer of oxidative stress (J. Rivera et al. 2017). Hypoxia is also another important source of ROS in DR, which results in ischemic areas in the retina, further contributing to ROS production, and leading to a vicious cycle (Kowluru and Mishra 2017). In glaucoma, hypoxia due to elevated pressure reduces the blood supply to the optic nerve, resulting in ischemia and subsequent ROS production, which causes direct or indirect retinal ganglion cell death (Gauthier and Liu 2016). ROS also induces inflammatory activation via NF-κB, as seen in DR, glaucoma, or AMD (Giacco and Brownlee 2010; Gauthier and Liu 2016; Datta et al. 2017).

In addition, a general (systemic) increase of ROS has been observed. For instance, in patients with AMD, serum levels of oxidation products such as malondialdehyde (MDA) are elevated (Totan et al. 2009). In a meta-analysis assessing oxidative stress markers in the serum and aqueous humor, patients with glaucoma presented an overall increase in oxidative stress markers with MDA being particularly increased (Benoist d'Azy et al. 2016). However, also a general increase of oxidative damage markers has been observed with age (Mecocci et al. 1999).

Even under physiologic conditions, the retina is constantly exposed to high amounts of oxidants (Cai et al. 2000). Due to the high oxygen demand of the retina and especially of the photoreceptors, the oxygen tension is high and mitochondria, a major source of oxidants (Balaban, Nemoto, and Finkel 2005), are highly active. Furthermore, short-wavelength light exposure contributes strongly to the oxidant burden in the retina (Glickman 2002).

When not counterbalanced, ROS may react with cellular components, causing an accumulation of cell damage over time. The polyunsaturated fatty acids (PUFA) found in abundance in photoreceptor membranes are especially vulnerable to peroxidization by oxidative stress, producing harmful lipid ROS such as MDA or 4-hydroxynonenal (Catala 2011; Saccà et al. 2018). ROS also attack amino acids in proteins, contributing to aggregates and forming cross-links, which leads to the inactivation of functional proteins and the aggregation of oxidized products (Hawkins and Davies 2019). ROS can also cause strand breaks in the DNA, with the DNA of mitochondria being especially susceptible (Evans, Dizdaroglu, and Cooke 2004).

The cells that are mostly affected by ROS in AMD development are the RPE. Due to the phagocytosis of the photoreceptor outer segment, RPE cells are exceptionally prone to lipid peroxidation. In addition, lipofuscin accumulation may contribute to intracellular oxidative stress responses (Rózanowska et al. 1995). Furthermore, RPE cells are enriched with mitochondria (Datta et al. 2017). Although RPE cells are highly resistant to ROS, and part of the oxidative stress protection of the retina (Klettner 2012; Datta et al. 2017), a life-long exposure to ROS, the accumulation of lipofuscin and a reduced mitochondrial DNA repair capability lead to a decline in their defense ability over time. RPE cells from AMD subjects display higher oxidative DNA damage, ROS production and more lipid peroxidation products (Jarrett Stuart and Boulton 2012; Abokyi et al. 2020). The alterations caused by oxidants reduce the capacity of the RPE to function and lead to cell death (Hanus, Anderson, and Wang 2015).

The main cells affected by oxidative damage in DR and ROP are the retinal endothelial cells, resulting in retinal microvascular degeneration (J. Rivera et al. 2017). In glaucoma, cells of the inner retina are the most affected. Oxidative stress may induce direct cell death of retinal ganglion cells, while the optic nerve degenerates progressively (Nucci et al. 2005; Tezel 2006).

A factor that is of special importance in the development of DR is hyperglycemia. An increase in superoxide production in the mitochondria leads to advanced glycation end products (AGE) that bind to their receptor (RAGE), inducing the further production of ROS. In addition, RAGE activates NF-κB inducing an inflammatory response and VEGF (Giacco and Brownlee 2010; Tangvarasittichai and Tangvarasittichai 2019). Extracellular advanced glycation

end products can also be found in glaucomatous optic nerve and retina. NO may be of importance for this pathway (Nucci et al. 2005). Furthermore, NO is involved in degeneration in ROP, as it has been shown to react with ROS, generating nitrites, nitrates, and peroxynitrites, which cause nitroxidative stress resulting in retinal microvascular degeneration in experimental ROP (J. Rivera et al. 2017).

In RP, oxidative stress due to the excessive oxygen present in the retina after the death of rods (which consume considerable amounts of oxygen) has been suggested to participate in RP photoreceptor degeneration (Campochiaro et al. 2015; Domènech and Marfany 2020). Oxidative alterations of DNA and proteins are increased in the vitreous or the aqueous humor of RP patients, while antioxidant molecules such as GSH and SOD3 are decreased (Murakami et al. 2012; Martínez-Fernández de la Cámara et al. 2013; Campochiaro et al. 2015). Conversely, activating the oxidative stress response displayed protective effects in RP animal models (Campello et al. 2020).

Marine animal products have been reported to reduce ROS generation or protect against ROS-induced damage. The oral administration of polysaccharides from the marine worm *Sipunculus nudus* reduced NO levels and hydroxyl radicals in Beagle dogs and mice exposed to γ-radiation (Cui et al. 2014; Li et al. 2016). Polysaccharides from sea cucumber were effective in scavenging 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals, hydroxyl radicals, and superoxide anion radicals in cell-free systems and were able to reduce MDA levels when administered in the diet in mice fed a high-fat diet (Qi et al. 2017). A diet enriched with oligopeptides from the bivalve *Meretrix meretrix* abrogated the increase of lipid peroxides in a mouse model of high-fat diet-induced nonalcoholic fatty liver disease (Huang et al. 2018). The oral administration of nanoparticles containing low-molecular-weight β-chitosan extracted from the gladius of squid *Sepioteuthis lessoniana* abolished the increase in lipid peroxides in the plasma and liver of rats subjected to hepatocellular carcinoma (Subhapradha, Shanmugam, and Shanmugam 2017).

A few studies investigated the effects of omega-3 fatty acid on reducing ROS production. The treatment with omega-3 fatty acids DHA and EPA, but not omega-6 fatty acid arachidonic acid (AA), at concentrations that can be achieved through diet, reduced superoxide anion production in human polymorphonuclear leukocytes in vitro (Chen, Lawson, and Mehta 1994). Similarly, superoxide and H_2O_2 generation were decreased in stimulated neutrophils and monocytes from healthy volunteers after high doses of marine DHA and EPA supplementation (Miles and Calder 2012). Pretreatment with omega-3 but not omega-6 or omega-9 fatty acid also decreased NO production in lipopolysaccharide-treated RAW 264.7 macrophages (Ohata et al. 1997). In contrast, ROS production in neutrophils, monocytes, and peripheral blood mononuclear cells from veal calves fed fish oil rich in omega-3 fatty acids was not affected when stimulated with ß-1,3/1,6-glucan which is able to induce ROS production in these cells (Masmeijer et al. 2020). While fish oil administered orally at a moderate dose reduced lipid peroxidation in the heart and brain but not in the liver in a D-galactose-induced aging mouse model, DHA and AA increased lipid peroxidation in the liver but also decreased lipid peroxidation in the brain (Chen et al. 2017).

Algae extracts have also been demonstrated to reduce ROS. The antioxidant properties of the xanthophyll astaxanthin have been extensively reviewed elsewhere (Giannaccare et al. 2020). Fucoxanthin exhibited antioxidant activity against H_2O_2, DPPH, superoxide radicals, and hydroxyl radicals (Nomura et al. 1997; Murakami et al. 2000; Sachindra et al. 2007; Zheng et al. 2013; Zhang et al. 2014). It also reduced lipid peroxides in the plasma and liver of retinol deficiency in rats after oral administration (Ravi Kumar, Narayan, and Vallikannan 2008). Extracts from brown algae *Fucus vesiculosus* were effective in scavenging H_2O_2, DPPH, and superoxide radicals in cell-free assays as well as NO and superoxide radicals in RAW 264.7 macrophages. They also reduced oxidants in the plasma and erythrocytes after 4 weeks of oral administration in rats (Zaragozá et al. 2008). Fucoidan from *Fucus vesiculosus* administered orally abrogated the increase in lipid peroxidation in a rat model of acetaminophen-induced liver injury (Hong et al. 2012). Similarly, the oral administration of lycopene extracted from green algae *Chlorella marina* abrogated the increase in lipid peroxides and restored the levels of GSH in rats fed a high-cholesterol diet (Renju, Kurup, and Saritha Kumari 2014). Algal cell extract from *Haematococcus pluvialis* rich in astaxanthin administered orally abrogated the increase in lipid peroxidation in the stomach, liver, and serum of ethanol-induced gastric ulcers in rats and a saponified astaxanthin extract demonstrated the highest free radical scavenging activity, reducing power, and lipoxygenase inhibition activity in cell-free assays (Kamath et al. 2008).

Our systematic search revealed twelve studies investigating the antioxidant properties of marine resources in the context of retinal diseases. Of these, ten studies assessed the generation of ROS or whether retinal cells were protected when exposed to oxidants (see Table 3). In an observational study in preterm infants suffering from ROP, lipid emulsion including fish oil, given from the first day of life for a median of seven days, decreased the total oxidant status and oxidative stress index with no adverse effects (Unal et al. 2018). However, in the DHAX trial, the supplementation with DHA from microalgae *Crypthecodinium cohnii* did not affect the plasma antioxidant activity after 4 years of treatment in patients with X-linked retinitis pigmentosa (XLRP) (Hughbanks-Wheaton et al. 2014). High-molecular-weight fucoidans extracted from five different brown algae protected uveal melanoma cells (OMM-1) against H_2O_2, while in ARPE-19, only fucoidan from *Saccharina latissima* abrogated tert-butylhydroperoxid-induced cell death (Dörschmann, Saskia Bittkau, et al. 2019). An ethanol extract from brown alga *Eisenia bicyclis* decreased H_2O_2, superoxide, and hydroxyl radical levels in retinal ganglion cells (RGC-5) exposed to L-buthionine-(S,R)-sulfoximine plus glutamate. Furthermore, it reduced MDA levels on rat brain homogenates exposed to sodium nitroprusside (Kim et al. 2012).

Decreased antioxidant defense in retinal diseases

The retina and specifically the RPE have developed several protective mechanisms to adapt to the highly oxygenated environment (Cai et al. 2000; Klettner 2012). Nuclear factor erythroid-2 related factor 2 (Nrf2) is a "master regulator" of oxidative defense orchestration (Hybertson et al. 2011). In addition, SOD is a major physiologic radical scavenger in the eye with SOD1 being most abundant in the retina (Rao et al. 1985; Handa 2012). Other important antioxidant protectors are catalase and the GSH system, with GSH, GPX and glutathione transferase (Hayes and Strange 1995; Masella et al. 2005).

The oxidative defense capability is reduced in AMD, including a decreased activation of Nrf2 in RPE cells, a decrease of SOD and catalase activity, and risk polymorphisms concerning the GSH pathway (Aiello et al. 1995; Kwak et al. 2000; Saint-Geniez et al. 2008, 2009; Byeon et al. 2010). In DR, the oxidative response mechanisms is impeded, as the transcriptional activity of Nrf2 is impaired (Kowluru and Mishra 2017). Furthermore, antioxidant capacity and SOD levels are reduced in patients with DR (for review see López-Contreras et al. 2020). For ROP, defective GSH recycling has been described (Miller et al. 2013). In addition, the antioxidant defense systems are not fully developed in the immature retina, leaving the retina especially susceptible to oxidative injury (J. C. Rivera et al. 2017). While the oxidative stress response is elevated in glaucoma patients, the expression of SOD1 is decreased (Tezel 2006; Canizales et al. 2016). In a meta-analysis assessing antioxidant makers in the serum and aqueous humor, patients with glaucoma presented reduced levels of total antioxidant status, while catalase, GPX or SOD levels were not different in the serum, but SOD and GSH levels were increased in the aqueous humor (Benoist d'Azy et al. 2016). Also, GSH and SOD are decreased in RP (Martínez-Fernández de la Cámara et al. 2013).

The oral administration of fish oil, DHA and AA increased SOD and catalase activity, but not GPX activity in the liver and SOD activity in the heart in a D-galactose-induced aging mouse model. Furthermore, fish oil and PUFA monomers increased SOD and decreased monoamine oxidase (also a ROS producer in the brain) levels in this model (Chen et al. 2017). Nanoparticles containing low-molecular-weight β-chitosan extracted from the gladius of squid *Sepioteuthis lessoniana* that were administered orally abrogated the decrease in liver GSH levels and the increases in plasma and liver SOD, catalase, GPX, and glutathione reductase in a model of hepatocellular carcinoma in rats (Subhapradha, Shanmugam, and Shanmugam 2017). Diet enriched with oligopeptides from the bivalve *Meretrix meretrix* increased the levels of SOD and GPX in a model of high-fat diet-induced nonalcoholic fatty liver disease in mice (Huang et al. 2018). Orally administered polysaccharides from the marine worm *Sipunculus nudus* enhanced SOD and GPX levels in Beagle dogs and mice exposed to γ-radiation (Cui et al. 2014; Li et al. 2016). Polysaccharides from sea cucumber increased catalase and SOD serum levels in mice fed a high-fat diet (Qi et al. 2017).

Extracts from brown algae *Fucus vesiculosus* increased SOD but not catalase activity in erythrocytes after 4 weeks of oral administration in rats (Zaragozá et al. 2008). Fucoidan from *Fucus vesiculosus* administered orally abrogated the decrease in GSH, SOD, and GPX levels in a rat model of acetaminophen-induced liver injury (Hong et al. 2012). The oral administration of fucoxanthin increased the levels of catalase and glutathione transferase in the plasma and liver of retinol deficiency in rats (Ravi Kumar, Narayan, and Vallikannan 2008). Oral lycopene extracted from green algae *Chlorella marina* increased the activity of catalase, SOD, GPX, and glutathione reductase in a rat model of hyperlipidemia (Renju, Kurup, and Saritha Kumari 2014). The oral administration of the green algae *Haematococcus pluvialis* cell extract rich in astaxanthin normalized the decrease in catalase, SOD, and GPX levels in the stomach, liver, and serum of ethanol-induced gastric ulcers in rats (Kamath et al. 2008).

Our systematic search revealed four studies demonstrating marine resources that increased antioxidant defense enzymes in the context of retinal diseases, including some of the studies aforementioned in the context of increased ROS generation (see Table 3). In addition, an ethanol extract from brown alga *Eisenia bicyclis* increased GSH levels in RGC-5 cells exposed to L-buthionine-(S,R)-sulfoximine plus glutamate (Kim et al. 2012). Overall, most studies were however rather preliminary due to limited sample sizes and hence were not further discussed here.

Taken together, a lot of studies in the context of antioxidant properties have been limited to in vitro effects so far, and thus, further studies are needed to determine the ROS-reducing properties of marine resources as part of dietary interventions.

Antiangiogenic and vasoprotective effects

Angiogenesis describes the new development of blood vessels originating from the existing vasculature. In the retina, two vascular systems are responsible for the blood supply, the retinal vessels, and the choroid. In ocular diseases, pathologic angiogenesis can either originate in retinal vessels, as seen in, e.g., DR, or originate from the choroid, invading the subretinal or even the retinal space, as seen in, e.g., exudative AMD (Campochiaro 2015). Severe retinal ischemia can initiate retinal neovascularization where vessels grow into the vitreous cavity and exert traction tension on the retina, causing detachment, as seen in severe cases of proliferative DR and ROP (Campochiaro 2015).

Angiogenesis comprises a complex molecular interaction, involving endothelial cells, extracellular cytokine gradients, and intracellular signal transduction cascades. The most important factor in angiogenesis is the cytokine VEGF, both in physiologic development and pathologic angiogenesis (Ferrara et al. 1996; Witmer 2003). In general, VEGF is a family of cytokines (VEGF-A to E, PlGF), but related to angiogenesis, the abbreviation VEGF is usually used synonymously for VEGF-A. VEGF-A binds to the VEGF receptors 1 and 2, with VEGFR-2 conveying most of the

angiogenic signal transduction (Otrock, Makarem, and Shamseddine 2007). The role of VEGFR-1 is less defined, and especially its soluble form is regarded as a decoy receptor. In addition, neuropilins act as co-receptors for VEGF (Otrock, Makarem, and Shamseddine 2007). VEGF-induced signaling in endothelial cells may induce proliferation as well as migration along a VEGF gradient (Siemerink et al. 2013).

VEGF expression can be induced by a variety of extracellular signals, the main being hypoxia, but also by oxidative stress, hyperthermia, or inflammatory stimuli (Ikeda et al. 2006; Klettner and Roider 2009; Klettner, Koinzer, et al. 2013; Faby et al. 2014). Several transcription factors are involved in the regulation of VEGF expression, with hypoxia-inducible factor 1 (HIF-1) being the main transcription factor in hypoxic upregulation (Tischer et al. 1991; Ozaki et al. 1999). Indeed, transcription factors and signaling pathways differ depending on the stimulus. VEGF expression is also regulated on the mRNA level (with a short half-life of the mRNA) and on the posttranslational level, controlling the polarized secretion of this cytokine (Klettner and Roider 2012).

In the retina, VEGF is vital for angiogenesis originating from both the retinal and the choroidal vessels (Aiello et al. 1995; Kwak et al. 2000). Importantly, VEGF is not only involved in developmental angiogenesis but also has important functions in the physiology of the retina, mediating protection for neurons in the retina, for the RPE, and playing a role in the maintenance of the choroid (Saint-Geniez et al. 2008, 2009; Byeon et al. 2010; Ford et al. 2011). VEGF is expressed by a variety of cells, with Müller and RPE cells being the main producers in the inner and outer retina, respectively (Klettner 2013). VEGF is constitutively secreted by RPE cells to protect retinal endothelial cells and to uphold the fenestration of the capillaries (Peters et al. 2007; Saint-Geniez et al. 2009). However, in addition to this physiological function, VEGF is an important factor in many retinal diseases which include an angiogenic pathology as well as pathology of vascular leakage (Miller et al. 2013).

VEGF is the main factor responsible for the development of exudative AMD and its inhibition is considered the main treatment modality (Schmidt-Erfurth et al. 2014). The vessels sprouting from the choroid are immature and prone to leakage and bleeding, causing edema, fibrosis, and tissue degeneration (Miller et al. 2013). Neovascularization is also found in DR and ROP, but in contrast to exudative AMD, it originates from the retinal vasculature (Penn et al. 2008). In addition, glaucoma can arise secondary to neovascularization (Barac et al. 2015). In all of these diseases, neovascularization occurs as a response of the retinal tissue to hypoxia or, in case of ROP, relative hypoxia, whereby the transcription factor HIF-1 plays a major role (Pe'er et al. 1995; Penn et al. 2008).

Furthermore, oxidative stress or inflammatory processes in the retina may induce VEGF in these diseases (Lu et al. 2019; Oltra et al. 2020). In RP, neovascularization and cystoid edemas have occasionally been reported and can be treated with anti-VEGF therapy (Yuzbasioglu et al. 2009; Sayadi et al. 2017; Miyata et al. 2018; Aloe et al. 2019; Montoya Delgado, Ríos Nequis, and Ramírez Estudillo 2019). However, neovascularization is not a common feature of RP. Moreover, a reduction of VEGF in ocular fluids of RP patients has also been reported (Salom et al. 2008).

In addition to neovascularization, VEGF increases the endothelial permeability of retinal (not choroidal) vessels, leading to (macular) edema. For DR, several factors involved in VEGF regulation have been identified, such as transforming growth factor beta, TNF, RAGE, or insulin-like growth factor 1 as inducing factors, and signal transducer and activator of transcription 3 (Penn et al. 2008).

A number of marine products with antiangiogenic properties with a focus on cancer therapy have been discussed elsewhere (Wang and Miao 2013; Kotoku, Arai, and Kobayashi 2016). These include marine animals (sponge, sea cucumber, bryozoan, tunicate, sea share, shark), marine microorganisms (fungi, bacteria, and actinomycetes), and marine phytoplanktons (mainly different algae).

The pro-angiogenic and antiangiogenic properties of fucoidan in endothelial and tumor cells have also been reviewed extensively elsewhere (Ustyuzhanina et al. 2014). They depend on the molecular weight of fucoidan with low-molecular-weight fractions (<15 kDa) acting more angiogenic and fucoidan with a higher molecular weight (>30 kDa) with a high degree of sulfation having more antiangiogenic effects (Bouvard et al. 2015; Marinval et al. 2016; Ohmes et al. 2020). In contrast, in a more recent study, low-molecular-weight fucoidan from brown alga *Sargassum hemiphyllum* suppressed VEGF-induced capillary tube-like structure formation in endothelial cells in vitro and oral administration inhibited tumor angiogenesis in vivo, resulting in decreased tumor growth. It also abrogated the increase in HIF-1 and VEGF protein levels as well as downstream PI3K/AKT/mTOR signaling after hypoxia in T24 cells as well as HIF-1 and VEGF protein expression in tumor tissue (Chen et al. 2015). In addition, fucoxanthin and its deacetylated product fucoxanthinol from brown algae *Undaria pinnatifida* as well as siphonaxanthin from green alga *Codium fragile* decreased microvessel length in an ex vivo rat aortic ring model (Sugawara et al. 2006; Ganesan et al. 2010).

In our systematic search, we identified 14 studies of marine products with antiangiogenic and vasoprotective activities (Table 4). In the Blue Mountains Eye Study, greater fish consumption (≥2 servings/week) was associated with an increased mean arteriolar diameter and decreased mean venular diameter as well as reduced arteriovenous nicking (Kaushik et al. 2008). Similarly, an increasing frequency of fish consumption was associated with wider retinal arteriolar and venular caliber in diabetics without retinopathy and a decreased likelihood of having severe DR (Chua et al. 2018). Fish avoidance was also associated with greater vascular risk and wider retinal venular caliber in children and adolescents with type 1 diabetes (Keel et al. 2016).

A screen of different fish species identified 27 species able to inhibit HIF-1 under $CoCl_2$ exposure in the mouse retinal cone cell line 661 W and ARPE-19 cells. These were

Table 5. Studies investigating cytoprotective effects of marine resources on retinal diseases.

Marine resource	Source, dose	Retinal disease/model	Species/cells	Cytoprotective effect	Reference
Fish oil	OmegaRx zone, 0.5 g/day DHA and 1 g/day EPA equals 400 mg EPA and 200 mg DHA/daily	Ischemic optic neuropathy	Rat	Decreased retinal ganglion cell loss (Fluoro-Gold retrograde labeling, number of TUNEL-positive cells)	Georgiou et al. (2017)
Fish oil	116 mg/day, 23.16% DHA, 5.83% DPA, 43.33 mg/day EPA	Progressive light-induced retinal degeneration	Rat	Decreased the number of apoptotic nuclei, photoreceptor cell apoptosis (Apoptag)	Ramchani-Ben Othman et al. (2015)
Fish oil	0.5% tuna oil, omega-6/omega-3 = 5.5 (1.58% DHA, 0.51% EPA, 8.72% linoleic acid)	DR	Rat	No change in the thickness of the outer nuclear, inner nuclear, or inner plexiform layers or total retinal thicknesses	Yee et al. (2010)
Fish oil	50% menhaden oil, 8% DHA, 9% EPA	DR	Mouse	Increased retinal ganglion cell complex thickness	Shevalye et al. (2015)
Algal oil	233 mg/kg/day, 33.34% DHA, 13.97% DPA	Visible-light-induced retinal damage	Rabbit	Increased antiapoptotic BCL2, decreased proapoptotic Bax, and active caspase-9	Deng et al. (2018)
Algae oil	*Schizochytrium* sp., 1.75 g/day DHA and 1 g/day EPA equals 350 mg/g DHA and 200 mg/g EPA	Anterior ischemic optic neuropathy	Rat	Reduced the number of TUNEL-positive cells in the retinal ganglion cell layer, cleaved caspase-3 protein level in the retina	Huang et al. (2020)
Macroalga, ethanol extract	*E. bicyclis*, 10 mg/kg in rats, 0.1–50 μg/mL in cells	Oxidative stress (BSO)	Rat, RGC-5 cells	In vivo: increased retinal layer thickness, in vitro: Increased cell viability (MTT, 50 μg/mL), decreased the number of propidium iodide-positive cells 10–50 μg/mL)	Kim et al. (2012)
Algae-derived Diphlorethohydroxycarmalol	*Ishige okamurae*, 25–50 μg-mL	Oxidative stress (H_2O_2)	ARPE-19 cells	Increased cell viability (MTT), abrogated the loss in mitochondrial membrane potential, reduced the BAX/BCL2 ratio, caspase-3 and −9 activation, poly (ADP-ribose) polymerase cleavage, cytochrome c release	Park et al. (2019)
Algae-derived polysaccharide compound	*Phaeophyceae*, 0.1–100 μg/mL	DR	ARPE-19 cells	Increased cell viability (MTT, LDH release, 0.1–100 μg/mL), decreased the number of annexin A5-positive cells (100 μg/mL)	Xie et al. (2012)
Fucoidan	*Fucus vesiculosus, Fucus distichus subsp. evanescens, Fucus serratus, Laminaria digitata, Saccharina latissima*, high-molecular-weight, 1–100 μg/mL	Oxidative stress (H_2O_2, TBHP)	OMM-1, ARPE-19 cells	All increased cell viability (MTT) in OMM-1 cells, only *Saccharina latissima* in ARPE-19 cells	Dörschmann, Saskia Bittkau, et al. (2019)
Fucoidan	*Fucus vesiculosus*, 100 μg/mL	DR	ARPE-19 cells	Increased cell viability (MTT, LDH release), decreased the number of annexin A5-positive cells	Li et al. (2015)
Fucoidan	*Fucus distichus* subsp. *evanescens*, containing 61.9% fucose, 26.2% uronic acids, 6.9% sulfate content, 1–250 μg/mL	Oxidative stress (TBHP)	ARPE-19 cells	No effect in cell viability (MTT)	Rohwer et al. (2019)
Fucan, sulfated	*Laminaria hyperborea*, high-molecular-weight, 1–100 μg/mL	Oxidative stress (H_2O_2, TBHP)	OMM-1, ARPE-19, primary porcine RPE cells	No change in cell viability in OMM-1 cells, further reduced in ARPE-19 cells (10–100 μg/mL)	Dörschmann, Kopplin, et al. (2019)

ARPE-19: retinal pigment epithelium cell line; BAD: BCL2 associated agonist of cell death; BAX: BCL2 associated X; BCL2: apoptosis regulator family; BSO: L-buthionine-(S,R)-sulfoximine; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; DR: diabetic retinopathy; EPA: eicosapentaenoic acid; LDH: lactate dehydrogenase; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; OMM-1: uveal melanoma cell line; RGC-5: retinal ganglion cell line 5; RPE: retinal pigment epithelium; TBHP: tert-butyl hydroperoxide; TUNEL: terminal deoxynucleotidyl transferase dUTP nick-end labeling.

subsequently assessed in a second screen under dimethyloxalylglycine stimulation identifying four species (*Selar crumenophthalmus*, *Spratelloides gracilis, Seriola dumerili, and Decapterus macarellus*) as well as two genealogically related species (*Decapterus muroadsi, Decapterus tabl*) with inhibitory effects. They also inhibited the expression of HIF target genes *VEGF,* erythropoietin, and phosphoinositide-dependent kinase 1 in ARPE-19 cells. *S. gracilis* and *D. tabl* were further investigated in a mouse model of oxygen-induced retinopathy, where the oral administration of *D. tabl* but not *S. gracilis* inhibited neovascularization. However, an effect on vaso-obliteration was not observed (Shoda et al. 2020). Orally administered fish oil inhibited the increase in VEGF and soluble VEGFR-1 protein, the endogenous negative regulator of VEGF, in the vitreous fluid, the retina, and in choroidal homogenates in a rat model of oxygen-induced retinopathy. In addition, fish oil increased the levels of insulin-like growth factor, a permissive factor for VEGF, reduced retinal vessel diameters and vascular abnormalities, and abrogated the increase in vascular density and tortuosity index (Beharry et al. 2018).

Furthermore, high-molecular-weight fucoidans from five different brown algae (*Fucus vesiculosus, Fucus distichus* subsp. *evanescens, Fucus serratus, Laminaria digitata, Saccharina latissima*, all over 100 kDa (Bittkau, Neupane, and Alban 2020)), displayed VEGF binding activities and reduced VEGF protein levels in ARPE-19. However, VEGF levels remained constant or were even increased in primary RPE cells that also exhibited higher overall VEGF production, with the exception of fucoidan from *Saccharina latissima*, which reduced VEGF secretion also in RPE (Dörschmann, Saskia Bittkau, et al. 2019). In another study, high-molecular-weight fucoidan from *Saccharina latissima* also decreased VEGF levels in ARPE-19 cells (Dörschmann et al. 2020). Similarly, fucoidans from *Laminaria hyperborean* and *Fucus vesiculosus* reduced VEGF secretion in ARPE-19 and RPE cells (Dithmer et al. 2014; Dörschmann, Kopplin, et al. 2019). The oral administration of low-molecular-weight fucoidan from *Laminaria japonica* abrogated retinal angiogenesis, the increase in retinal VEGF protein and gene expression as well as retinal HIF-1 protein in streptozotocin-induced diabetic mice (Yang et al. 2013).

Cytoprotective effects

A cell is considered dead when at least one of three criteria is met: (1) the plasma membrane is disintegrated, (2) the nucleus and cell organelles are dissolved, and/or (3) the residuals of the dead cells are engulfed by neighboring cells in vivo (Kroemer et al. 2009). During the last century, cell death was categorized into apoptosis and necrosis based on their morphological features that can be identified with electron microscopy. Apoptosis occurs when cells shrink, their nucleus and chromosomal DNA fragments, and the chromatin condenses (Kerr, Wyllie, and Currie 1972). In contrast, necrosis is characterized by the swelling of organelles and plasma membrane disruption resulting in the release of intracellular content (Clarke 1990). However, during the last two decades, a number of different regulated cell death mechanisms besides apoptosis have been identified, including autophagy-dependent cell death, ferroptosis, necroptosis, parthanatos, and pyroptosis (for review see Galluzzi et al. 2018).

In AMD, cell death is an important factor in disease progression and involves the degeneration of photoreceptors and RPE cells. While the death of the photoreceptor is generally considered to be apoptotic cell death, the pathways of cell death in RPE cells may include necrotic, apoptotic and pyroptotic cell death (Somasundaran et al. 2020). Major inducers of cell death are inflammatory stimuli (see Subsection anti-inflammatory effects) and oxidative stress (see Subsection antioxidant effects).

In DR, cell death occurs primarily in the retinal endothelial cells, pericytes, and Müller cells. While endothelial cells are described to die via apoptotic pathways, pericytes have been reported to die via apoptosis and necrosis, and Müller cells may undergo inflammation-induced pyroptosis (Feenstra, Chepchumba Yego, and Mohr 2013).

In glaucoma, cell death of the retinal ganglion cells is the main pathomechanism. Retinal ganglion cell death is mediated by neurotrophic factor deprivation, toxic pro-neurotrophins, excitotoxic damage, or oxidative stress (Almasieh et al. 2012). Inflammation also plays an important part in neurodegeneration in glaucoma (Russo et al. 2016). The major pathway of retinal ganglion cell death investigated so far is apoptosis (Nickells 1996).

In ROP models, hypoxia may induce cell death in the retina and especially in retinal ganglion cells and astrocytes (Chan-Ling and Stone 1992; Sivakumar et al. 2011; Kaur et al. 2013; Olivares-González et al. 2016).

In RP, the causative mutations in the rod photoreceptors (or RPE cells) induce their cell death, which has been described to occur via caspase-mediated, apoptotic cell death pathways. Depending on the originating mutation, also cell death via additional pathways, e.g., ferroptosis, has been suggested (Newton and Megaw 2020). Results on the impact of autophagy or endoplasmic reticulum stress on rod cell death are conflicting, with both degenerating and protecting effects being described (Chiang et al. 2015; Rodríguez-Muela et al. 2015; Yao et al. 2018; Comitato et al. 2019). The exact pathways of cell death are most likely related to the specific mutations causing RP (Newton and Megaw 2020). Oxidative stress-mediated cell death has been described as an important inducer of late cone degeneration in RP, irrespective of the mutation causing RP (Campochiaro 2015).

While algal extracts have mostly been investigated in the context of promoting cell death of tumor cells (for review see Juarez-Portilla et al. 2019; Wali et al. 2019; Khotimchenko et al. 2020; Méresse et al. 2020), a number of natural products from marine resources have also been described to exert cytoprotective effects, especially in the context of neurological diseases (for review see Choi and Choi 2015). Omega-3 fatty acids and their mediators such as resolvins have been demonstrated to reduce cell death in the heart, brain, and spinal cord after injury (for review see Bazan, Calandria, and Gordon 2013; Zirpoli et al. 2020). In

Table 6. Studies investigating metabolic changes of marine resources on retinal diseases.

Marine resource	Source, dose	Retinal disease/model	Species/cells	Metabolic effect	Reference
Fish	Diet, ≥2 servings/week	Retinopathy (vascular mortality)	Human	Increased fasting serum cholesterol level, no change in fasting serum glucose level	Kaushik et al. (2008)
Fish	Diet, 1–7 servings/week	DR	Human	No difference in high-density lipoprotein and triglycerides levels	Chua et al. (2018)
Fish oil	840 mg/day DHA and 270 mg/day EPA	AMD	Human	Increased serum and red blood cell DHA and EPA levels, plasma lipoprotein profiles improved, decreased lipoprotein cholesterol levels, increased HDL cholesterol levels	Souied et al. (2013)
Fish oil and EPA ethyl ester	3 g/day fish oil containing 24% DHA (0.7 g) and 44% EPA (1.3 g), EPA ethyl ester (99.4% purity)	RP (autosomal dominant inheritance, rhodopsin gene mutations Pro23His, Asp 190Asn, and Leu46Arg)	Human	Increased EPA and omega-3 DHA levels in red blood cells, no change in DPA	Hoffman, Uauy, and Birch (1995)
Fish oil	SMOFLipid emulsion, 20%, fish oil 30 g/dL	ROP	Human	No effect on triglyceride level	Beken et al. (2014)
Fish oil	Two Promega capsules/day containing 15.7% DHA (240 mg, ca. 27 mg/kg) and 39.4% EPA; 2 mL/day fish oil containing 9.1% DHA (150 mg, 14–42 mg/kg) and 18.5% EPA	Progressive rod-cone degeneration	Dog	Increased DHA and EPA levels, decreased omega-6 fatty acids in the plasma and liver, no change in the retinal outer segment	Aguirre et al. (1997)
Fish oil emulsion	SMOFlipid, containing omega-6- and omega–3 long-chain PUFA, 10 g/kg/day	Retinal function	Piglet	Increase in retinal omega-3 long-chain and very-long-chain PUFA levels, increased ratio of very-long-chain omega-3 to omega-6 PUFA	Turner et al. (2016)
Fish oil	1 mL, rich in EPA	RP (rhodopsin gene mutation Pro23His)	Rat	Increased DHA level and decreased omega-6 fatty acid level in the rod outer segment	Bicknell et al. (2002)
Fish oil	0.5% tuna oil, omega-6/omega-3 = 5.5 (1.58% DHA, 0.51% EPA, 8.72% linoleic acid)	DR	Rat	Increased retinal DHA and omega-3 DPA levels, decreased omega-6 DPA levels and omega-6/omega-3 fatty acid ratio	Yee et al. (2010)
Fish oil	5%, 1.2 g/kg in rats, 3.13 g/kg in mice	DR	Rat, mouse	Increased retinal omega-3 very long-chain PUFA levels, omega-3/omega-6 very long-chain PUFA ratio and precursor ratio, and blood glucose levels	Gorusupudi et al. (2019)
Fish oil	MaxEPA, 750 mg/day, containing 14% EPA and 10.6% DHA, equals 500 mg/day omega-3 fatty acid	DR	Rat	Increased EPA level in the serum, polymorphonuclear neutrophil granulocytes, and erythrocytes, no change in plasma glucose levels	Hammes et al. (1996)
Fish oil	116 mg/day, 23.16% DHA, 5.83% DPA, 43.33 mg/day EPA	Progressive light-induced retinal degeneration	Rat	Increased plasma and retinal EPA, DHA, omega-3 DPA, and linolenic acid levels, no change in omega-6 fatty acids in the retina and plasma	Ramchani-Ben Othman et al. (2015)
Fish oil	50% menhaden oil, 8% DHA, 9% EPA, 8% linoleic acid	DR	Mouse	No change in serum cholesterol and glucose levels, increased serum resolvin D1 levels	Shevalye et al. (2015)
Fish oil	YS-2636, 36% EPA and 26% DHA and 3.6 mg/g mixed tocopherol	DR	ARPE-19 cells	Increased EPA and omega-3 and -6 fatty acids composition in cells, decreased AA composition, no change in DHA composition	Dutot et al. (2011)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, 1,200 mg DHA/day	RP (of diverse origin)	Human	Increased red blood cell DHA and serum total cholesterol levels, decreased serum LDL cholesterol level, no change in serum HDL cholesterol level	Berson, Rosner, et al. (2004)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, two 500 mg capsules daily, equals to 400 mg DHA/day	XLRP	Human	Increased red blood cell DHA level, decreased omega-6 fatty acids	Hoffman et al. (2004)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, 30 mg/kg/day, 3–18 capsules/day providing 600–3,600 mg/day DHA	XLRP	Human	Increased plasma and red blood cell DHA, EPA, omega-3 DPA levels, decreased omega-6 fatty acid levels, no change in plasma total, HDL, or LDL cholesterol or triglyceride levels	Hughbanks-Wheaton et al. (2014)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, two 500 mg capsules daily, equals to 400 mg DHA/day	XLRP	Human	Increased plasma DHA level, decreases omega-6 fatty acids	Wheaton (2003)

AA: arachidonic acid; AMD: age-related macular degeneration; ARPE-19: retinal pigment epithelium cell line; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; DR: diabetic retinopathy; EPA: eicosapentaenoic acid; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PUFA: polyunsaturated fatty acid; ROP: retinopathy of prematurity; RP: retinitis pigmentosa; RPE: retinal pigment epithelium; XLRP: X-linked retinitis pigmentosa.

addition, a diet enriched with oligopeptides from the clam *Meretrix meretrix* reduced pro-apoptotic and increased anti-apoptotic protein expression in a mouse model of high-fat diet-induced nonalcoholic fatty liver disease (Huang et al. 2018). The xantophyll astaxanthin has also been demonstrated to reduce cell death by inhibiting apoptosis (Giannaccare et al. 2020).

Our systematic search revealed 13 studies assessing marine resources in the context of cell death in retinal diseases (Table 5). Fucoidan extracts from five different brown algae decreased H_2O_2-induced cell death in OMM-1 cells, while only fucoidan from *Saccharina latissima* reduced TBHP-induced cell death in ARPE-19 cells (Dörschmann, Saskia Bittkau, et al. 2019). Similarly, ethanol extracts from six brown and red algae were tested in the retinal ganglion cell line RGC-5 exposed to a model of oxidative stress induced by L-buthionine-(S,R)-sulfoximin plus glutamate. Among those, only the extract from *Eisenia bicyclis* demonstrated cytoprotective potential (Kim et al. 2012). Furthermore, the intragastric administration of algal oil abrogated the decrease in outer nuclear layer thickness in a model of visible-light-induced retinal damage in rabbits (Deng et al. 2018). In contrast, the thickness of the outer nuclear, inner nuclear, or inner plexiform layers or total retinal thicknesses were not changed in rats fed a diet rich in omega-3 fatty acids from fish oil starting at conception and subjected to streptozotocin as a model of diabetes (Yee et al. 2010).

With respect to specific cell death mechanisms, only single markers of apoptosis were investigated. The oral administration of fish oil reduced the number of TUNEL-positive cells and abrogated the loss of retinal ganglion cells, concomitant with a recovery of optic nerve evoked potentials, in a rat model of anterior ischemic optic neuropathy (Georgiou et al. 2017). In a more recent study of the same group, the authors reported the same effects using algal oil and additionally demonstrated that it abrogated the cleavage of caspase-3, another apoptosis marker (Huang et al. 2020).

Taken together, more studies are needed to investigate the cytoprotective effects of marine resources in the context of retinal diseases, including investigations of other modes of regulated cell death. In addition, it is recommended to use at least two independent markers or criteria to validate the specific cell death subroutine (Galluzzi et al. 2009; Galluzzi et al. 2018).

Metabolic changes

The retina is adapted to its extremely high energy demand (Country 2017). The neurons of the retina rely mainly on glycolysis for their ATP production, even in the presence of oxygen. This has been attributed to the utilization of glucose as a provider of metabolic intermediates for the generation of nucleotides or amino acids (Ng et al. 2015). Also, there is a tight relationship between the metabolism of the RPE and the photoreceptors. It has been hypothesized that RPE cells transport glucose to the photoreceptors. Photoreceptors produce lactate during glycolysis which in turn is taken up by the RPE and used as an energy source for oxidative phosphorylation (Léveillard, Philp, and Sennlaub 2019).

As an additional source for energy generation, fatty acids are important for oxidative phosphorylation in photoreceptors (Joyal et al. 2016; Fu et al. 2019) and photoreceptors provide lipids to the RPE, which are used for ß-oxidation (Fisher and Ferrington 2018). In addition to metabolic usage, fatty acids have important structural and protective functions in the retina. The retina is rich in lipids with a high content of polyunsaturated fatty acids. Especially the photoreceptors are rich in the omega-3-fatty acids DHA, EPA, and the omega-6-fatty acid AA (Eynard and Repossi 2019).

Glucose metabolism

It is not fully elucidated whether glucose metabolism plays a role in AMD development. High blood glucose has been proposed as a predictor of AMD progression (Ghaem Maralani et al. 2015). Also, it has been hypothesized that AMD is driven by an energy crisis in the RPE, in which the RPE grows more dependent on glycolysis, decreasing the supply for the photoreceptors and disturbing the connection between the RPE and photoreceptor metabolism (Fisher and Ferrington 2018).

In contrast, excess glucose is the primary pathomechanism in DR, leading to damage in the microvasculature of the retina (Škrha et al. 2016; Country 2017). The studies on the effect of hyperglycemia on the development of ROP, conversely, are conflicting, with some but not all studies regarding it as a risk factor (Mohamed et al. 2013; Mohsen et al. 2014; Nicolaeva, Sidorenko, and Iosifovna 2015). In experimental models, hyperglycemia has been shown to delay vascular development (Fu et al. 2019). Concerning glaucoma, little association has been observed with the glucose metabolism (Wiggs 2015). However, diabetes and fasting glucose levels have been associated with an increased risk of developing glaucoma (Zhao et al. 2015).

In RP, insufficient glucose supply has been suggested as a major causative factor for secondary cone degeneration, with different mechanisms being proposed (Wong and Kwok 2016; Campochiaro and Mir 2018; Wang et al. 2019). Rods secrete the so-called rod-derived cone viability factor which helps the cones to increase their glucose metabolism by facilitating an increased uptake of glucose in the cell. Therefore, it has been hypothesized that the secondary cone degeneration is connected to the reduction of glucose supply because of the death of cones (Aït-Ali et al. 2015). The glucose supply of photoreceptors is provided by the RPE. It has been suggested that due to the loss of photoreceptor outer segments, the glucose transport of the RPE is diminished via an AKT mediating signaling pathway (Wang et al. 2019). In addition, a synaptic remodeling of cone synapses after rod degeneration, leading to an increased oxygen supply, has also been proposed (Wong and Kwok 2016).

A number of bioactive compounds from marine organisms have been described to inhibit glucose metabolism enzymes (for review, see Lauritano and Ianora 2016). In particular, protein hydrolysates from different fish species

promoted insulin and incretin hormone secretion and inhibited dipeptidylpeptidase-4 enzyme activity in cell culture and animal models. However, plasma insulin remained unaffected in human studies with fish hydrolysates (Sharkey et al. 2020). Algal polyphenols blocked glucose metabolism enzymes and reduced fasting blood glucose levels in rodent models of diabetes and obesity. In randomized controlled trials, algal polyphenols had only small effects on decreasing fasting blood glucose, while results regarding fasting insulin were inconsistent (Murray et al. 2018). The oral administration of fucoidan from *Fucus vesiculosus* decreased fasting blood glucose levels in diabetic mice (Shan et al. 2016).

In our systematic search, we identified four studies investigating the effect of the administration of marine resources on glucose metabolism in the context of retinal diseases (Table 6). In the Blue Mountains Eye Study including data from more than 2,600 participants, fish consumption (as assessed by food questionnaire) was not associated with changes in fasting serum glucose levels (Kaushik et al. 2008), while having effects on the retinal microvasculature (see Subsection antiangiogenic and vasoprotective effects). In a randomized double-blind interventional trial assessing the safety of DHA supplementation from microalgae *Crypthecodinium cohnii* in patients with XLRP (DHAX trial), fasting serum glucose levels were only slightly reduced after 4 years of treatment (Hughbanks-Wheaton et al. 2014). A diet rich in omega-3 fatty acids abrogated the increase in serum glucose levels in hyperglycemic Nile rats and diabetic Akita mice, a genetic model of type 1 diabetes (Gorusupudi et al. 2019). The supplementation of the diet with menhaden fish oil or injections of the omega-3 fatty acid metabolite resolvin D1 did not improve elevated blood glucose levels or glucose utilization in a mouse model of DR induced by streptozotocin (Shevalye et al. 2015).

Fatty acid metabolism

The influence of fatty acids in AMD is complex. High serum levels of high density lipoprotein (HDL) have been associated with a higher risk of AMD development, while triglycerides may be associated with a decreased risk (Fu et al. 2019). Higher trans-unsaturated fat consumption has been associated with an increased prevalence of late AMD (Chong et al. 2009). Accordingly, the omega-3 fatty acids DHA and EPA are considered to reduce the risk of AMD, while omega-6 fatty acid, such as linoleic acids, are associated with a higher risk of developing AMD (SanGiovanni et al. 2007; Merle et al. 2013; van Leeuwen et al. 2018; Skowronska-Krawczyk and Chao 2019). In addition, the eyes of AMD patients contain lower levels of very long-chain PUFA (Elmasry et al. 2019). Omega-3 fatty acids also reduce choroidal neovascularization in AMD and protect photoreceptors against oxidative stress (Elmasry et al. 2019). Conversely, accumulated cholesterol in cells, such as RPE or endothelial cells, may be involved in the pathogenesis of AMD (Elmasry et al. 2019).

In diabetes, both systemic and retinal-specific lipids are affected and may contribute to the progression of DR (Hammer and Busik 2017). Studies indicate that elevated circulating levels of low-density lipoprotein (LDL) cholesterol are a significant risk factor for diabetic macular edema, and dyslipidemia is associated with a faster progression of DR as well as with more retinal abnormalities (Fu et al. 2019). Deficiency of omega-3 and omega-6 fatty acids has been suggested to result in a dysfunction of the blood-retinal barrier, resulting in the leakage of macromolecules and cholesterol from the blood vessels into the retina (Hammer and Busik 2017; Eynard and Repossi 2019).

The severity of ROP has been associated with high amounts of circulating triglycerides (Fu et al. 2019). Also, retinas of preterm birth infants contain reduced levels of DHA (Fu et al. 2019). while, conversely, the dietary uptake of omega-3 fatty acid can reduce retinal angiogenesis (Elmasry et al. 2019). In contrast, little association has been observed for glaucoma (Wiggs 2015).

Dose-dependent increases in serum EPA, DHA, and further omega-3 fatty acids as well as adiponectin were observed after three and twelve months of supplementation with fish oil in healthy volunteers in randomized controlled trials (Handeland et al. 2018; Song et al. 2018; Ostermann et al. 2019). A systematic review identified 38 clinical intervention studies that overall report a 26% decrease in circulating triglycerides when $\geq$4 g/day of omega-3 fatty acids were consumed from either marine or EPA/DHA-enriched food sources (Leslie et al. 2015). Similarly, a meta-analysis including eleven randomized controlled trials demonstrated that DHA from algal oil decreased serum triglycerides and increased HDL and LDL cholesterol in persons without coronary heart disease (Bernstein et al. 2012).

Furthermore, algal polyphenols have been reported to reduce serum triglyceride, LDL and total cholesterol levels in randomized clinical trials and animal models of hyperglycemia (for review, see Murray et al. 2018). The oral administration of nanoparticles containing low-molecular-weight β-chitosan extracted from the gladius of squid *Sepioteuthis lessoniana* abrogated the decrease in HDL and increase in LDL levels in a rat model of hepatocellular carcinoma (Subhapradha, Shanmugam, and Shanmugam 2017).

We identified 17 studies on the effect of marine resources on fatty acid metabolism in the context of retinal diseases in our systematic search (Table 6). In the Blue Mountains Eye Study, greater fish consumption ($\geq$2/week) was associated with an increase in fasting serum cholesterol levels (Kaushik et al. 2008). However, in a smaller cohort including 357 participants (Singapore Diabetes Management Project), greater fish consumption did not affect triglyceride levels but reduced the total to HDL cholesterol ratio, while reducing the severity of DR (Chua et al. 2018). In the Nutritional AMD Treatment 2 study, a randomized, placebo-controlled, double-blind trial, DHA and EPA supplementation increased DHA and EPA levels in the serum and red blood cells. It also increased HDL levels, while reducing LDL levels, leading to an overall absence of change in total cholesterol levels, while triglycerides also remained unchanged (Souied et al. 2013). In the DHAX trial, supplementation with DHA from microalgae *Crypthecodinium cohnii* increased the level of DHA in the plasma and red blood cells, while total, LDL,

and HDL cholesterol as well as triglyceride levels were not significantly altered after four years of treatment (Hughbanks-Wheaton et al. 2014).

Similarly, the daily supplementation with algal-derived DHA for four years increased red blood cell DHA and serum total cholesterol, while decreasing serum LDL cholesterol in a randomized, controlled trial in patients with RP of diverse origin (Berson, Rosner, et al. 2004). In patients with XLRP, DHA from algae increased plasma DHA level, and decreased omega-6 fatty acids (Wheaton 2003). However, no changes in plasma total, HDL, and LDL cholesterol as well as triglyceride levels were observed in the follow-up study (Hughbanks-Wheaton et al. 2014).

Furthermore, very low birth weight infants that received fish-oil lipid emulsions did not demonstrate differences in serum triglyceride levels, while the rate of ROP was reduced compared to soybean oil-based lipid emulsions (Beken et al. 2014). Neonatal piglets fed fish-oil lipid emulsion rich in omega-3 long-chain fatty acids had greater levels of omega-3 long and very long-chain fatty acids in the retina compared to plant-based lipid emulsion fed animals (Turner et al. 2016).

A diet rich in omega-3 fatty acids improved the ratio of omega-3/omega-6 fatty acids in the retina and the serum of hyperglycemic Nile rats and diabetic Akita mice (Gorusupudi et al. 2019). Serum triglycerides and free fatty acids were not changed in a mouse model of DR induced by streptozotocin when the diet was supplemented with menhaden fish oil or mice were injected with resolvin D1 (Shevalye et al. 2015). The levels of DHA in the rod outer segment were restored in P23H transgenic rats (a model of human RP where the rhodopsin gene is mutated with proline at position 23 replaced by histidine) on an linoleic acid-deficient diet when fed fish oil, while serum cholesterol levels remained unchanged (Bicknell et al. 2002). The supplementation of fish oil increased plasma and retinal EPA as well as retinal DHA levels, while most omega-6 fatty acids remained unchanged, except retinal docosatrienoic acid, in a rat model of progressive light-induced retinal degeneration (Ramchani-Ben Othman et al. 2015).

Overall, fish oil and omega-3 fatty acids have been demonstrated to change fatty acid metabolism in the retina. However, further research is needed to elucidate the downstream mechanisms leading to the beneficial effects in the context of retinal diseases.

Retinal function

The retina uses a biochemical reaction to detect light referred to as phototransduction. As a detector for light, rhodopsin is embedded in the membranes of the outer segments of the photoreceptors. Rhodopsin is a protein (opsin) that is connected with 11-cis-retinal. Light changes the conformation of 11-cis-retinal to all trans-retinal, which induces a conformational shift in the opsin protein, which, in turn, activates a signal transduction pathway leading to the closure of ion-channels in the photoreceptors and a shutting down of the inward cation current (dark current) (Ridge and Palczewski 2007; Arshavsky and Burns 2012). Cone opsins differ in their protein but also utilize 11-cis-retinal and employ similar downstream mechanisms (Mustafi, Engel, and Palczewski 2009). To be recognized by the brain, the information about light detection is transferred via bipolar cells to ganglion cells which connect to the brain via the optic nerve, with additional neurons, horizontal and amacrine cells, modifying the information for better temporal and spatial resolution (Sung and Chuang 2010).

Different areas of the retinal function are affected during disease. In AMD, photoreceptors degenerate secondarily because of the alteration of the RPE (Bhutto and Lutty 2012). In DR, recent studies have suggested that photoreceptors and the phototransduction pathway may be involved in the development of early DR (Kern and Berkowitz 2015; Liu et al. 2019). In ROP, the age of onset coincides with the elongation of the rod outer segments and the increase in rhodopsin content (Fulton et al. 2009). Furthermore, the residual visual loss has been described to be linked to the loss of photoreceptors (J. C. Rivera et al. 2017). The photoreceptors and the impairment of the visual functions are also vital for disease development and progression of RP. While many mutations have been described for RP, most affect rhodopsin, phototransduction, or the recycling of the rhodopsin (Verbakel et al. 2018). Conversely, ganglion cells are mainly affected in glaucoma (Casson et al. 2012).

A valuable tool to assess retinal function both in research and clinical evaluation is the electroretinogram (ERG). The ERG measures the summed response of the cells of the retina responding to change in illumination (Frishman and Wang 2011). The major waves recorded are the (negative) a-wave, which originates from the photoreceptors, and the (positive) b-wave which is generated by the bipolar cells (Frishman and Wang 2011). The a-wave reflects mainly the answer of the rod photoreceptors, as these comprise the majority of photoreceptors, but special forms of ERG can be performed to target the cone response. Correspondingly, the dark-adapted ERG targets the rod response, while the light-adapted ERG assesses the cone.

A special form of ERG that targets the cone-driven response only and is clinically used to monitor cone function in degenerative disease is the fast flicker ERG, as rods do not respond to such a stimulation (Frishman and Wang 2011). To target foveal cones in particular, multifocal ERG can be conducted. The activity of neurons of the inner retina, such as amacrine cells, is evaluated using very bright flashes that induce small wavelets superimposed on the b-wave (oscillatory potentials) (Wachtmeister 1998). To investigate the function of the ganglion cells, a pattern ERG can be conducted, which uses a structured pattern of white and black elements as a stimulus (Pescosolido et al. 2015).

When using ERG in the assessment of age-related diseases such as AMD, it has to be considered that aged individuals generally display a decrease in amplitude and latency as measured in full field ERG and in cone-mediated multifocal ERG that is unrelated to specific diseases. Moreover, studies of ERG in AMD show divergent results. Consequently, ERG is not standard in the assessment of

Table 7. Studies investigating retinal function of marine resources on retinal diseases.

Marine resource	Source, dose	Retinal disease/model	Species/cells	Effect on retinal function	Reference
Fish oil and EPA ethyl ester	3 g/day fish oil containing 24% DHA (0.7 g) and 44% EPA (1.3 g), EPA ethyl ester (99.4% purity)	RP (autosomal dominant inheritance, rhodopsin gene mutations Pro23His, Asp 190Asn, and Leu46Arg)	Human	No change in retinal ERG response (rod and cone amplitude, maximal amplitude)	Hoffman, Uauy, and Birch (1995)
Fish oil	Two Promega capsules/day containing 15.7% DHA (240 mg, ca. 27 mg/kg) and 39.4% EPA; 2 mL/day fish oil containing 9.1% DHA (150 mg, 14–42 mg/kg) and 18.5% EPA	Progressive rod-cone degeneration	Dog	No change in ERG response	Aguirre et al. (1997)
Fish oil emulsion	SMOFlipid, containing omega-6- and omega–3 long-chain PUFA, 10 g/kg/day	Retinal function	Piglet	Increased photopic a-wave and b-wave ERG amplitude, cone-driven a- and b-wave ERG amplitudes, and photopic flicker ERG amplitudes	Turner et al. (2016)
Fish oil	1 mL, rich in EPA	RP (rhodopsin gene mutation Pro23His)	Rat	No change in retinal rhodopsin levels	Bicknell et al. (2002)
Fish oil	OmegaRx zone, 0.5 g/day DHA and 1 g/day EPA equals 400 mg EPA and 200 mg DHA/daily	Ischemic optic neuropathy	Rat	Increased amplitude of the P1-N2 waves of the optic nerve	Georgiou et al. (2017)
Fish oil	MaxEPA, 750 mg/day, containing 14% EPA and 10.6% DHA, equals 500 mg/day omega-3 fatty acid	DR	Rat	Increased the number of acellular capillaries, no change in retinal autofluorescence	Hammes et al. (1996)
Fish oil	0.5% tuna oil, omega-6/omega-3 = 5.5 (1.58% DHA, 0.51% EPA, 8.72% linoleic acid)	DR	Rat	Increased rod amplitudes, oscillatory potential amplitude and implicit times, no change in cone amplitudes	Yee et al. (2010)
Fish oil	116 mg/day, 23.16% DHA, 5.83% DPA, 43.33 mg/day EPA	Progressive light-induced retinal degeneration	Rat	Increased the b-wave amplitude of the ERG response, no change in rhodopsin content	Ramchani-Ben Othman et al. (2015)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, 1,200 mg DHA/day	RP (of diverse origin)	Human	Reduced the decline in the 30-Hz ERG amplitude	Berson, Rosner, et al. (2004)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, 1,200 mg DHA/day	RP (of diverse origin)	Human	Reduced the decline in the 30-Hz ERG amplitude and visual field sensitivity	Berson, Bernard, et al. (2004)
DHA	DHASCO from microalgae *Crypthecodinium cohnii*, two 500 mg capsules daily, equals to 400 mg DHA/day	XLRP	Human	Increased cone and rod ERG amplitude	Hoffman et al. (2004)
DHA	DHASCO from microalgae *Crypthecodinium cohnii,* 30 mg/kg/day, 3–18 capsules/day providing 600–3,600 mg/day DHA	XLRP	Human	No change in the light-adapted cone, rod, or maximal ERG amplitudes, or cone implicit time	Hoffman et al. (2014)
DHA	DHASCO from microalgae *Crypthecodinium cohnii,* 30 mg/kg/day, 3–18 capsules/day providing 600–3,600 mg/day DHA	XLRP	Human	Reduced the decline of visual field sensitivity, decreased the rate in progression of final dark-adapted thresholds (not statistically significant)	Hoffman et al. (2015)
Algal oil	233 mg/kg/day, 33.34% DHA, 13.97% DPA	Visible-light-induced retinal damage	Rabbit	Increased the b-wave amplitudes of scotopic, photopic and maximal response ERG	Deng et al. (2018)
Fucoxanthin	*Laminaria japonica,* 100 μg/kg/day	Visible light-induced retinal damage	Rabbit	Increased dark-adapted rod-ERG b-wave, light-adapted cone-ERG b-wave, Max-ERG b-wave, and oscillatory potential amplitudes	Liu et al. (2016)
9-cis-β-carotene	*Dunaliella bardawil* extract, 125 μg/mL containing 84.3% 9-cis-β-carotene	Vision loss	Mouse retinal explants	Increased M-opsin protein levels in the photoreceptor outer segment	Ozaki et al. (2014)
9-cis-β-carotene	300 mg *Dunaliella bardawil* powder containing 20 mg beta-carotene	RP (of diverse origin)	Human	Increased dark-adapted ERG b-wave amplitude, dark-adapted and light-adapted ERG response, no change in visual field area and visual acuity	Rotenstreich et al. (2013)
9-cis-β-carotene	1 μM synthetic 9-cis-β-carotene	Retinal dystrophy	Mouse eye cups	Increased S-cone and M-cone opsins	Sher et al. (2018)

DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; DR: diabetic retinopathy; EPA: eicosapentaenoic acid; ERG: electroretinogram; PUFA: polyunsaturated fatty acid; RP: retinitis pigmentosa; XLRP: X-linked retinitis pigmentosa.

retinal dysfunction in AMD (Gerth 2009). However, prolonged ERG latency in the a-wave in light-adapted flicker ERG may be an indicator of the progression of AMD (Forshaw et al. 2020).

In DR, ERG can be used to detect an early alteration in the retina, not yet visible in the ophthalmologic examination. In diabetic patients with preclinical retinopathy, oscillatory potentials are frequently absent. Also, in preclinical patients, a reduced answer to flicker stimulation, multifocal ERG and pattern ERG can be detected (Pescosolido et al. 2015).

Conversely, when used in (very young) ROP patients, it has to be considered that the ERG response undergoes maturation during postnatal development, with a fast maturation in the first four months, reaching adult values between 3 and 5 years. The ERG response can be detected in preterm infants, provided that the light stimulus is strong enough (Parness-Yossifon and Mets 2008). In children with a history of mild ROP, the (cone) response in multifocal ERG is attenuated (Fulton et al. 2005), while generally, ERG investigations indicate that rods are more affected in ROP than cones (Fulton, Hansen, and Moskowitz 2008).

In glaucoma, the most frequently used electrophysiological test is pattern ERG, as the most affected cell type is the ganglion cell. The pattern ERG response reflects the loss of function of retinal ganglion cells and the decrease in thickness of the retinal nerve fiber layer. The mean amplitude of the pattern ERG values decreases with the severity of the disease, and can, therefore, be used to monitor glaucoma progression (Senger et al. 2020).

In RP, ERG testing is a valuable diagnostic tool. In the early stage of the disease, rods are most affected which is mirrored by a reduced or absent response in a dark-adapted ERG. Abnormalities in cone function, which occur later in the disease, typically manifest in delayed and reduced amplitudes in the photopic (light-adapted) response and in flicker stimulation. Also, oscillatory potentials are reduced in RP (Whatham et al. 2014).

In our systematic search, we identified 15 studies investigating the effect of the administration of marine resources on retinal function (Table 7). Rats fed a diet rich in omega-3 fatty acids from fish oil starting at conception and subjected to streptozotocin as a model of diabetes were protected from the reduction in rod a- and b-wave amplitudes at 20 weeks of age. They also demonstrated an increased amplitude and frequency of oscillatory potentials, reflecting the activity of inner retinal neurons, while the diet had no effect on cone function (Yee et al. 2010). The oral administration of fish oil recovered the amplitude of the P1-N2 wave of flash visual-evoked potentials in a rat model of anterior ischemic optic neuropathy (Georgiou et al. 2017). Neonatal piglets fed fish-oil lipid emulsion rich in omega-3 fatty acids displayed greater photoreceptor a- and b-wave amplitudes under dark and light adaptation as well as increased peak-to-peak amplitudes of photopic flicker compared to plant-based lipid emulsion fed animals (Turner et al. 2016). A diet deficient in linoleic acid with or without supplementation of fish oil did not affect retinal rhodopsin or DNA levels in P23H transgenic rats, a model of RP, while the levels of DHA in the rod outer segment were restored in the fish oil-treated group (Bicknell et al. 2002). The supplementation of fish oil in combination with antioxidants attenuated the decrease in the b-wave amplitude in a rat model of progressive light-induced retinal degeneration, while a-wave sensitivity was only slightly improved (Ramchani-Ben Othman et al. 2015).

There were also a number of reports from algal-derived marine resources. In a randomized, controlled trial in patients with RP of diverse origin, the daily supplementation with DHA from microalgae *Crypthecodinium cohnii* for four years slowed the decline in the 30-Hz ERG amplitude and visual field sensitivity (Berson, Bernard, et al. 2004; Berson, Rosner, et al. 2004). Similarly, the long-term intake of algal-derived DHA did not attenuate the loss of cone or rod ERG function associated with XLRP in patients (Hoffman et al. 2014), whereas the rate of progression in final dark-adapted thresholds and visual field sensitivity were reduced (Hoffman et al. 2015). The administration of algal oil (33.34% DHA) or fucoxanthin isolated from *Laminaria japonica* attenuated the reduction in b-wave amplitude under dark and light adaptation as well as the maximal response b-waves induced by visible light in rabbits (Liu et al. 2016; Deng et al. 2018).

Furthermore, the oral supplementation with 9-cis-carotene from green alga *Dunaliella bardawil* improved the dark-adapted electroretinographic b-wave amplitude as well as dark-adapted and light-adapted ERG response in patients with RP of diverse origin, while visual field area and visual acuity remained unchanged (Rotenstreich et al. 2013). In *Rpe65*$^{-/-}$ mouse retina explants, an experimental model to study vision loss, the administration of *Dunaliella bardawil* extract also abrogated the decrease in M-opsin protein levels in the photoreceptor outer segment (Ozaki et al. 2014).

While there is substantial evidence on the beneficial effects of omega-3 fatty acids on retinal function and the first evidence for 9-cis-carotene in experimental models, other marine resources should be investigated in the future.

Implementation of marine resources for human diet and their beneficial health effects

Diet contributes to many non-communicable diseases that are a major threat to health systems worldwide. Thus, strategies to influence diet and nutrition are of increasing interest to prevent or modify these diseases.

As outlined above, marine resources have a tremendous potential in the prevention or slowing of retinal diseases. Thus, the use of special food or food supplements from marine resources may offer an important contribution to a healthy lifestyle and nutrition with a lower risk for retinal diseases. However, new products based on marine resources have to be taken through several regulatory steps, before they can be launched on the market. We first outline these regulatory steps that are necessary to approve food or food products, and then, discuss the specific approved health

claims as well as the potential of new foods from marine resources, their safety, and oral bioavailability.

Regulatory steps

The use of marine resources as food is generally possible without prior authorization in compliance with the requirements of food law regulations (e.g., good manufacturing practice, labeling) of the respective countries. In Europe, novel foods are exceptions. Novel foods are defined as foods that were not consumed in significant quantities before May 1997, and hence, approval by the European Food Safety Authority (EFSA) has to be obtained before they can be placed on the European market (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Turck, Bresson, Burlingame, Dean, Fairweather-Tait, Panel and Heinonen 2016b). This includes new foods as well as new substances or food from new sources. Traditional foods are important distinction, which form a subset of novel foods and have already been consumed outside Europe. They do not need approval as novel foods, but evidence has to be provided demonstrating their safe use in at least one country outside the EU for a period of at least 25 years (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Turck, Bresson, Burlingame, Dean, Fairweather-Tait, Heinonen, Hirsch-Ernst, et al. 2016a).

As seaweed or macroalgae are not part of a traditional diet in Europe, they first need to be assessed according to the Novel Food regulation and classified as either novel food or traditional food before they enter the market. Currently, 25 different food products from seaweed are listed in the Novel Food catalogue of the European Commission (see https://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm), of which four are confirmed as novel food while 21 have already been consumed before May 1997 and are, therefore, classified as traditional food (Supporting Information Table S6). Novel foods include *Sphaerotrichia divaricate, Ecklonia cava* phlorotannins as well as fucoidan extracts from *Fucus vesiculosus* and *Undaria pinnatifida*.

In the United States, the Food & Drug Administration (FDA) regulates the approval of new marine food products. Any food substance requires a premarket approval by the FDA before it can be marketed unless the substance is already generally recognized as safe (GRAS). Food is recognized as safe after scientific evaluation or if the food product was commonly used before 1958 (FDA; 21CFR170.30). Seaweed is GRAS but is restricted for the use as a food additive (FDA, 21CFR172.365). Seaweed can only be used in a dried form and grounded or chopped as spices, seasonings, and flavorings. Otherwise, they will require a food additive petition. Supporting Information Table S7 lists the algae that can be added to human food in the United States. Fucoidan from *Undaria pinnatifida* (GRAS No. 565) and *Fucus vesiculosus* (GRAS no. 661) were confirmed as GRAS by the FDA in 2015 and 2017, respectively, and thus, do not need a premarket approval (Food and Drug Administration 2016).

Besides being part of the diet (as regular food), marine resources may be further processed and used as food/dietary supplements or additives. Food additives are added to food to affect certain functional properties such as color, odor, taste, structure, or shelf life. In Europe, food supplements also need to be approved by the EFSA. Approved additives receive an E number and are listed in the Regulation (EC) No. 1333/2008 (The European Parliament and the Council of the European Union 2010). In the United States, under the Federal Food, Drug, and Cosmetic Act, food additives similarly need to have a premarket approval by the FDA, unless the substance is already recognized as safe.

Conversely, food/dietary supplements are intended to complement a regular diet of a healthy person. These are concentrated nutrients, such as vitamins, minerals or amino acids, and are usually sold as pills or capsules. They have nutritional or physiological effects but must be clearly distinguished from a pharmaceutical effect that entails to reduce, prevent or cure a disease. Food supplements are legally defined as food and are, therefore, subjected to the food law regulations of the respective countries. For example, in Germany, they need to be registered with the federal authority and if under compliance with the requirements of the food law, food supplements can be placed on the German market. According to the FDA, dietary supplements are also considered as food, but must be declared as such and are not intended for use as conventional food (Senate and House of Representatives of the United States of America 1994). They are regulated under the Dietary Supplement Health and Education Act. Dietary ingredients, which were not on the market in the United States before October 1994, are considered as "new dietary ingredients" and need a premarket notification with the FDA (Senate and House of Representatives of the United States of America 1994).

There are other terms that are frequently used in the food industry, such as "functional food" or "nutraceuticals" that are not regulated by law but are under the control and supervision of the appropriate food authorities. Regardless of whether marine resources enter the market as conventional food, food component or dietary supplement ingredient, they should not be adulterated or misleading. Each food business is responsible for the safety and correct labeling of its marketed products.

Health claims to promote the beneficial effects of foods

In addition to the legal requirements of food labeling such as the compositional or nutritional information, food companies also use claims to promote certain health effects of food ingredients, particularly in food supplements or functional foods, and thus, influence the consumer behavior (Díaz, Fernández-Ruiz, and Cámara 2020). Health claims make a connection between a food substance and the risk of developing a disease or maintaining a certain health condition.

There is a clear legal framework for the use of claims in Europe (The European Parliament and the Council of the

European Union 2007). They need to be authorized by the EFSA to protect consumers from inaccurate and non-evidence-based claims. There are two types of claims: (1) Nutrition claims advertise the food regarding the nutritional information such as reduced fat, a source of magnesium or high in insoluble fiber. (2) Health claims refer to the contribution of the food to the maintenance of health ("function health claims" or "Article 13 claims"), to the reduction of the development of a disease ("Risk Reduction Claims" or "Article 14(1)(a) claims") or to the development of children ("Article 14(1)(b) claims").

Similarly, in the United States, authorized health claims are approved after the FDA has reviewed and evaluated the scientific evidence. Authorized health claims that meet the significant scientific agreement (SSA) standard are listed and allowed to be used as labels on food products (see https://www.fda.gov/food/food-labeling-nutrition/authorized-health-claims-meet-significant-scientific-agreement-ssa-standard#approved). Furthermore, there are health claims which are authorized based on authoritative statements by federal scientific bodies. But these claims are not valid for dietary supplements and require specific wording, e.g., "Diets rich in whole grain foods and other plant foods, and low in total fat, saturated fat, and cholesterol may help reduce the risk of heart disease." The third possibility is a qualified health claim that allow food labeling under certain considerations. Health claims that do not meet the SSA standard but have some scientific evidence may be used under exercise enforcement discretion.

According to the FDA, there are currently no authorized health claims for marine resources, only qualified health claims (see https://www.fda.gov/food/food-labeling-nutrition/qualified-health-claims-letters-enforcement-discretion).
Below, we describe the current health claims for the marine resources that were investigated in the context of retinal diseases. The EFSA has authorized nine health claims related to marine resources and retinal diseases.

Fish and shrimp

The increasing knowledge about the health-promoting effects of the consumption of fish and its ingredients has led to an enhanced demand for fish products in high-income countries and is one of the reasons for the growing fish production independent of the overall world population growth (Supartini, Oishi, and Yagi 2018).

Fish as a whole is sold mainly live, fresh, chilled, or frozen for human consumption and currently accounts for the majority of the fish production (FAO 2018a). Just a small number of high-value products enter the market such as collagen, chitosan, enzymes, and bioactive peptides derived from fish by-products (Olsen, Toppe, and Karunasagar 2014). Besides decreasing production costs and increasing production quantities, scientific evidence beyond correlative observations is needed to increase the nutritional use of fish or fish products for promoting retinal health. Importantly, health claims authorized by the EFSA can help to promote these products on the market. However, only one claim related to fish has been approved so far, i.e., that "meat or fish contributes to the improvement of iron absorption when eaten with other foods containing iron" (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2011). No health claims for fish have been approved by the FDA.

Both fish and shrimp can also be a source of other, potentially bioactive substances as discussed above. Further studies will be needed to demonstrate their beneficial effects on retinal and general health.

Omega-3 fatty acids

While most fish meal and fish oil production is used as feed, the most promising product currently produced from fish is fish oil as food supplement/constituents (Olsen, Toppe, and Karunasagar 2014). The unsaturated fatty acids found in fish oil but also algal oil, including EPA and DHA, are essential for human nutrition and must be supplied by the diet. Several health benefits are linked to the ingestion of omega-3 fatty acids (Hu, Hu, and Manson 2019) and have already been confirmed by the EFSA. Eight health claims are authorized, of which five are related to article 13 (function in health) and three are related to article 14 (reduction of disease risk). Accordingly, the FDA has confirmed new qualified health claims for EPA and DHA consumption (Supporting Information Table S5).

Algal extracts, polysaccharides, and carotenoids

Seaweed has been part of the Asian cuisine for centuries. However, the European cuisine just starts to explore the varieties of macroalgae. Accordingly, most of the seaweed production occurs in Asia, just a small amount is cultivated in Europe and the United States. Whereas in East Asia most of the seaweed is directly consumed fresh, dried or processed to food products, most of the seaweed in Europe and the United States are used as hydrocolloid (FAO 2018b). Macroalgae contain large amounts of carbohydrates such as agar and carrageenan from red seaweeds as well as alginate from brown seaweed which are used as binders, stabilizers, and thickeners in food, biochemical, cosmetic, or biotechnological industry (Kraan 2012; Ścieszka and Klewicka 2019). The increasing awareness of health benefits of bioactive compounds from seaweed are one reason to provide health-conscious consumer new functional foods and nutraceuticals (Lafarga, Acién-Fernández, and Garcia-Vaquero 2020). However, no health claims are currently accepted by the EFSA or FDA for algae extracts, polysaccharides, or carotenoids.

Safety

Safety for human consumption is the prerequisite for approval by the regulatory authorities. In this section, we discuss the evidence on the safety of marine resources with the potential for use in preventing or treating retinal diseases.

Fish and shrimp

Overall, the consumption of fish is considered to be safe. However, some adverse health impacts remain with certain fish and shellfish containing chemicals or illness-causing microorganisms due to ocean pollution. As for chemicals, polychlorinated biphenyls and methyl mercury have been extensively studied and the exposure of infants *in utero* can have detrimental effects for the development of the child. Heavy metals have also been detected in the human retina (Pamphlett et al. 2020). Whether these levels are sufficient to cause damage to the retina in humans remains to be investigated. Other manufactured chemicals such as bisphenol A can disrupt endocrine signaling and have neurotoxic and reproductive effects. Microorganisms such as marine bacteria can cause wound infections and gastrointestinal diseases, and Vibrio infections are on the rise (for an extensive review on the risks of fish consumption and ocean pollution, refer to (Landrigan et al. 2020)).

Another important aspect is that fish and shrimp are major food allergens (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2014). However, patients with fish allergies do not necessarily need to avoid all fish species. Recent findings and practical information regarding the management of fish allergies have been summarized elsewhere (Dijkema et al. 2020).

Omega-3 fatty acids

Safety is well documented for DHA and EPA with no side effects up to an intake of 3000 mg/day, according to the FDA that performed a comprehensive evaluation of more than 2600 articles (FDA Docket No. 2003Q-0401). When consuming very high quantities (>4,000 mg/day), digestive intolerance and some modifications of biochemical parameters related to platelet aggregation can be observed. A systematic review and meta-analysis including 21 randomized controlled trials assessing the safety and tolerability of prescription omega-3 fatty acid products in patients reported that there was no evidence for serious adverse events, but associations with treatment-related dysgeusia due to the fishy taste and skin abnormalities such as itching, eczema, eruption, and exanthema. Moreover, increases in elevated fasting blood sugar, alanine transaminase, blood urea nitrogen were observed, while hemoglobin and hematocrit decreased (Chang et al. 2018).

Related to retinal diseases, several studies also declare no side effects or only minor side effects after the consumption of omega-3 fatty acids. The oral supplementation with fish oil containing 480 mg/day DHA and 720 mg/day EPA for six months in AMD patients did not lead to significant side effects or dropouts (Querques et al. 2009). Similarly, a 3-year supplementation with 840 mg/day DHA and 270 mg/day EPA from fish oil in AMD patients also did not increase the number of adverse events compared to placebo (Souied et al. 2013). In the AREDS2 trial assessing 350 mg DHA and 650 mg EPA oral supplementation in patients at risk for progression to advanced AMD, no differences in adverse events were reported after 5-years of follow-up (Age-Related Eye Disease Study 2 Research Group 2013). In a 4-year randomized, placebo-controlled trial assessing 400 mg/day DHA supplementation from microalgae *Crypthecodinium cohnii* for XLRP, all reported adverse events were minor and equally distributed between the DHA and placebo groups (Wheaton 2003). In the follow-up DHAX trial, doses based on body weight resulting in up to 3,600 mg/day DHA intake with only transient, not severe side effects such as gastrointestinal irritability and blood chemistry alterations (Hughbanks-Wheaton et al. 2014). A randomized, controlled clinical trials in patients with RP of diverse origin that received daily supplementation with 1,200 mg DHA from microalgae *Crypthecodinium cohnii* in addition to 15,000 IU/day of vitamin A over four to six years, reported no toxic adverse effects reported (Berson, Rosner, et al. 2004).

Lipid emulsions are an important part of the nutrition for critically ill, late preterm or term infants. A systematic review of nine randomized clinical trials concluded that the addition of fish oil to lipid emulsions is safe for infants (Kapoor, Malviya, and Soll 2019). Trials on ROP also confirmed that there were no safety concerns associated with the administration of fish oil-containing lipid emulsions (Pawlik, Lauterbach, and Hurkała 2011a; Pawlik, Lauterbach, and Turyk 2011b; Beken et al. 2014; Pawlik et al. 2014; Najm et al. 2017; Unal et al. 2018; Torgalkar et al. 2019; Gharehbaghi et al. 2020; Tu et al. 2020).

Algal extracts, polysaccharides, and carotenoids

As outlined above, seaweed and dietary ingredients from seaweed including fucoidan and fucoxanthin are GRAS (Supporting Information Table S7). The consumption of fucoidan extracts from *Undaria pinnatifida* or *Fucus vesiculosus* up to 250 mg/day has been approved by regulatory agencies (Fitton et al. 2019). In a randomized, controlled clinical trial, 300 mg of a *Fucus vesiculosus* extract containing 88.5% fucoidan administered orally was safe and well-tolerated in patients with osteoarthritis (Fitton et al. 2016).

No adverse effects of capsules containing 300 mg 9-cis β-carotene from microalga *Dunaliella bardawil* were observed in a randomized, controlled clinical trial in patients with RP of diverse origin in the 3 years of follow-up after the trial end (Rotenstreich et al. 2013). *Dunaliella* capsules are available over-the-counter in the United States, have been approved by the FDA and been used for more than 20 years with no known significant adverse effects (Rotenstreich et al. 2013).

Bioavailability

Another important aspect for the dietary use of marine resources is that they can be digested and reach the intended target organ, i.e., the eye, or exert their effects through systemic ways. We here discuss the current evidence about the bioavailability of those marine resources with the potential for preventing or treating retinal diseases.

Fish and shrimp

Fish and shrimp as well as other marine animals are a major source of omega-3 fatty acids (Ahmmed et al. 2020) and their bioavailability is reviewed below.

Omega-3 fatty acids

In general, omega-3 fatty acids are absorbed and transported to the target site. An extensive overview of the sources of omega-3 fatty acids, their absorption and bioavailability can be found elsewhere (Ahmmed et al. 2020).

Dose-dependent increases in serum EPA, DHA, omega-3 fatty acids, and adiponectin were observed after three and twelve months of supplementation with fish oil in healthy volunteers in randomized controlled trials (Handeland et al. 2018; Song et al. 2018; Ostermann et al. 2019). A number of randomized controlled trials and prospective studies demonstrated that algal supplementation increases DHA concentrations in the plasma, serum, platelets, and red blood cells (for review, see Craddock et al. 2017). Lipid emulsions containing fish oil have been demonstrated to increase plasma and red blood cell DHA and EPA levels in pediatric patients, while reducing AA levels (for review, see Edward et al. 2018).

Related to retinal diseases, 3-year supplementation with 840 mg/day DHA and 270 mg/day EPA from fish oil capsules increased EPA and DHA levels in the serum and red blood cells in patients with AMD by 95% and 70%, respectively (Souied et al. 2013). In another AMD study, the oral supplementation with fish oil containing 480 mg/day DHA and 720 mg/day EPA led to 1.4- to 2.8-fold increases in DHA and EPA levels in the serum and red blood cells after six months (Querques et al. 2009). The supplementation with 400 mg/day DHA in patients with XLRP led to a 2.5-fold increase in mean plasma DHA levels compared to baseline (Wheaton 2003). In the follow-up study, 3,600 mg/day DHA elevated plasma and red blood cell DHA levels 4.4- and 3.6-fold, respectively (Hughbanks-Wheaton et al. 2014). In a randomized, controlled trial in patients with RP of diverse origin, daily supplementation with 1,200 mg DHA increased red blood cell DHA levels 2.7-fold (Berson, Rosner, et al. 2004).

Lipid emulsions used as part of the nutrition of preterm infants are also able to increase DHA and EPA levels in the plasma and in erythrocytes while decreasing AA levels in studies of ROP (Pawlik et al. 2014; Najm et al. 2017).

Algal extracts, polysaccharides, and carotenoids

Biomarkers enable the evaluation of seaweed intake in dietary intervention studies as well as observational studies. While no marker for red and green seaweed has been suggested, phlorotannins and fucoxanthinol, the main metabolite of fucoxanthin, have been proposed as markers for brown seaweed (Xi and Dragsted 2019). Phlorotannins from seaweed have been demonstrated to be digested and their metabolites in plasma and urine are mainly identified in the samples collected at 8–24 h suggesting colonic metabolism (Corona et al. 2016). The authors further suggested IL-8 as a marker for phlorotannin activity as it was increased at 8 h. Conversely, fucoxanthin has been demonstrated to be esterified or hydrolyzed to fucoxanthinol in the gastrointestinal tract and further converted into amarouciaxanthin A in the liver. However, the bioaccessibility of fucoxanthin is considered to be low in humans (for review, see Viera, Pérez-Gálvez, and Roca 2018).

Regarding the brown algae compound fucoidan, measurement also remains technically challenging (Fitton et al. 2019). However, a recent study demonstrated the uptake of fucoidan from *Fucus vesiculosus* into cells via clathrin-mediated endocytosis using fluorescein isothiocyanate labeled fucoidan (Bai et al. 2020). Furthermore, tissue distribution studies in rodents suggest the uptake of fucoidan in the kidney, spleen, and liver (Pozharitskaya et al. 2018; Bai et al. 2020). A human study assessing the biodistribution of radiolabeled fucoidan is currently underway (NCT03422055).

Other potential biomarkers are the composition and diversity of gut microbiota. A recent review summarized the available evidence on the effects of algal polysaccharides on modulating gut microbiota. While the non-sulfated alginate and laminarin have been described to be well-fermented generating short-chain fatty acids and inhibiting H_2S production, sulfated polysaccharides including agarans, carrageenan, and fucoidan are less easily fermented (Gotteland et al. 2020). However, the combination of 1 g wheat peptides and 0.3 g fucoidan daily for 45 days has been reported to alter the composition of gut microbiota in a randomized, controlled trial in patients with gastritis (Kan et al. 2020). Further preclinical evidence on the effects of fucoidan on the microbiome are summarized elsewhere (Fitton et al. 2019).

Taken together, there is a need for further human studies assessing the bioavailability of algal extracts, polysaccharides, and carotenoids and how their metabolites can reach the retina to exert their beneficial functions. Concerning required intakes for beneficial functions, there is only limited data that can inform about the daily/weekly dosages and further research is needed. Fish consumption of two servings/week were demonstrated to improve retinal function and prevent retinal diseases (Tables 2–6). For omega-3 fatty acids, the approved health claims suggest an intake of 250 mg DHA daily in general (Subsection health claims to promote the beneficial effects of food and Supporting Information Table S5). According to the clinical trials, doses of up to 3,600 mg/day DHA were safe (Subsection safety). Daily supplementation with 270–3,600 mg DHA and EPA were demonstrated to increase plasma and red blood cell DHA and EPA levels (Subsection bioavailability). Regarding other marine resources, the current data is not sufficient to derive any suggestions.

Outlook

Marine resources from animals and plants have an immense potential for health-promoting effects (Figure 2). In particular, the prevention of retinal diseases through nutrition offers a promising avenue. While a considerable body of

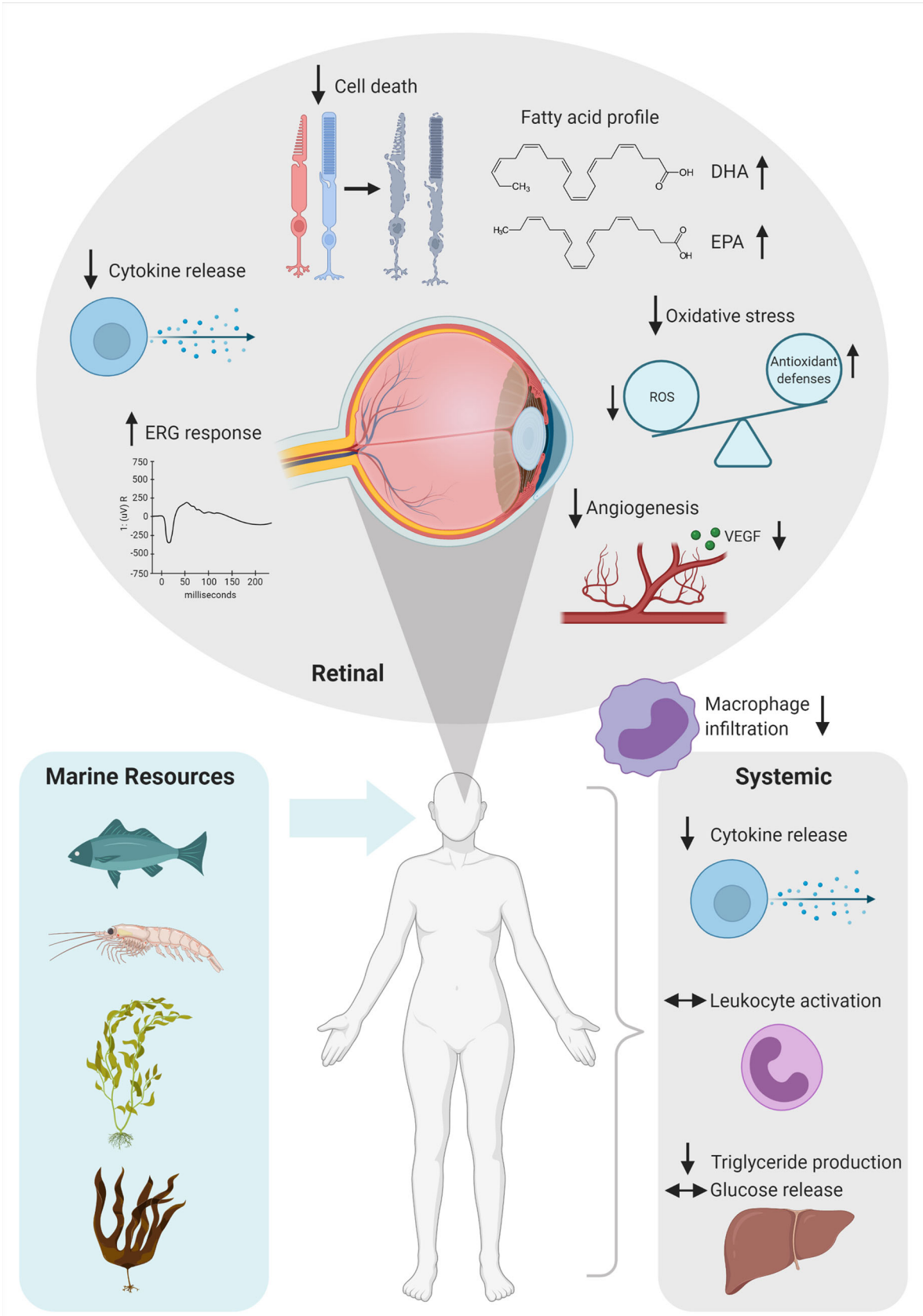

Figure 2. The potential of marine resources for retinal diseases. Marine resources such as fish, shrimp, algae, and their bioactive ingredients have been demonstrated to promote beneficial effects including anti-inflammatory, antioxidant, antiangiogenic/vasoprotective, cytoprotective, and metabolic effects in the retina and to improve retinal function. Furthermore, they are able to reduce macrophage infiltration, systemic cytokine release, and triglyceride production, while the evidence on systemic glucose release and leukocyte activation is insufficient. Created with BioRender.com.

literature exists on omega-3 fatty acids and their potential to reduce the incidence of retinal diseases, other marine resources are less well studied. The variety of potential ingredients that can be obtained from marine animals and plants should certainly foster more studies evaluating their contribution to improve retinal function and health.

Apart from establishing associative effects, a major future focus should be on elucidating the underlying mechanisms. The identified mechanisms including anti-inflammatory, antioxidant, antiangiogenic/vasoprotective, cytoprotective, metabolic, and retinal function effects should be further studied in preclinical models as well as in human patients.

Furthermore, human studies about the bioavailability and dosing of algal extracts and their compounds should be a priority.

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Authors' contributions

K.K., E.B., and M.Z. screened the abstracts for the systematic review. K.K., M.Z. reviewed the full-text versions of the potentially eligible studies for the systematic review. K.K., A.K.K., and M.Z. wrote the manuscript. All authors read and commented on the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Abbreviations

AA	arachidonic acid;
AGE	advanced glycation end products;
AMD	age-related macular degeneration;
COX-2	cyclooxygenase-2;
CHD	coronary heart disease;
CRP	c-reactive protein;
DHA	docosahexaenoic acid;
DPA	docosapentaenoic acid;
DPPH	1,1-diphenyl-2-picrylhydrazyl;
DR	diabetic retinopathy;
EFSA	European Food Safety Authority;
EPA	eicosapentaenoic acid;
ERG	electroretinogram;
ERK	extracellular-signal-regulated kinase;
FDA	Food & Drug Administration;
GPX	glutathione peroxidase;
GRAS	generally recognized as safe;
GSH	glutathione;
H_2O_2	hydrogen peroxide;
HDL	high-density lipoprotein;
HIF-1	hypoxia-inducible factor 1;
IFNγ	interferon gamma;
IL	interleukin;
iNOS	inducible nitric oxide synthase;
LDL	low-density lipoprotein;
MAP	mitogen-activated protein;
MCP-1	monocyte chemotactic protein-1;
MDA	malondialdehyde;
Mt	megaton;
NF-κB	nuclear factor "kappa-light-chain-enhancer" of activated B-cells;
Nrf2	Nuclear factor erythroid-2 related factor 2;
NO	nitric oxide;
PUFA	polyunsaturated fatty acid;
RAGE	receptor of advanced glycation end products;
ROP	retinopathy of prematurity;
ROS	reactive oxygen species;
RP	retinitis pigmentosa;
RPE	retinal pigment epithelium;
SSA	significant scientific agreement;
SOD	superoxide dismutase;
TLR	toll-like receptor;
TNF	tumor necrosis factor;
XLRP	X-linked retinitis pigmentosa

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References

Abokyi, S., C.-H. To, T. T. Lam, and D. Y. Tse. 2020. Central role of oxidative stress in age-related macular degeneration: Evidence from a review of the molecular mechanisms and animal models. *Oxidative Medicine and Cellular Longevity* 2020 (February):1–19. doi:10.1155/2020/7901270.

Age-Related Eye Disease Study 2 Research Group. 2013. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The age-related eye disease study 2 (AREDS2) randomized clinical trial. *JAMA* 309 (19):2005–15. doi:10.1001/jama.2013.4997.

Aguirre, G. D., G. M. Acland, M. B. Maude, and R. E. Anderson. 1997. Diets enriched in docosahexaenoic acid fail to correct progressive rod-cone degeneration (prcd) Phenotype. *Investigative Ophthalmology & Visual Science* 38 (11):2387–407.

Ahmmed, M. K., F. Ahmmed, H. S. Tian, A. Carne, and A. E.-D. Bekhit. 2020. Marine omega-3 (N-3) phospholipids: A comprehensive review of their properties, sources, bioavailability, and relation to brain health. *Comprehensive Reviews in Food Science and Food Safety* 19 (1):64–123. doi:10.1111/1541-4337.12510.

Ai, W., X.-P. Lin, Z. Tu, X.-P. Tian, X. Lu, F. Mangaladoss, Z.-L. Zhong, and Y. Liu. 2014. Axinelline A, a new COX-2 inhibitor from *Streptomyces Axinellae* SCSIO02208. *Natural Product Research* 28 (16):1219–24. doi:10.1080/14786419.2014.891204.

Aiello, L. P., E. A. Pierce, E. D. Foley, H. Takagi, H. Chen, L. Riddle, N. Ferrara, G. L. King, and L. E. Smith. 1995. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. *Proceedings of the National Academy of Sciences of the United States of America* 92 (23):10457–61. doi:10.1073/pnas.92.23.10457.

Aït-Ali, N., R. Fridlich, G. Millet-Puel, E. Clérin, F. Delalande, C. Jaillard, F. Blond, L. Perrocheau, S. Reichman, L. C. Byrne, et al. 2015. Rod-derived cone viability factor promotes cone survival by stimulating aerobic glycolysis. *Cell* 161 (4):817–32. doi:10.1016/j.cell.2015.03.023.

Almasieh, M., A. M. Wilson, B. Morquette, J. L. Cueva Vargas, and A. Di Polo. 2012. The molecular basis of retinal ganglion cell death in glaucoma. *Progress in Retinal and Eye Research* 31 (2):152–81. doi:10.1016/j.preteyeres.2011.11.002.

Aloe, G., C. M. De Sanctis, C. Strafella, R. Cascella, F. Missiroli, M. Cesareo, E. Giardina, and F. Ricci. 2019. Bilateral retinal angiomatous proliferation in a variant of retinitis pigmentosa. *Case Reports in Ophthalmological Medicine* 2019:8547962. doi:10.1155/2019/8547962.

Altmann, C., and M. H. H. Schmidt. 2018. The role of microglia in diabetic retinopathy: Inflammation, microvasculature defects and neurodegeneration. *International Journal of Molecular Sciences* 19 (1):110. doi:10.3390/ijms19010110.

Ambati, J., J. P. Atkinson, and B. D. Gelfand. 2013. Immunology of age-related macular degeneration. *Nature Reviews Immunology* 13 (6):438–51. doi:10.1038/nri3459.

Amirul Islam, F. M., E. W. Chong, A. M. Hodge, R. H. Guymer, K. Z. Aung, G. A. Makeyeva, P. N. Baird, J. L. Hopper, D. R. English, G. G. Giles, et al. 2014. Dietary patterns and their associations with age-related macular degeneration: The Melbourne Collaborative Cohort Study. *Ophthalmology* 121 (7):1428–34.e2. doi:10.1016/j.ophtha.2014.01.002.

Antonetti, D. A., R. Klein, and T. W. Gardner. 2012. Diabetic retinopathy. *The New England Journal of Medicine* 366 (13):1227–39. doi:10.1056/NEJMra1005073.

Appeltans, W., S. T. Ahyong, G. Anderson, M. V. Angel, T. Artois, N. Bailly, R. Bamber, A. Barber, I. Bartsch, A. Berta, et al. 2012. The magnitude of global marine species diversity. *Current Biology: CB* 22 (23):2189–202. doi:10.1016/j.cub.2012.09.036.

Arrieta, J. M., S. Arnaud-Haond, and C. M. Duarte. 2010. What Lies underneath: Conserving the oceans' genetic resources. *Proceedings of the National Academy of Sciences of the United States of America* 107 (43):18318–24. doi:10.1073/pnas.0911897107.

Arshavsky, V. Y., and M. E. Burns. 2012. Photoreceptor signaling: Supporting vision across a wide range of light intensities. *The Journal of Biological Chemistry* 287 (3):1620–6. doi:10.1074/jbc.R111.305243.

Arslan, S., S. Kadayifçilar, and G. Samur. 2019. The potential role of dietary antioxidant capacity in preventing age-related macular degeneration. *Journal of the American College of Nutrition* 38 (5):424–32. doi:10.1080/07315724.2018.1538830.

Augood, C., U. Chakravarthy, I. Young, J. Vioque, P. T. V. M. de Jong, G. Bentham, M. Rahu, J. Seland, G. Soubrane, L. Tomazzoli, et al. 2008. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. *The American Journal of Clinical Nutrition* 88 (2):398–406. doi:10.1093/ajcn/88.2.398.

Bai, X., E. Zhang, B. Hu, H. Liang, S. Song, and A. Ji. 2020. Study on absorption mechanism and tissue distribution of fucoidan. *Molecules* 25 (5):1087. doi:10.3390/molecules25051087.

Balaban, R. S., S. Nemoto, and T. Finkel. 2005. Mitochondria, oxidants, and aging. *Cell* 120 (4):483–95. doi:10.1016/j.cell.2005.02.001.

Barac, I. R., M. D. Pop, A. I. Gheorghe, and C. Taban. 2015. Neovascular secondary glaucoma, etiology and pathogenesis. *Romanian Journal of Ophthalmology* 59 (1):24–8.

Bazan, N. G., J. M. Calandria, and W. C. Gordon. 2013. Docosahexaenoic acid and its derivative neuroprotectin D1 display neuroprotective properties in the retina, brain and central nervous system. *Nestlé Nutrition Institute Workshop Series* 77, 121–31. doi:10.1159/000351395.

Beckman, J. S., and J. P. Crow. 1993. Pathological implications of nitric oxide, superoxide and peroxynitrite formation. *Biochemical Society Transactions* 21 (2):330–4. doi:10.1042/bst0210330.

Beharry, K., C. Cai, F. Siddiqui, S. Chowdhury, C. D'Agrosa, G. Valencia, and J. Aranda. 2018. Comparative effects of coenzyme Q10 or N-3 polyunsaturated fatty acid supplementation on retinal angiogenesis in a rat model of oxygen-induced retinopathy. *Antioxidants* 7 (11):160. doi:10.3390/antiox7110160.

Beken, S., D. Dilli, N. D. Fettah, E. U. Kabataş, A. Zenciroğlu, and N. Okumuş. 2014. The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: A randomized controlled trial. *Early Human Development* 90 (1):27–31. doi:10.1016/j.earlhumdev.2013.11.002.

Bell, K., O. W. Gramlich, N. Von Thun Und Hohenstein-Blaul, S. Beck, S. Funke, C. Wilding, N. Pfeiffer, and F. H. Grus. 2013. Does autoimmunity play a part in the pathogenesis of glaucoma? *Progress in Retinal and Eye Research* 36:199–216. doi:10.1016/j.preteyeres.2013.02.003.

Benoist d'Azy, C., B. Pereira, F. Chiambaretta, and F. Dutheil. 2016. Oxidative and anti-oxidative stress markers in chronic glaucoma: A systematic review and meta-analysis. *PLoS One* 11 (12):e0166915. doi:10.1371/journal.pone.0166915.

Bernstein, A. M., E. L. Ding, W. C. Willett, and E. B. Rimm. 2012. A meta-analysis shows that docosahexaenoic acid from algal oil reduces serum triglycerides and increases HDL-cholesterol and LDL-cholesterol in persons without coronary heart disease. *The Journal of Nutrition* 142 (1):99–104. doi:10.3945/jn.111.148973.

Berra, A., J. Tau, G. Zapata, and P. Chiaradia. 2017. Effects of PUFAs in a mouse model of HSV-1 chorioretinitis. *Ocular Immunology and Inflammation* 25 (6):844–54. doi:10.1080/09273948.2016.1184287.

Berson, E. L., R. Bernard, M. A. Sandberg, W.-D. Carol, M. Ann, R. J. Brockhurst, K. C. Hayes, C. A. Johnson, E. J. Anderson, A. R. Gaudio, et al. 2004. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment: Subgroup analyses. *Archives of Ophthalmology* 122 (9):1306–14. doi:10.1001/archopht.122.9.1306.

Berson, E. L., B. Rosner, M. A. Sandberg, C. Weigel-DiFranco, A. Moser, R. J. Brockhurst, K. C. Hayes, C. A. Johnson, E. J. Anderson, A. R. Gaudio, et al. 2004. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. *Archives of Ophthalmology (Chicago, Ill: 1960)* 122 (9):1297–305. doi:10.1001/archopht.122.9.1297.

Bhutto, I., and G. Lutty. 2012. Understanding age-related macular degeneration (AMD): Relationships between the photoreceptor/retinal pigment epithelium/bruch's membrane/choriocapillaris complex . *Molecular Aspects of Medicine* 33 (4):295–317. doi:10.1016/j.mam.2012.04.005.

Bicknell, I., Rea, R. Darrow, L. Barsalou, S. J. Fliesler, and D. T. Organisciak. 2002. Alterations in retinal rod outer segment fatty acids and light-damage susceptibility in P23H rats. *Molecular Vision* 8:333–40.

Bittkau, K. S., S. Neupane, and S. Alban. 2020. Initial evaluation of six different brown algae species as source for crude bioactive fucoidans. *Algal Research* 45:101759. doi:10.1016/j.algal.2019.101759.

Boehm, M. R., P. Oellers, and S. Thanos. 2011. Inflammation and immunology of the vitreoretinal compartment. *Inflammation & Allergy Drug Targets* 10 (4):283–309. doi:10.2174/187152811796117717.

Bourne, R. R. A., S. R. Flaxman, T. Braithwaite, M. V. Cicinelli, A. Das, J. B. Jonas, J. Keeffe, J. H. Kempen, J. Leasher, H. Limburg, et al. 2017. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: A systematic review and meta-analysis. *The Lancet. Global Health* 5 (9):e888–e897. doi:10.1016/S2214-109X(17)30293-0.

Bourne, R. R. A., J. B. Jonas, A. M. Bron, M. V. Cicinelli, A. Das, S. R. Flaxman, D. S. Friedman, J. E. Keeffe, J. H. Kempen, J. Leasher, et al. 2018. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: Magnitude, temporal trends and projections. *The British Journal of Ophthalmology* 102 (5):575–85. doi:10.1136/bjophthalmol-2017-311258.

Bouvard, C., I. Galy-Fauroux, F. Grelac, W. Carpentier, A. Lokajczyk, S. Gandrille, S. Colliec-Jouault, A.-M. Fischer, and D. Helley. 2015. Low-molecular-weight fucoidan induces endothelial cell migration via the PI3K/AKT pathway and modulates the transcription of genes involved in angiogenesis. *Marine Drugs* 13 (12):7446–62. doi:10.3390/md13127075.

Broadhead, G. K., J. R. Grigg, A. A. Chang, and P. McCluskey. 2015. Dietary modification and supplementation for the treatment of age-related macular degeneration. *Nutrition Reviews* 73 (7):448–62. doi:10.1093/nutrit/nuv005.

Byeon, S. H., S. C. Lee, S. H. Choi, H. K. Lee, J. H. Lee, Y. K. Chu, and O. W. Kwon. 2010. Vascular endothelial growth factor as an

autocrine survival factor for retinal pigment epithelial cells under oxidative stress via the VEGF-R2/PI3K/Akt. *Investigative Ophthalmology & Visual Science* 51 (2):1190–7. doi:10.1167/iovs.09-4144.

Cai, J., K. C. Nelson, M. Wu, P. Sternberg, and D. P. Jones. 2000. Oxidative damage and protection of the RPE. *Progress in Retinal and Eye Research* 19 (2):205–21. doi:10.1016/S1350-9462(99)00009-9.

Calder, P. C. 2015. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochimica et Biophysica Acta* 1851 (4):469–84. doi:10.1016/j.bbalip.2014.08.010.

Campello, L., O. Kutsyr, A. Noailles, P. Michalska, L. Fernández-Sánchez, N. Martínez-Gil, I. Ortuño-Lizarán, X. Sánchez-Sáez, E. de Juan, P. Lax, et al. 2020. New Nrf2-inducer compound ITH12674 slows the progression of retinitis pigmentosa in the mouse model Rd10. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology* 54 (1):142–59. doi:10.33594/000000210.

Campochiaro, P. A. 2015. Molecular pathogenesis of retinal and choroidal vascular diseases. *Progress in Retinal and Eye Research* 49: 67–81. doi:10.1016/j.preteyeres.2015.06.002.

Campochiaro, P. A., and T. A. Mir. 2018. The mechanism of cone cell death in retinitis pigmentosa. *Progress in Retinal and Eye Research* 62:24–37. doi:10.1016/j.preteyeres.2017.08.004.

Campochiaro, P. A., R. W. Strauss, L. Lu, G. Hafiz, Y. Wolfson, S. M. Shah, R. Sophie, T. A. Mir, and H. P. Scholl. 2015. Is there excess oxidative stress and damage in eyes of patients with retinitis pigmentosa? *Antioxidants & Redox Signaling* 23 (7):643–8. doi:10.1089/ars.2015.6327.

Canizales, L., L. Rodriguez, C. Rivera, A. Martinez, F. Mendez, and A. Castillo. 2016. Low-level expression of *SOD1* in peripheral blood samples of patients diagnosed with primary open-angle glaucoma. *Biomarkers in Medicine* 10 (12):1218–23. doi:10.2217/bmm-2016-0167.

Cao, S., A. Ko, M. Partanen, K. Pakzad-Vaezi, A. B. Merkur, D. A. Albiani, A. W. Kirker, A. Wang, J. Z. Cui, F. Forooghian, et al. 2013. Relationship between systemic cytokines and complement factor H Y402H polymorphism in patients with dry age-related macular degeneration. *American Journal of Ophthalmology* 156 (6): 1176–83. doi:10.1016/j.ajo.2013.08.003.

Carresi, C., F. Cruciani, F. Paolucci, T. Curto, L. Mazzeo, G. Cuozzo, A. Moramarco, and M. Gharbiya. 2009. Montelparo study: Risk factors for age-related macular degeneration in a little rural community in Italy. *La Clinica Terapeutica* 160 (3):e43–51.

Casson, R. J., G. Chidlow, J. P. Wood, J. G. Crowston, and I. Goldberg. 2012. Definition of glaucoma: Clinical and experimental concepts. *Clinical & Experimental Ophthalmology* 40 (4):341–9. doi:10.1111/j.1442-9071.2012.02773.x.

Catala, A. 2011. Lipid peroxidation of membrane phospholipids in the vertebrate retina. *Frontiers in Bioscience (Scholar Edition)* 3:52–60. doi:10.2741/s131.

Chalam, K. V., V. Khetpal, R. Rusovici, and S. Balaiya. 2011. A review: Role of ultraviolet radiation in age-related macular degeneration. *Eye & Contact Lens: Science & Clinical Practice* 37 (4):225–32. doi:10.1097/ICL.0b013e31821fbd3e.

Chang, C.-H., P.-T. Tseng, N.-Y. Chen, P.-C. Lin, P.-Y. Lin, J. P.-C. Chang, F.-Y. Kuo, J. Lin, M.-C. Wu, and K.-P. Su. 2018. Safety and tolerability of prescription omega-3 fatty acids: A systematic review and meta-analysis of randomized controlled trials. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 129:1–12. doi:10.1016/j.plefa.2018.01.001.

Chan-Ling, T., and J. Stone. 1992. Degeneration of astrocytes in feline retinopathy of prematurity causes failure of the blood-retinal barrier. *Investigative Ophthalmology & Visual Science* 33 (7):2148–59.

Chapman, N. A., R. J. Jacobs, and A. J. Braakhuis. 2019. Role of diet and food intake in age-related macular degeneration: A systematic review. *Clinical & Experimental Ophthalmology* 47 (1):106–27. doi:10.1111/ceo.13343.

Charoensiddhi, S., M. A. Conlon, C. M. M. Franco, and W. Zhang. 2017. The development of seaweed-derived bioactive compounds for use as prebiotics and nutraceuticals using enzyme technologies. *Trends in Food Science & Technology* 70:20–33. doi:10.1016/j.tifs.2017.10.002.

Chaudry, I., G. C. Brown, and M. M. Brown. 2015. Medical student and patient perceptions of quality of life associated with vision loss. *Canadian Journal of Ophthalmology* 50 (3):217–24. doi:10.1016/j.jcjo.2015.02.004.

Chen, J., Y. Wei, X. Chen, J. Jiao, and Y. Zhang. 2017. Polyunsaturated fatty acids ameliorate aging *via* redox-telomere-antioncogene axis. *Oncotarget* 8 (5):7301–14. doi:10.18632/oncotarget.14236.

Chen, L. Y., D. L. Lawson, and J. L. Mehta. 1994. Reduction in human neutrophil superoxide anion generation by N-3 polyunsaturated fatty acids: Role of cyclooxygenase products and endothelium-derived relaxing factor. *Thrombosis Research* 76 (4):317–22. doi:10.1016/0049-3848(94)90160-0.

Chen, M., and H. Xu. 2015. Parainflammation, chronic inflammation, and age-related macular degeneration. *Journal of Leukocyte Biology* 98 (5):713–25. doi:10.1189/jlb.3RI0615-239R.

Chen, M.-C., W.-L. Hsu, P.-A. Hwang, and T.-C. Chou. 2015. Low molecular weight fucoidan inhibits tumor angiogenesis through downregulation of HIF-1/VEGF signaling under hypoxia. *Marine Drugs* 13 (7):4436–51. doi:10.3390/md13074436.

Chew, B. P., B. D. Mathison, M. G. Hayek, S. Massimino, G. A. Reinhart, and J. S. Park. 2011. Dietary astaxanthin enhances immune response in dogs. *Veterinary Immunology and Immunopathology* 140 (3–4):199–206. doi:10.1016/j.vetimm.2010.12.004.

Chiang, W.-C., H. Kroeger, S. Sakami, C. Messah, D. Yasumura, M. T. Matthes, J. A. Coppinger, K. Palczewski, M. M. LaVail, and J. H. Lin. 2015. Robust endoplasmic reticulum-associated degradation of rhodopsin precedes retinal degeneration. *Molecular Neurobiology* 52 (1):679–95. doi:10.1007/s12035-014-8881-8.

Choi, D.-Y., and H. Choi. 2015. Natural products from marine organisms with neuroprotective activity in the experimental models of Alzheimer's disease, Parkinson's disease and ischemic brain stroke: Their molecular targets and action mechanisms. *Archives of Pharmacal Research* 38 (2):139–70. doi:10.1007/s12272-014-0503-5.

Chong, E. W.-T., A. J. Kreis, T. Y. Wong, J. A. Simpson, and R. H. Guymer. 2008. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: A systematic review and meta-analysis. *Archives of Ophthalmology (Chicago, Ill: 1960)* 126 (6):826–33. doi:10.1001/archopht.126.6.826.

Chong, E. W.-T., L. D. Robman, J. A. Simpson, A. M. Hodge, K. Z. Aung, T. K. Dolphin, D. R. English, G. G. Giles, and R. H. Guymer. 2009. Fat consumption and its association with age-related macular degeneration. *Archives of Ophthalmology* 127 (5):674–80. doi:10.1001/archophthalmol.2009.60.

Chua, B., V. Flood, E. Rochtchina, J. J. Wang, W. Smith, and P. Mitchell. 2006. Dietary fatty acids and the 5-year incidence of age-related maculopathy. *Archives of Ophthalmology (Chicago, Ill: 1960)* 124 (7):981–6. doi:10.1001/archopht.124.7.981.

Chua, J., A.-R. Chia, M. L. Chee, R. E. K. Man, G. S. W. Tan, E. L. Lamoureux, T. Y. Wong, M. F.-F. Chong, and L. Schmetterer. 2018. The relationship of dietary fish intake to diabetic retinopathy and retinal vascular caliber in patients with type 2 diabetes. *Scientific Reports* 8 (1):730. doi:10.1038/s41598-017-18930-6.

Clarke, P. G. H. 1990. Developmental cell death: Morphological diversity and multiple mechanisms. *Anatomy and Embryology* 181 (3): 195–213. doi:10.1007/BF00174615.

Clarkson, P. M., and H. S. Thompson. 2000. Antioxidants: What role do they play in physical activity and health? *The American Journal of Clinical Nutrition* 72 (2 Suppl):637S–46S. doi:10.1093/ajcn/72.2.637S.

Comitato, A., D. Schiroli, C. La Marca, and V. Marigo. 2019. Differential contribution of calcium-activated proteases and ER-stress in three mouse models of retinitis pigmentosa expressing P23H mutant RHO. *Advances in Experimental Medicine and Biology* 1185:311–6. doi:10.1007/978-3-030-27378-1_51.

Copland, D. A., S. Theodoropoulou, J. Liu, and A. D. Dick. 2018. A Perspective of AMD through the eyes of immunology. *Investigative*

Ophthalmology & Visual Science 59 (4):AMD83–92. doi:10.1167/iovs.18-23893.

Corona, G., Y. Ji, P. Anegboonlap, S. Hotchkiss, C. Gill, P. Yaqoob, J. P. E. Spencer, and I. Rowland. 2016. Gastrointestinal modifications and bioavailability of brown seaweed phlorotannins and effects on inflammatory markers. *British Journal of Nutrition* 115 (7): 1240–53. doi:10.1017/S0007114516000210.

Country, M. W. 2017. Retinal metabolism: A comparative look at energetics in the retina. *Brain Research* 1672:50–7. doi:10.1016/j.brainres.2017.07.025.

Craddock, J. C., E. P. Neale, Y. C. Probst, and G. E. Peoples. 2017. Algal supplementation of vegetarian eating patterns improves plasma and serum docosahexaenoic acid concentrations and omega-3 indices: A systematic literature review. *Journal of Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association* 30 (6):693–9. doi:10.1111/jhn.12474.

Cui, F., M. Li, Y. Chen, Y. Liu, Y. He, D. Jiang, J. Tong, J. Li, and X. Shen. 2014. Protective effects of polysaccharides from Sipunculus nudus on Beagle dogs exposed to γ-radiation. *PLoS One* 9 (8): e104299. doi:10.1371/journal.pone.0104299.

Curcio, C. A., M. Johnson, M. Rudolf, and J. D. Huang. 2011. The oil spill in ageing bruch membrane. *British Journal of Ophthalmology* 95 (12):1638–45. doi:10.1136/bjophthalmol-2011-300344.

Darlow, B. A., J. L. Hutchinson, D. J. Henderson-Smart, D. A. Donoghue, J. M. Simpson, N. J. Evans, and Australian and New Zealand Neonatal Network. 2005. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand neonatal network. *Pediatrics* 115 (4): 990–6. doi:10.1542/peds.2004-1309.

Datta, S., M. Cano, K. Ebrahimi, L. Wang, and J. T. Handa. 2017. The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD. *Progress in Retinal and Eye Research* 60: 201–18. doi:10.1016/j.preteyeres.2017.03.002.

de Bus, I., R. Witkamp, H. Zuilhof, B. Albada, and M. Balvers. 2019. The role of N-3 PUFA-derived fatty acid derivatives and their oxygenated metabolites in the modulation of inflammation. *Prostaglandins & Other Lipid Mediators* 144:106351. doi:10.1016/j.prostaglandins.2019.106351.

de Koning-Backus, A. P. M., G. H. S. Buitendijk, J. C. Kiefte-de Jong, J. M. Colijn, A. Hofman, J. R. Vingerling, E. B. Haverkort, O. H. Franco, and C. C. W. Klaver. 2019. Intake of vegetables, fruit, and fish is beneficial for age-related macular degeneration. *American Journal of Ophthalmology* 198:70–9. doi:10.1016/j.ajo.2018.09.036.

De Nardo, D. 2015. Toll-like receptors: Activation, signalling and transcriptional modulation. *Cytokine* 74 (2):181–9. doi:10.1016/j.cyto.2015.02.025.

Delorme, J., B. Claudine, C. Névéna, V. Geneviève, S. Lia, and N. Emmanuel. 1984. Age-dependent responses of the serum non-esterified fatty acids to adrenalectomy and ovariectomy in developing rats. *Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism* 792 (1):6–10. doi:10.1016/0005-2760(84)90275-3.

Deng, Q., Y. Wang, C. Wang, B. Ji, R. Cong, L. Zhao, P. Chen, X. Zang, F. Lu, F. Han, et al. 2018. Dietary supplementation with omega-3 polyunsaturated fatty acid-rich oils protects against visible-light-induced retinal damage in vivo. *Food & Function* 9 (4): 2469–79. doi:10.1039/C7FO01168G.

Díaz, L. D., V. Fernández-Ruiz, and M. Cámara. 2020. An international regulatory review of food health-related claims in functional food products labeling. *Journal of Functional Foods* 68:103896. doi:10.1016/j.jff.2020.103896.

Dijkema, D., J. A. M. Emons, A. A. J. M. Van de Ven, and J. N. G. Oude Elberink. 2020. Fish allergy: Fishing for novel diagnostic and therapeutic options. *Clinical Reviews in Allergy & Immunology*. doi:10.1007/s12016-020-08806-5.

Dinu, M., P. Giuditta, C. Alessandro, and S. Francesco. 2018. Food groups and risk of age-related macular degeneration: A systematic review with meta-analysis. *European Journal of Nutrition* 58: 2123–2143. doi:10.1007/s00394-018-1771-5.

Dithmer, M., F. Sabine, S. Yang, S. Harald, R. Elisabeth, R. Johann, and K. Alexa. 2014. Fucoidan reduces secretion and expression of vascular endothelial growth factor in the retinal pigment epithelium and reduces angiogenesis in vitro. *PLoS One* 9 (2):e89150. doi:10.1371/journal.pone.0089150.

Doganay, S., C. Evereklioglu, H. Er, Y. Türköz, A. Sevinç, N. Mehmet, and H. Şavli. 2002. Comparison of serum NO, TNF-alpha, IL-1beta, SIL-2R, IL-6 and IL-8 levels with grades of retinopathy in patients with diabetes mellitus. *Eye* 16 (2):163–70. doi:10.1038/sj/eye/6700095.

Domènech, E. B., and G. Marfany. 2020. The relevance of oxidative stress in the pathogenesis and therapy of retinal dystrophies. *Antioxidants* 9 (4):347. doi:10.3390/antiox9040347.

Dörschmann, P., M. Dalgaard Mikkelsen, T. Nguyen Thi, J. Roider, A. S. Meyer, and A. Klettner. 2020. Effects of a newly developed enzyme-assisted extraction method on the biological activities of fucoidans in ocular cells. *Marine Drugs* 18 (6):282. doi:10.3390/md18060282.

Dörschmann, P., G. Kopplin, J. Roider, and A. Klettner. 2019. Effects of sulfated fucans from laminaria hyperborea regarding VEGF secretion, cell viability, and oxidative stress and correlation with molecular weight. *Marine Drugs* 17 (10):548. doi:10.3390/md17100548.

Dörschmann, P., K. Saskia Bittkau, S. Neupane, J. Roider, S. Alban, and A. Klettner. 2019. Effects of fucoidans from five different brown algae on oxidative stress and VEGF interference in ocular cells. *Marine Drugs* 17 (5):258. doi:10.3390/md17050258.

Dow, C., F. Mancini, K. Rajaobelina, M.-C. Boutron-Ruault, B. Balkau, F. Bonnet, and G. Fagherazzi. 2018. Diet and risk of diabetic retinopathy: A systematic review. *European Journal of Epidemiology* 33 (2):141–56. doi:10.1007/s10654-017-0338-8.

Doyle, S. L., M. Campbell, E. Ozaki, R. G. Salomon, A. Mori, P. F. Kenna, G. J. Farrar, A.-S. Kiang, M. M. Humphries, E. C. Lavelle, et al. 2012. NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components. *Nature Medicine* 18 (5):791–8. doi:10.1038/nm.2717.

Dreyfuss, J. L., C. V. Regatieri, M. A. Lima, E. J. Paredes-Gamero, A. S. Brito, S. F. Chavante, R. Belfort, M. E. Farah, and H. B. Nader. 2010. A heparin mimetic isolated from a marine shrimp suppresses neovascularization. *Journal of Thrombosis and Haemostasis* 8 (8): 1828–37. doi:10.1111/j.1538-7836.2010.03916.x.

Duarte, C. M., W. Jiaping, X. Xi, B. Annette, and K.-J. Dorte. 2017. Can seaweed farming play a role in climate change mitigation and adaptation? *Frontiers in Marine Science* 4:100. doi:10.3389/fmars.2017.00100.

Durand, R., P. Geneviève, T. Jacinthe, F. Erwann, M. André, and B. Laurent. 2020. Screening for metabolic syndrome application of a herring by-product hydrolysate after its separation by electrodialysis with ultrafiltration membrane and identification of novel anti-inflammatory peptides. *Separation and Purification Technology* 235: 116205. doi:10.1016/j.seppur.2019.116205.

Dutot, M., V. de la Tourrette, R. Fagon, and P. Rat. 2011. New approach to modulate retinal cellular toxic effects of high glucose using marine epa and dha. *Nutrition & Metabolism* 8 (1):39. doi:10.1186/1743-7075-8-39.

Edward, R.-R., J. K. Innes, L. V. Marino, and P. C. Calder. 2018. Influence of different intravenous lipid emulsions on growth, development and laboratory and clinical outcomes in hospitalised paediatric patients: A systematic review. *Clinical Nutrition (Edinburgh, Scotland)* 37 (3):765–83. doi:10.1016/j.clnu.2017.07.003.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). 2011. Scientific opinion on the substantiation of health claims related to sodium and potassium salts of citric acid and maintenance of normal bone (ID 330) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal* 9 (7):2302. doi:10.2903/j.efsa.2011.2302.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). 2014. Scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. *EFSA Journal* 12 (11):3894. doi:10.2903/j.efsa.2014.3894.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), D. Turck, J.-L. Bresson, B. Burlingame, T. Dean, S. Fairweather-Tait, and M. Heinonen. 2016a. Guidance on the preparation and

presentation of the notification and application for authorisation of traditional foods from third countries in the context of Regulation (EU) 2015/2283. *EFSA Journal* 14 (11):4590. doi:10.2903/j.efsa.2016.4590.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), D. Turck, J.-L. Bresson, B. Burlingame, T. Dean, S. Fairweather-Tait, M. Heinonen, K. I. Hirsch-Ernst, I. Mangelsdorf, H. McArdle, et al. 2016b. Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. *EFSA Journal* 14 (11):4594. doi:10.2903/j.efsa.2016.4594.

Eggersdorfer, M., and A. Wyss. 2018. Carotenoids in human nutrition and health. *Archives of Biochemistry and Biophysics* 652:18–26. doi:10.1016/j.abb.2018.06.001.

Elmasry, K., A. S. Ibrahim, S. Abdulmoneim, and M. Al-Shabrawey. 2019. Bioactive lipids and pathological retinal angiogenesis: (PUFAs)-derived metabolites in proliferative retinopathies. *British Journal of Pharmacology* 176 (1):93–109. doi:10.1111/bph.14507.

Ersoy, L., T. Ristau, Y. T. Lechanteur, M. Hahn, C. B. Hoyng, B. Kirchhof, A. I. den Hollander, and S. Fauser. 2014. Nutritional risk factors for age-related macular degeneration. *BioMed Research International* 2014:413150. doi:10.1155/2014/413150.

Evangelho, K., M. Mogilevskaya, M. Losada-Barragan, and J. K. Vargas-Sanchez. 2019. Pathophysiology of primary open-angle glaucoma from a neuroinflammatory and neurotoxicity perspective: A review of the literature. *International Ophthalmology* 39 (1):259–71. doi:10.1007/s10792-017-0795-9.

Evans, M. D., M. Dizdaroglu, and M. S. Cooke. 2004. Oxidative DNA damage and disease: Induction, repair and significance. *Mutation Research* 567 (1):1–61. doi:10.1016/j.mrrev.2003.11.001.

Eynard, A. R., and G. Repossi. 2019. Role of ω3 polyunsaturated fatty acids in diabetic retinopathy: A morphological and metabolically cross talk among blood retina barriers damage, autoimmunity and chronic inflammation. *Lipids in Health and Disease* 18 (1):114. doi:10.1186/s12944-019-1049-9.

Faby, H., J. Hillenkamp, J. Roider, and A. Klettner. 2014. Hyperthermia-induced upregulation of vascular endothelial growth factor in retinal pigment epithelial cells is regulated by mitogen-activated protein kinases. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie* 252 (11):1737–45. doi:10.1007/s00417-014-2750-z.

FAO. 2016. *The state of world fisheries and aquaculture 2016. Contributing to food security and nutrition for all,* Rome, Italy. 200 pp.

FAO. 2018a. The state of world fisheries and aquaculture 2018 - *Meeting the sustainable development goals,* Rome, Italy.

FAO. 2018b. *The global status of seaweed production, trade and utilization*. Globefish Research Programme, vol. 124, Rome, Italy. 120 pp.

FAO. 2019. *The state of the world's aquatic genetic resources for food and agriculture*. FAO Commission on Genetic Resources for Food and Agriculture assessments, Rome, Italy.

Feenstra, D. J., E. Chepchumba Yego, and S. Mohr. 2013. Modes of retinal cell death in diabetic retinopathy. *Journal of Clinical & Experimental Ophthalmology* 04 (05). doi:10.4172/2155-9570.1000298.

Fernando, I. P., S. J.-W. Nah, and Y.-J. Jeon. 2016. Potential anti-inflammatory natural products from marine algae. *Environmental Toxicology and Pharmacology* 48:22–30. doi:10.1016/j.etap.2016.09.023.

Fernando, K. H. N., H.-W. Yang, Y. Jiang, Y.-J. Jeon, and BoMi Ryu. 2019. Ishige okamurae extract and its constituent ishophloroglucin a attenuated in vitro and in vivo high glucose-induced angiogenesis. *International Journal of Molecular Sciences* 20 (22):5542. doi:10.3390/ijms20225542.

Ferrara, N., K. Carver-Moore, H. Chen, M. Dowd, L. Lu, K. S. O'Shea, L. Powell-Braxton, K. J. Hillan, and M. W. Moore. 1996. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature* 380 (6573):439–42. doi:10.1038/380439a0.

Finger, R. P., E. Fenwick, M. Marella, M. Dirani, F. G. Holz, P. P.-C. Chiang, and E. L. Lamoureux. 2011. The impact of vision impairment on vision-specific quality of life in Germany. *Investigative Opthalmology & Visual Science* 52 (6):3613. doi:10.1167/iovs.10-7127.

Fisher, C. R., and D. A. Ferrington. 2018. Perspective on AMD pathobiology: A bioenergetic crisis in the RPE. *Investigative Ophthalmology & Visual Science* 59 (4):AMD41–7. doi:10.1167/iovs.18-24289.

Fitton, H., M. Stephen, B. Lyndon, M. Ann, R. Margaret, B. Don, and R. Shelley. 2016. Effects of fucoidan from fucus vesiculosus in reducing symptoms of osteoarthritis: A randomized placebo-controlled trial. *Biologics: Targets and therapy* 10:81-88. doi:10.2147/BTT.S95165.

Fitton, H. J., D. S. Stringer, A. Y. Park, and S. N. Karpiniec. 2019. Therapies from fucoidan: New developments. *Marine Drugs* 17 (10):571. doi:10.3390/md17100571.

Flaxman, S. R., R. R. A. Bourne, S. Resnikoff, P. Ackland, T. Braithwaite, M. V. Cicinelli, A. Das, J. B. Jonas, J. Keeffe, J. H. Kempen, et al. 2017. Global causes of blindness and distance vision impairment 1990–2020: A systematic review and meta-analysis. *The Lancet Global Health* 5 (12):e1221–34. doi:10.1016/S2214-109X(17)30393-5.

Food and Drug Administration. 2016. *GRAS notice (GRN) No.661 for Fucus vesiculosus* concentrate, College Park, MD, USA.

Ford, K. M., M. Saint-Geniez, T. Walshe, A. Zahr, and P. A. D'Amore. 2011. Expression and role of VEGF in the adult retinal pigment epithelium. *Investigative Ophthalmology & Visual Science* 52 (13):9478–87. doi:10.1167/iovs.11-8353.

Forrester, J. V., and H. Xu. 2012. Good news-bad news: The Yin and Yang of immune privilege in the eye. *Frontiers in Immunology.* 3:338. doi:10.3389/fimmu.2012.00338.

Forshaw, T. R. J., H. J. Ahmed, T. W. Kjaer, S. Andréasson, and T. L. Sørensen. 2020. Full-field electroretinography in age-related macular degeneration: An overall retinal response. *Acta Ophthalmologica* 98 (7):693–700. doi:10.1111/aos.14571.

Freire, M. O., and T. E. Van Dyke. 2013. Natural resolution of inflammation. *Periodontology 2000* 63 (1):149–64. doi:10.1111/prd.12034.

Frishman, L., and M. Wang. 2011. Electroretinogram of human, monkey and mouse. In *Adler's physiology of the eye*, ed. Leonard A. Levin, Paul L. Kaufman, and Francis Heed Adler, 11 ed., 480–501. Edinburgh: Saunders Elsevier.

Fu, Z., C. T. Chen, G. Cagnone, E. Heckel, Y. Sun, B. Cakir, Y. Tomita, S. Huang, Q. Li, W. Britton, et al. 2019. Dyslipidemia in retinal metabolic disorders. *EMBO Molecular Medicine* 11 (10). doi:10.15252/emmm.201910473.

Fulton, A. B., J. D. Akula, J. A. Mocko, R. M. Hansen, I. Y. Benador, S. C. Beck, E. Fahl, M. W. Seeliger, A. Moskowitz, and M. E. Harris. 2009. Retinal degenerative and hypoxic ischemic disease. *Documenta Ophthalmologica. Advances in Ophthalmology* 118 (1):55–61. doi:10.1007/s10633-008-9127-8.

Fulton, A. B., R. M. Hansen, and A. Moskowitz. 2008. The cone electroretinogram in retinopathy of prematurity. *Investigative Ophthalmology & Visual Science* 49 (2):814–9. doi:10.1167/iovs.07-1226.

Fulton, A. B., R. M. Hansen, A. Moskowitz, and A. M. Barnaby. 2005. Multifocal ERG in subjects with a history of retinopathy of prematurity. *Documenta Ophthalmologica. Advances in Ophthalmology* 111 (1):7–13. doi:10.1007/s10633-005-2621-3.

Fung, S.-Y., V. Sofiyev, J. Schneiderman, A. F. Hirschfeld, R. E. Victor, K. Woods, J. S. Piotrowski, R. Deshpande, S. C. Li, N. J. de Voogd, et al. 2014. Unbiased screening of marine sponge extracts for anti-inflammatory agents combined with chemical genomics identifies girolline as an inhibitor of protein synthesis. *ACS Chemical Biology* 9 (1):247–57. doi:10.1021/cb400740c.

Galluzzi, L., S. A. Aaronson, J. Abrams, E. S. Alnemri, D. W. Andrews, E. H. Baehrecke, N. G. Bazan, M. V. Blagosklonny, K. Blomgren, C. Borner, et al. 2009. Guidelines for the use and interpretation of assays for monitoring cell death in higher eukaryotes. *Cell Death and Differentiation* 16 (8):1093–107. doi:10.1038/cdd.2009.44.

Galluzzi, L., I. Vitale, S. A. Aaronson, J. M. Abrams, D. Adam, P. Agostinis, E. S. Alnemri, L. Altucci, I. Amelio, D. W. Andrews, et al. 2018. Molecular mechanisms of cell death: Recommendations of the nomenclature committee on cell death 2018. *Cell Death and Differentiation* 25 (3):486–541. doi:10.1038/s41418-017-0012-4.

Ganesan, P., K. Matsubara, T. Ohkubo, Y. Tanaka, K. Noda, T. Sugawara, and T. Hirata. 2010. Anti-angiogenic effect of siphonaxanthin from green alga, codium fragile. *Phytomedicine* 17 (14): 1140–4. doi:10.1016/j.phymed.2010.05.005.

Gauthier, A. C., and J. Liu. 2016. Neurodegeneration and neuroprotection in glaucoma. *The Yale Journal of Biology and Medicine* 89 (1): 73–9.

Georgiou, T., Y.-T. Wen, C.-H. Chang, P. Kolovos, M. Kalogerou, E. Prokopiou, A. Neokleous, C.-T. Huang, and R.-K. Tsai. 2017. Neuroprotective effects of omega-3 polyunsaturated fatty acids in a rat model of anterior ischemic optic neuropathy. *Investigative Opthalmology & Visual Science* 58 (3):1603–11. doi:10.1167/iovs.16-20979.

Gerth, C. 2009. The role of the ERG in the diagnosis and treatment of age-related macular degeneration. *Documenta Ophthalmologica. Advances in Ophthalmology* 118 (1):63–8. doi:10.1007/s10633-008-9133-x.

Ghaem Maralani, H., B. C. Tai, T. Y. Wong, E. Shyong Tai, J. Li, J. J. Wang, and P. Mitchell. 2015. Metabolic syndrome and risk of age-related macular degeneration. *Retina* 35 (3):459–66. doi:10.1097/IAE.0000000000000338.

Gharehbaghi, G., P. Mohagheghi, A. Sedaghat, H. Riazi-Esfahani, M. Mirghorbani, and N. Khosravi. 2020. Parenteral fish-oil lipid emulsions in retinopathy of prematurity: A retrospective comparative study. *Journal of Current Ophthalmology* 32 (1):69–74. doi:10.4103/JOCO.JOCO_23_20.

Giacco, F., and M. Brownlee. 2010. Oxidative stress and diabetic complications. *Circulation Research* 107 (9):1058–70. doi:10.1161/CIRCRESAHA.110.223545.

Giannaccare, G., M. Pellegrini, C. Senni, F. Bernabei, V. Scorcia, and A. F. G. Cicero. 2020. Clinical applications of astaxanthin in the treatment of ocular diseases: Emerging insights. *Marine Drugs* 18 (5):239. doi:10.3390/md18050239.

Glickman, R. D. 2002. Phototoxicity to the retina: Mechanisms of damage. *International Journal of Toxicology* 21 (6):473–90. doi:10.1080/10915810290169909.

González-Périz, A., R. Horrillo, N. Ferré, K. Gronert, B. Dong, E. Morán-Salvador, E. Titos, M. Martínez-Clemente, M. López-Parra, V. Arroyo, et al. 2009. Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: A role for resolvins and protectins . *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology* 23 (6): 1946–57. doi:10.1096/fj.08-125674.

Gopinath, B., G. Liew, J. Russell, V. Cosatto, G. Burlutsky, and P. Mitchell. 2017. Intake of key micronutrients and food groups in patients with late-stage age-related macular degeneration compared with age-sex-matched controls. *British Journal of Ophthalmology* 101 (8):1027–31. doi:10.1136/bjophthalmol-2016-309490.

Gorusupudi, A. F.-Y., Chang, K. Nelson, G. S. Hageman, and P. S. Bernstein. 2019. N-3 PUFA supplementation alters retinal very-long-chain-PUFA levels and ratios in diabetic animal models. *Molecular Nutrition & Food Research* 63 (15):1801058. doi:10.1002/mnfr.201801058.

Gotteland, M., K. Riveros, N. Gasaly, C. Carcamo, F. Magne, G. Liabeuf, A. Beattie, and S. Rosenfeld. 2020. The pros and cons of using algal polysaccharides as prebiotics. *Frontiers in Nutrition* 7: 163. doi:10.3389/fnut.2020.00163.

Guillonneau, X., C. M. Eandi, M. Paques, J. A. Sahel, P. Sapieha, and F. Sennlaub. 2017. On phagocytes and macular degeneration. *Progress in Retinal and Eye Research* 61:98–128. doi:10.1016/j.preteyeres.2017.06.002.

Guiry, M. D. 2012. How many species of algae are there? *Journal of Phycology* 48 (5):1057–63. doi:10.1111/j.1529-8817.2012.01222.x.

Gürbüz Yurtseven, Ö., S. Aksoy, A. Karatay Arsan, Y. Buyru Özkurt, and H. K. Kökçen. 2018. Evaluation of the relationship between age-related macular degeneration and refractive error, socio-demographic features, and biochemical variables in a Turkish population. *Turkish Journal of Ophthalmology* 48 (5):238–44. doi:10.4274/tjo.97254.

Hammer, S. S., and J. V. Busik. 2017. The role of dyslipidemia in diabetic retinopathy. *Vision Research* 139:228–36. doi:10.1016/j.visres.2017.04.010.

Hammes, H. P., A. Weiss, D. Führer, H. J. Krämer, C. Papavassilis, and F. Grimminger. 1996. Acceleration of experimental diabetic retinopathy in the rat by omega-3 fatty acids. *Diabetologia* 39 (3): 251–5. doi:10.1007/BF00418338.

Handa, J. T. 2012. How does the macula protect itself from oxidative stress? *Molecular Aspects of Medicine* 33 (4):418–35. doi:10.1016/j.mam.2012.03.006.

Handeland, K., S. Skotheim, V. Baste, I. E. Graff, L. Frøyland, Ø. Lie, M. Kjellevold, M. W. Markhus, K. M. Stormark, J. Øyen, et al. 2018. The effects of fatty fish intake on adolescents' nutritional status and associations with attention performance: Results from the FINS-TEENS randomized controlled trial. *Nutrition Journal* 17 (1):30. doi:10.1186/s12937-018-0328-z.

Hanus, J., C. Anderson, and S. Wang. 2015. RPE necroptosis in response to oxidative stress and in AMD. *Ageing Research Reviews* 24:286–98. doi:10.1016/j.arr.2015.09.002.

Hartnett, M. E., and R. H. Lane. 2013. Effects of oxygen on the development and severity of retinopathy of prematurity. *Journal of AAPOS: The Official Publication of the American Association for Pediatric Ophthalmology and Strabismus* 17 (3):229–34. doi:10.1016/j.jaapos.2012.12.155.

Hawkins, C. L., and M. J. Davies. 2019. Detection, identification, and quantification of oxidative protein modifications. *The Journal of Biological Chemistry* 294 (51):19683–708. doi:10.1074/jbc.REV119.006217.

Hayes, J. D., and R. C. Strange. 1995. Invited commentary potential contribution of the glutathione S-transferase supergene family to resistance to oxidative stress. *Free Radical Research* 22 (3):193–207. doi:10.3109/10715769509147539.

Heesterbeek, T. J., L. Lorés-Motta, C. B. Hoyng, Y. T. E. Lechanteur, and A. I. den Hollander. 2020. Risk factors for progression of age-related macular degeneration. *Ophthalmic & Physiological Optics: The Journal of the British College of Ophthalmic Opticians (Optometrists)* 40 (2):140–70. doi:10.1111/opo.12675.

Hellmann, J., Y. Tang, M. Kosuri, A. Bhatnagar, and M. Spite. 2011. Resolvin D1 decreases adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology* 25 (7):2399–407. doi:10.1096/fj.10-178657.

Hellström, A., L. E. Smith, and O. Dammann. 2013. Retinopathy of prematurity. *The Lancet* 382 (9902):1445–57. doi:10.1016/S0140-6736(13)60178-6.

Higgins, J. P. T., and S. Green. 2011. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration. www.handbook.cochrane.org.

Hoffman, D. R., D. K. Hughbanks-Wheaton, N. S. Pearson, G. E. Fish, R. Spencer, A. Takacs, M. Klein, K. G. Locke, and D. G. Birch. 2014. Four-year placebo-controlled trial of docosahexaenoic acid in X-linked retinitis pigmentosa (DHAX Trial): A randomized clinical trial. *JAMA Ophthalmology* 132 (7):866–73. doi:10.1001/jamaophthalmol.2014.1634.

Hoffman, D. R., D. K. Hughbanks-Wheaton, R. Spencer, G. E. Fish, N. S. Pearson, Y.-Z. Wang, M. Klein, A. Takacs, K. G. Locke, and D. G. Birch. 2015. Docosahexaenoic acid slows visual field progression in X-linked retinitis pigmentosa: Ancillary outcomes of the DHAX trial. *Investigative Opthalmology & Visual Science* 56 (11): 6646–53. doi:10.1167/iovs.15-17786.

Hoffman, D. R., K. G. Locke, D. H. Wheaton, G. E. Fish, R. Spencer, and D. G. Birch. 2004. A randomized, placebo-controlled clinical trial of docosahexaenoic acid supplementation for X-linked retinitis pigmentosa. *American Journal of Ophthalmology* 137 (4):704–18. doi:10.1016/j.ajo.2003.10.045.

Hoffman, D. R., R. Uauy, and D. G. Birch. 1995. Metabolism of omega-3 fatty acids in patients with autosomal dominant retinitis pigmentosa. *Experimental Eye Research* 60 (3):279–89. doi:10.1016/S0014-4835(05)80110-1.

Hollingsworth, T. J., and A. K. Gross. 2020. Innate and autoimmunity in the pathogenesis of inherited retinal dystrophy. *Cells* 9 (3):630. doi:10.3390/cells9030630.

Hong, S.-W., H.-S. Lee, K. H. Jung, H. Lee, and S.-S. Hong. 2012. Protective effect of fucoidan against acetaminophen-induced liver injury. *Archives of Pharmacal Research* 35 (6):1099–105. doi:10.1007/s12272-012-0618-5.

Hosseini, S. F., M. Rezaei, and D. J. McClements. 2020. Bioactive functional ingredients from aquatic origin: A review of recent progress in marine-derived nutraceuticals. *Critical Reviews in Food Science and Nutrition*. doi:10.1080/10408398.2020.1839855.

Hu, Y., F. B. Hu, and J. E. Manson. 2019. Marine omega-3 supplementation and cardiovascular disease: An updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. *Journal of the American Heart Association* 8 (19):e013543. doi:10.1161/JAHA.119.013543.

Huang, F., J. Wang, F. Yu, Y. Tang, G. Ding, Z. Yang, and Y. Sun. 2018. Protective effect of meretrix meretrix oligopeptides on high-fat-diet-induced non-alcoholic fatty liver disease in mice. *Marine Drugs* 16 (2):39. doi:10.3390/md16020039.

Huang, J., Y. Tang, T. Zhu, Y. Li, H. Chun, Y. Qu, and D. Mu. 2019. Cumulative evidence for association of sepsis and retinopathy of prematurity. *Medicine* 98 (42):e17512. doi:10.1097/MD.0000000000017512.

Huang, T.-L., Y.-T. Wen, Y.-C. Ho, J.-K. Wang, K.-H. Lin, and R.-K. Tsai. 2020. Algae oil treatment protects retinal ganglion cells (RGCs) via ERK signaling pathway in experimental optic nerve ischemia. *Marine Drugs* 18 (2):83. doi:10.3390/md18020083.

Hughbanks-Wheaton, D. K., David, G. Birch, G. E. Fish, R. Spencer, N. S. Pearson, A. Takacs, and D. R. Hoffman. 2014. Safety assessment of docosahexaenoic acid in X-linked retinitis pigmentosa: The 4-year DHAX trial. *Investigative Opthalmology & Visual Science* 55 (8):4958–66. doi:10.1167/iovs.14-14437.

Hybertson, B. M., Bifeng, G. Swapan, K. Bose, and J. M. McCord. 2011. Oxidative stress in health and disease: The therapeutic potential of Nrf2 activation. *Molecular Aspects of Medicine* 32 (4–6):234–46. doi:10.1016/j.mam.2011.10.006.

Ikeda, Y., Y. Yonemitsu, M. Onimaru, T. Nakano, M. Miyazaki, R. Kohno, K. Nakagawa, A. Ueno, K. Sueishi, and T. Ishibashi. 2006. The regulation of vascular endothelial growth factors (VEGF-A, -C, and -D) expression in the retinal pigment epithelium. *Experimental Eye Research*. 83 (5):1031–40. doi:10.1016/j.exer.2006.05.007.

Jarrett Stuart, G., and M. E. Boulton. 2012. Consequences of oxidative stress in age-related macular degeneration. *Molecular Aspects of Medicine* 33 (4):399–417. doi:10.1016/j.mam.2012.03.009.

Javitt, J. C., Z. Zhou, and R. J. Willke. 2007. Association between vision loss and higher medical care costs in medicare beneficiaries. *Ophthalmology* 114 (2):238–45. e1. doi:10.1016/j.ophtha.2006.07.054.

Jia, L., X. L. Shen, R. Fan, Y. Sun, X. Y. Pan, H. M. Yanh, and L. Liu. 2011. Risk factors for age-related macular degeneration in elderly Chinese population in Shenyang of China. *Biomedical and Environmental Sciences: BES* 24 (5):506–11. doi:10.3967/0895-3988.2011.05.008.

Jiang, J., K. Li, F. Wang, B. Yang, Y. Fu, J. Zheng, and D. Li. 2016. Effect of marine-derived n-3 polyunsaturated fatty acids on major eicosanoids: A systematic review and meta-analysis from 18 randomized controlled trials. *PLoS One* 11 (1): e0147351. doi:10.1371/journal.pone.0147351.

Jiang, L. Q., J. W. Streilein, and C. McKinney. 1994. Immune privilege in the eye: An evolutionary adaptation. *Developmental & Comparative Immunology* 18 (5):421–31. doi:10.1016/0145-305X(94)90007-8.

Jing, H., J. Yao, X. Liu, H. Fan, F. Zhang, Z. Li, X. Tian, and Y. Zhou. 2014. Fish-oil emulsion (omega-3 polyunsaturated fatty acids) attenuates acute lung injury induced by intestinal ischemia–reperfusion through adenosine 5′-monophosphate-activated protein kinase–sirtuin1 pathway. *Journal of Surgical Research* 187 (1):252–61. doi:10.1016/j.jss.2013.10.009.

Joachim, N., A. Kifley, J. M. Colijn, K. E. Lee, G. H. S. Buitendijk, B. E. K. Klein, C. Myers, S. M. Meuer, A. G. Tan, V. Flood, et al. 2018. Joint contribution of genetic susceptibility and modifiable factors to the progression of age-related macular degeneration over 10 years: The three continent AMD consortium report. *Ophthalmology Retina* 2 (7):684–93. doi:10.1016/j.oret.2017.10.019.

Joachim, N., P. Mitchell, G. Burlutsky, A. Kifley, and J. J. Wang. 2015. The incidence and progression of age-related macular degeneration over 15 years: The blue mountains eye study. *Ophthalmology* 122 (12):2482–9. doi:10.1016/j.ophtha.2015.08.002.

Joyal, J.-S., Y. Sun, M. L. Gantner, Z. Shao, L. P. Evans, N. Saba, T. Fredrick, S. Burnim, J. S. Kim, G. Patel, et al. 2016. Retinal lipid and glucose metabolism dictates angiogenesis through the lipid sensor Ffar1. *Nature Medicine* 22 (4):439–45. doi:10.1038/nm.4059.

Juárez-Portilla, C., T. Olivares-Bañuelos, T. Molina-Jiménez, J. A. Sánchez-Salcedo, D. I. D. Moral, T. Meza-Menchaca, M. Flores-Muñoz, Ó. López-Franco, G. Roldán-Roldán, A. Ortega, et al. 2019. Seaweeds-derived compounds modulating effects on signal transduction pathways: A systematic review. *Phytomedicine* 63:153016. doi:10.1016/j.phymed.2019.153016.

Kaas, J. H. 2008. The evolution of the complex sensory and motor systems of the human brain. *Brain Research Bulletin* 75 (2–4):384–90. doi:10.1016/j.brainresbull.2007.10.009.

Kamath, B. S., B. M. Srikanta, S. M. Dharmesh, R. Sarada, and G. A. Ravishankar. 2008. Ulcer preventive and antioxidative properties of astaxanthin from haematococcus pluvialis. *European Journal of Pharmacology* 590 (1–3):387–95. doi:10.1016/j.ejphar.2008.06.042.

Kan, J., J. Cheng, L. Xu, M. Hood, D. Zhong, M. Cheng, Y. Liu, L. Chen, and J. Du. 2020. The combination of wheat peptides and fucoidan protects against chronic superficial gastritis and alters gut microbiota: A double-blinded, placebo-controlled study. *European Journal of Nutrition* 59 (4):1655–66. doi:10.1007/s00394-019-02020-6.

Kang, K. T., and Y. C. Kim. 2019. Dietary patterns and age-related macular degeneration in Korea: The Korea National Health and Nutrition Examination Survey 2010-2011. *Scientific Reports* 9 (1):8200. doi:10.1038/s41598-019-44632-2.

Kapoor, V., M. N. Malviya, and R. Soll. 2019. Lipid emulsions for parenterally fed preterm infants. *The Cochrane Database of Systematic Reviews* 6:CD013163. doi:10.1002/14651858.CD013163.pub2.

Kaur, C., V. Sivakumar, R. Robinson, W. S. Foulds, C. D. Luu, and E.-A. Ling. 2013. Neuroprotective effect of melatonin against hypoxia-induced retinal ganglion cell death in neonatal rats. *Journal of Pineal Research* 54 (2):190–206. doi:10.1111/jpi.12016.

Kaushik, S., J. J. Wang, V. Flood, G. Liew, W. Smith, and P. Mitchell. 2008. Frequency of fish consumption, retinal microvascular signs and vascular mortality. *Microcirculation* 15 (1):27–36. doi:10.1080/10739680701411080.

Keel, S., C. Itsiopoulos, K. Koklanis, M. Vukicevic, F. Cameron, H. Gilbertson, and L. Brazionis. 2016. Dietary patterns and retinal vascular calibre in children and adolescents with type 1 diabetes. *Acta Ophthalmologica* 94 (5):e345–52. doi:10.1111/aos.12941.

Keenan, T. D., Agrón, E. J. Mares, T. E. Clemons, F. van Asten, A. Swaroop, E. Y. Chew, and Age-Related Eye Disease Studies (AREDS) 1 and 2 Research Groups. 2020. Adherence to the mediterranean diet and progression to late age-related macular degeneration in the age-related eye disease studies 1 and 2. *Ophthalmology* 127 (11):1515–28. doi:10.1016/j.ophtha.2020.04.030.

Kern, T. S., and B. A. Berkowitz. 2015. Photoreceptors in diabetic retinopathy. *Journal of Diabetes Investigation* 6 (4):371–80. doi:10.1111/jdi.12312.

Kerr, J. F. R., A. H. Wyllie, and A. R. Currie. 1972. Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer* 26 (4):239–57. doi:10.1038/bjc.1972.33.

Khotimchenko, M., V. Tiasto, A. Kalitnik, M. Begun, R. Khotimchenko, E. Leonteva, I. Bryukhovetskiy, and Y. Khotimchenko. 2020. Antitumor potential of carrageenans from

marine red algae. *Carbohydrate Polymers* 246:116568. doi:10.1016/j.carbpol.2020.116568.

Kim, C. Y., E. Jung, E. N. Kim, C. J. Kim, J. Y. Lee, J. H. Hwang, W. S. Song, B. S. Lee, E. A. Kim, and K. S. Kim. 2018. Chronic placental inflammation as a risk factor of severe retinopathy of prematurity. *Journal of Pathology and Translational Medicine* 52 (5):290–7. doi:10.4132/jptm.2018.07.09.

Kim, K.-A., S. M. Kim, S. W. Kang, S. I. Jeon, B. H. Um, and S. H. Jung. 2012. Edible seaweed, eisenia bicyclis, protects retinal ganglion cells death caused by oxidative stress. *Marine Biotechnology (New York, N.Y.)* 14 (4):383–95. doi:10.1007/s10126-012-9459-y.

Kim, K.-N., S.-J. Heo, W.-J. Yoon, S.-M. Kang, G. Ahn, T.-H. Yi, and Y.-J. Jeon. 2010. Fucoxanthin inhibits the inflammatory response by suppressing the activation of NF-KB and MAPKs in lipopolysaccharide-induced RAW 264.7 macrophages. *European Journal of Pharmacology* 649 (1–3):369–75. doi:10.1016/j.ejphar.2010.09.032.

Klein, R. J., C. Zeiss, E. Y. Chew, J. Y. Tsai, R. S. Sackler, C. Haynes, A. K. Henning, J. P. SanGiovanni, S. M. Mane, S. T. Mayne, et al. 2005. Complement factor H polymorphism in age-related macular degeneration. *Science* 308 (5720):385–9. doi:10.1126/science.1109557.

Klettner, A. 2012. Oxidative stress induced cellular signaling in RPE cells. *Frontiers in Bioscience* S4 (2):392–411. doi:10.2741/275.

Klettner, A. 2013. Physiological functions of VEGF in the retina and its possible implications for prolonged anti-VEGF therapy. In *Vascular endothelial growth factor (VEGF): Biology, regulation and clinical significance*, ed. Marcellus L. Parker, 117–36. New York: Nova Biomedical.

Klettner, A. 2015a. The retinal pigment epithelium in the immune regulation of the retina. In *Recent advances in eye research*, ed. Adelle Hogarth, 31–52. New York: Nova Science Publishers.

Klettner, A. 2015b. Age-related macular degeneration - Biology and treatment. *Medizinische Monatsschrift Fur Pharmazeuten* 38 (7):258–64.

Klettner, A., A. Kauppinen, J. Blasiak, J. Roider, A. Salminen, and K. Kaarniranta. 2013. Cellular and molecular mechanisms of age-related macular degeneration: From impaired autophagy to neovascularization. *The International Journal of Biochemistry & Cell Biology* 45 (7):1457–67. doi:10.1016/j.biocel.2013.04.013.

Klettner, A., S. Koinzer, T. Meyer, and J. Roider. 2013. Toll-like receptor 3 activation in retinal pigment epithelium cells - mitogen-activated protein kinase pathways of cell death and vascular endothelial growth factor secretion. *Acta Ophthalmologica* 91 (3):e211–e218. doi:10.1111/aos.12031.

Klettner, A., and J. Roider. 2009. Constitutive and oxidative-stress-induced expression of VEGF in the RPE are differently regulated by different mitogen-activated protein kinases. *Graefe's Archive for Clinical and Experimental Ophthalmology* 247 (11):1487–92. doi:10.1007/s00417-009-1139-x.

Klettner, A., and J. Roider. 2012. Mechanisms of pathological VEGF production in the retina and modification with VEGF-antagonists. In *Studies on retinal and choroidal disorders. Oxidative stress in applied basic research and clinical practice*. New York: Humana Press.

Klettner, A. K., and G. Lingelbach, eds. 2018. *Blindheit in der gesellschaft: Historischer wandel und interdisziplinäre zugänge*. In *Disability history, Band 6*. Frankfurt New York: Campus Verlag.

Knauer, C., and N. Pfeiffer. 2008. The value of vision. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie* 246 (4):477–82. doi:10.1007/s00417-007-0668-4.

Kotoku, N., M. Arai, and M. Kobayashi. 2016. Search for anti-angiogenic substances from natural sources. *Chemical & Pharmaceutical Bulletin* 64 (2):128–34. doi:10.1248/cpb.c15-00744.

Kowluru, R. A., and M. Mishra. 2017. Epigenetic regulation of redox signaling in diabetic retinopathy: Role of Nrf2. *Free Radical Biology & Medicine* 103:155–64. doi:10.1016/j.freeradbiomed.2016.12.030.

Kraan, S. 2012. Algal polysaccharides, novel applications and outlook. In *Carbohydrates - Comprehensive studies on glycobiology and glycotechnology*, ed. Chuan-Fa Chang. InTech. London, UK. doi:10.5772/51572.

Krause-Jensen, D., and C. M. Duarte. 2016. Substantial role of macroalgae in marine carbon sequestration. *Nature Geoscience* 9 (10):737–42. doi:10.1038/ngeo2790.

Križaj, D., D. A. Ryskamp, N. Tian, G. Tezel, C. H. Mitchell, V. Z. Slepak, and V. I. Shestopalov. 2014. From mechanosensitivity to inflammatory responses: New players in the pathology of glaucoma. *Current Eye Research* 39 (2):105–19. doi:10.3109/02713683.2013.836541.

Kroemer, G., L. Galluzzi, P. Vandenabeele, J. Abrams, E. S. Alnemri, E. H. Baehrecke, M. V. Blagosklonny, W. S. El-Deiry, P. Golstein, D. R. Green, et al. 2009. Classification of cell death: Recommendations of the nomenclature committee on cell death 2009. *Cell Death and Differentiation* 16 (1):3–11. doi:10.1038/cdd.2008.150.

Kuznetsova, T. A., L. A. Ivanushko, E. V. Persiyanova, S. P. Ermakova, and N. N. Besednova. 2019. Markers of systemic inflammation in experimental dyslipidemia induced by P-407: Modulation with fucoidan from brown alga fucus evanescens. *Bulletin of Experimental Biology and Medicine* 166 (6):766–9. doi:10.1007/s10517-019-04436-w.

Kwak, N., N. Okamoto, J. M. Wood, and P. A. Campochiaro. 2000. VEGF is major stimulator in model of choroidal neovascularization. *Investigative Ophthalmology & Visual Science* 41 (10):3158–64

Lafarga, T., F. G. Acién-Fernández, and M. Garcia-Vaquero. 2020. Bioactive peptides and carbohydrates from seaweed for food applications: Natural occurrence, isolation, purification, and identification. *Algal Research* 48:101909. doi:10.1016/j.algal.2020.101909.

Landrigan, P. J., J. J. Stegeman, L. E. Fleming, D. Allemand, D. M. Anderson, L. C. Backer, F. Brucker-Davis, N. Chevalier, L. Corra, D. Czerucka, et al. 2020. Human health and ocean pollution. *Annals of Global Health* 86 (1):151. doi:10.5334/aogh.2831.

Laubertová, L., K. Koňariková, H. Gbelcová, Z. Ďuračková, J. Muchová, I. Garaiova, and I. Žitňanová. 2017. Fish oil emulsion supplementation might improve quality of life of diabetic patients due to its antioxidant and anti-inflammatory properties. *Nutrition Research (New York, N.Y.)* 46:49–58. doi:10.1016/j.nutres.2017.07.012.

Lauritano, C., and A. Ianora. 2016. Marine organisms with anti-diabetes properties. *Marine Drugs* 14 (12):220. doi:10.3390/md14120220.

Leal, E. C., A. Manivannan, K.-I. Hosoya, T. Terasaki, J'. Cunha-Vaz, Án F. AmbróSio, and J. V. Forrester. 2007. Inducible nitric oxide synthase isoform is a key mediator of leukostasis and blood-retinal barrier breakdown in diabetic retinopathy. *Investigative Opthalmology & Visual Science* 48 (11):5257. doi:10.1167/iovs.07-0112.

Lee, J., and O. Dammann. 2012. Perinatal infection, inflammation, and retinopathy of prematurity. *Seminars in Fetal and Neonatal Medicine* 17 (1):26–9. doi:10.1016/j.siny.2011.08.007.

Leslie, M. A., D. J. A. Cohen, D. M. Liddle, L. E. Robinson, and D. W. L. Ma. 2015. A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. *Lipids in Health and Disease* 14 (1):53. doi:10.1186/s12944-015-0049-7.

Léveillard, T., N. Philp, and F. Sennlaub. 2019. Is retinal metabolic dysfunction at the center of the pathogenesis of age-related macular degeneration? *International Journal of Molecular Sciences* 20 (3):762. doi:10.3390/ijms20030762.

Lew, D. S., F. Mazzoni, and S. C. Finnemann. 2020. Microglia inhibition delays retinal degeneration due to MerTK phagocytosis receptor deficiency. *Frontiers in Immunology* 11:1463. doi:10.3389/fimmu.2020.01463.

Li, N., X. Shen, Y. Liu, J. Zhang, Y. He, Q. Liu, D. Jiang, J. Zong, J. Li, D. Hou, et al. 2016. Isolation, characterization, and radiation protection of *Sipunculus nudus* L. polysaccharide. *International Journal of Biological Macromolecules* 83:288–96. doi:10.1016/j.ijbiomac.2015.11.071.

Li, X., H. Zhao, Q. Wang, H. Liang, and X. Jiang. 2015. Fucoidan protects ARPE-19 cells from oxidative stress via normalization of reactive oxygen species generation through the Ca^{2+}-dependent ERK

signaling pathway. *Molecular Medicine Reports* 11 (5):3746–52. doi:10.3892/mmr.2015.3224.

Liddle, D. M., J. M. Monk, A. L. Hutchinson, D. W. L. Ma, and L. E. Robinson. 2020. CD8+ T cell/adipocyte inflammatory cross talk and ensuing M1 macrophage polarization are reduced by fish-oil-derived n-3 polyunsaturated fatty acids, in part by a TNF-α-dependent mechanism. *The Journal of Nutritional Biochemistry* 76:108243. doi:10.1016/j.jnutbio.2019.108243.

Liguori, I., G. Russo, F. Curcio, G. Bulli, L. Aran, D. Della-Morte, G. Gargiulo, G. Testa, F. Cacciatore, D. Bonaduce, et al. 2018. Oxidative stress, aging, and diseases. *Clinical Interventions in Aging* 13:757–72. doi:10.2147/CIA.S158513.

Liu, H., J. Tang, Y. Du, A. Saadane, I. Samuels, A. Veenstra, J. Z. Kiser, K. Palczewski, and T. S. Kern. 2019. Transducin1, phototransduction and the development of early diabetic retinopathy. *Investigative Ophthalmology & Visual Science* 60 (5):1538–46. doi:10.1167/iovs.18-26433.

Liu, Y., M. Liu, X. Zhang, Q. Chen, H. Chen, L. Sun, and G. Liu. 2016. Protective effect of fucoxanthin isolated from laminaria japonica against visible light-induced retinal damage both in vitro and in vivo. *Journal of Agricultural and Food Chemistry* 64 (2):416–24. doi:10.1021/acs.jafc.5b05436.

López-Contreras, A. K., M. G. Martínez-Ruiz, C. Olvera-Montaño, R. R. Robles-Rivera, D. E. Arévalo-Simental, J. A. Castellanos-González, A. Hernández-Chávez, S. G. Huerta-Olvera, E. G. Cardona-Muñoz, and A. D. Rodríguez-Carrizalez. 2020. Importance of the use of oxidative stress biomarkers and inflammatory profile in aqueous and vitreous humor in diabetic retinopathy. *Antioxidants* 9 (9):891. doi:10.3390/antiox9090891.

Lorbeer, A. J., R. Tham, and W. Zhang. 2013. Potential products from the highly diverse and endemic macroalgae of Southern Australia and pathways for their sustainable production. *Journal of Applied Phycology* 25 (3):717–32. doi:10.1007/s10811-013-0003-x.

Lu, Z., V. Lin, A. May, B. Che, X. Xiao, D. H. Shaw, F. Su, Z. Wang, H. Du, and P. X. Shaw. 2019. HTRA1 synergizes with oxidized phospholipids in promoting inflammation and macrophage infiltration essential for ocular VEGF expression. *PLoS One* 14 (5): e0216808. doi:10.1371/journal.pone.0216808.

Marinval, N., P. Saboural, O. Haddad, M. Maire, K. Bassand, F. Geinguenaud, N. Djaker, K. Ben Akrout, M. Lamy de la Chapelle, R. Robert, et al. 2016. Identification of a pro-angiogenic potential and cellular uptake mechanism of a LMW highly sulfated fraction of fucoidan from *Ascophyllum nodosum*. *Marine Drugs* 14 (10):185. doi:10.3390/md14100185.

Martínez-Fernández de la Cámara, C., D. Salom, M. D. Sequedo, D. Hervás, C. Marín-Lambíes, E. Aller, T. Jaijo, M. Díaz-Llopis, J. M. Millán, and R. Rodrigo. 2013. Altered antioxidant-oxidant status in the aqueous humor and peripheral blood of patients with retinitis pigmentosa. *PLoS One.* 8 (9):e74223. doi:10.1371/journal.pone.0074223.

Masella, R., R., Di Benedetto, R. Varì, C. Filesi, and C. Giovannini. 2005. Novel mechanisms of natural antioxidant compounds in biological systems: Involvement of glutathione and glutathione-related enzymes. *The Journal of Nutritional Biochemistry* 16 (10):577–86. doi:10.1016/j.jnutbio.2005.05.013.

Masmeijer, C., K. van Leenen, L. De Cremer, P. Deprez, E. Cox, B. Devriendt, and B. Pardon. 2020. Effects of omega-3 fatty acids on immune, health and growth variables in veal calves. *Preventive Veterinary Medicine* 179:104979. doi:10.1016/j.prevetmed.2020.104979.

Mayer, A. M. S., A. J. Guerrero, A. D. Rodríguez, O. Taglialatela-Scafati, F. Nakamura, and N. Fusetani. 2019. Marine pharmacology in 2014–2015: Marine compounds with antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, antiviral, and anthelmintic activities; affecting the immune and nervous systems, and other miscellaneous mechanisms of action. *Marine Drugs* 18 (1):5. doi:10.3390/md18010005.

McCarter, R. V., C. E. Neville, G. Silvestri, S. Montgomery, E. Moore, V. Silvestri, C. R. Cardwell, R. E. Hogg, J. V. Woodside, and G. J. McKay. 2018. Dietary patterns were not associated with age-related macular degeneration: A cross-sectional analysis in the Irish Nun Eye study. *Irish Journal of Medical Science*. doi:10.1007/s11845-018-1932-9.

McMurtrey, J. J., and M. O. M. Tso. 2018. A review of the immunologic findings observed in retinitis pigmentosa. *Survey of Ophthalmology* 63 (6):769–81. doi:10.1016/j.survophthal.2018.03.002.

Mecocci, P., G. Fanó, S. Fulle, U. MacGarvey, L. Shinobu, M. C. Polidori, A. Cherubini, J. Vecchiet, U. Senin, and M. F. Beal. 1999. Age-dependent increases in oxidative damage to DNA, lipids, and proteins in human skeletal muscle. *Free Radical Biology and Medicine* 26 (3–4):303–8. doi:10.1016/S0891-5849(98)00208-1.

Medzhitov, R. 2008. Origin and physiological roles of inflammation. *Nature* 454 (7203):428–35. doi:10.1038/nature07201.

Méresse, S., M. Fodil, F. Fleury, and B. Chénais. 2020. Fucoxanthin, a marine-derived carotenoid from brown seaweeds and microalgae: A promising bioactive compound for cancer therapy. *International Journal of Molecular Sciences* 21 (23):9273. doi:10.3390/ijms21239273.

Merle, B. M. J., P. Benlian, N. Puche, A. Bassols, C. Delcourt, and E. H. Souied, and Nutritional AMD Treatment 2 Study Group. 2014. Circulating omega-3 fatty acids and neovascular age-related macular degeneration. *Investigative Opthalmology & Visual Science* 55 (3):2010–9. doi:10.1167/iovs.14-13916.

Merle, B. M. J., J. M. Colijn, A. Cougnard-Grégoire, A. P. M. de Koning-Backus, M.-N. Delyfer, J. C. Kiefte-de Jong, M. Meester-Smoor, C. Féart, T. Verzijden, C. Samieri, et al. 2019. Mediterranean diet and incidence of advanced age-related macular degeneration: The EYE-RISK Consortium. *Ophthalmology* 126 (3):381–90. doi:10.1016/j.ophtha.2018.08.006.

Merle, B. M. J., M.-N. Delyfer, J.-F. Korobelnik, M.-B. Rougier, F. Malet, C. Féart, M. Le Goff, E. Peuchant, L. Letenneur, J.-F. Dartigues, et al. 2013. High concentrations of plasma n3 fatty acids are associated with decreased risk for late age-related macular degeneration. *The Journal of Nutrition* 143 (4):505–11. doi:10.3945/jn.112.171033.

Merle, B. M. J., F. Richard, P. Benlian, N. Puche, C. Delcourt, and E. H. Souied. 2015. CFH Y402H and ARMS2 A69S polymorphisms and oral supplementation with docosahexaenoic acid in neovascular age-related macular degeneration patients: The NAT2 study. *PLoS One* 10 (7):e0130816. doi:10.1371/journal.pone.0130816.

Merle, B. M. J., B. Rosner, and J. M. Seddon. 2020. Genetic susceptibility, diet quality, and two-step progression in drusen size. *Investigative Opthalmology & Visual Science* 61 (5):17. doi:10.1167/iovs.61.5.17.

Merle, B. M. J., R. E. Silver, B. Rosner, and J. M. Seddon. 2015. Adherence to a mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: A prospective cohort study. *The American Journal of Clinical Nutrition* 102 (5):1196–206. doi:10.3945/ajcn.115.111047.

Mesquida, M., F. Drawnel, and S. Fauser. 2019. The role of inflammation in diabetic eye disease. *Seminars in Immunopathology* 41 (4): 427–45. doi:10.1007/s00281-019-00750-7.

Milam, A. H., Z.-Y. Li, and R. N. Fariss. 1998. Histopathology of the human retina in retinitis pigmentosa. *Progress in Retinal and Eye Research* 17 (2):175–205. doi:10.1016/S1350-9462(97)00012-8.

Miles, E. A., and P. C. Calder. 2012. Influence of marine *n* -3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. *British Journal of Nutrition* 107 (S2):S171–S84. doi:10.1017/S0007114512001560.

Miller, J. W. 2016. Beyond VEGF-the Weisenfeld lecture. *Investigative Ophthalmology & Visual Science* 57 (15):6911–8. doi:10.1167/iovs.16-21201.

Miller, J. W., J. Le Couter, E. C. Strauss, and N. Ferrara. 2013. Vascular endothelial growth factor A in intraocular vascular disease. *Ophthalmology* 120 (1):106–14. doi:10.1016/j.ophtha.2012.07.038.

Miyata, M., A. Oishi, M. Oishi, T. Hasegawa, H. O. Ikeda, and A. Tsujikawa. 2018. Long-term efficacy and safety of anti-VEGF therapy in retinitis pigmentosa: A case report. *BMC Ophthalmology* 18 (1):248. doi:10.1186/s12886-018-0914-z.

Mohamed, S., J. C. Murray, J. M. Dagle, and T. Colaizy. 2013. Hyperglycemia as a risk factor for the development of retinopathy of prematurity. *BMC Pediatrics* 13 (1):78. doi:10.1186/1471-2431-13-78.

Moher, D., Liberati, A. J. Tetzlaff, D. G. Altman, and The PRISMA Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine* 6 (7): e1000097. doi:10.1371/journal.pmed.1000097.

Mohsen, L., M. Abou-Alam, M. El-Dib, M. Labib, M. Elsada, and H. Aly. 2014. A prospective study on hyperglycemia and retinopathy of prematurity. *Journal of Perinatology* 34 (6):453–7. doi:10.1038/jp.2014.49.

Montgomery, M. P., F. Kamel, M. A. Pericak-Vance, J. L. Haines, E. A. Postel, A. Agarwal, M. Richards, W. K. Scott, and S. Schmidt. 2010. Overall diet quality and age-related macular degeneration. *Ophthalmic Epidemiology* 17 (1):58–65. doi:10.3109/09286580903450353.

Montoya Delgado, M. J., G. Ríos Nequis, and A. Ramírez Estudillo. 2019. Choroidal neovascular membrane associated with unilateral retinitis pigmentosa. *Archivos De La Sociedad Espanola De Oftalmologia* 94 (9):465–8. doi:10.1016/j.oftal.2019.04.007.

Murakami, A., M. Nakashima, T. Koshiba, T. Maoka, H. Nishino, M. Yano, T. Sumida, O. Kyung Kim, K. Koshimizu, and H. Ohigashi. 2000. Modifying effects of carotenoids on superoxide and nitric oxide generation from stimulated leukocytes. *Cancer Letters* 149 (1–2):115–23. doi:10.1016/S0304-3835(99)00351-1.

Murakami, Y., Y. Ikeda, N. Yoshida, S. Notomi, T. Hisatomi, S. Oka, and G. De Luca. 2012. MutT homolog-1 attenuates oxidative DNA damage and delays photoreceptor cell death in inherited retinal degeneration. *The American Journal of Pathology* 181 (4):1378–86. doi:10.1016/j.ajpath.2012.06.026.

Murray, M., A. L. Dordevic, M. P. Bonham, and L. Ryan. 2018. Do marine algal polyphenols have antidiabetic, antihyperlipidemic or anti-inflammatory effects in humans? A systematic review. *Critical Reviews in Food Science and Nutrition* 58 (12):2039–54. doi:10.1080/10408398.2017.1301876.

Mustafi, D., A. H. Engel, and K. Palczewski. 2009. Structure of cone photoreceptors. *Progress in Retinal and Eye Research* 28 (4):289–302. doi:10.1016/j.preteyeres.2009.05.003.

Nahavandipour, A., M. Krogh Nielsen, T. L. Sørensen, and Y. Subhi. 2020. Systemic levels of interleukin-6 in patients with age-related macular degeneration: A systematic review and meta-analysis. *Acta Ophthalmologica* 98 (5):434–44. doi:10.1111/aos.14402.

Najm, S., C. Löfqvist, G. Hellgren, E. Engström, P. Lundgren, A.-L. Hård, A. Lapillonne, K. Sävman, A. K. Nilsson, M. X. Andersson, et al. 2017. Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial. *Clinical Nutrition ESPEN* 20:17–23. doi:10.1016/j.clnesp.2017.04.004.

Nano, M. E., V. C. Lansingh, M. S. Pighin, N. Zarate, H. Nano, M. J. Carter, J. M. Furtado, C. C. Nano, L. F. Vernengo, J. D. Luna, et al. 2013. Risk factors of age-related macular degeneration in Argentina. *Arquivos Brasileiros de Oftalmologia* 76 (2):80–4. doi:10.1590/S0004-27492013000200005.

Nentwich, M. M., and M. W. Ulbig. 2015. Diabetic retinopathy - ocular complications of diabetes mellitus. *World Journal of Diabetes* 6 (3): 489–99. doi:10.4239/wjd.v6.i3.489.

Newton, F., and R. Megaw. 2020. Mechanisms of photoreceptor death in retinitis pigmentosa. *Genes* 11 (10):1120. doi:10.3390/genes11101120.

Neyrinck, A. M., A. Mouson, and N. M. Delzenne. 2007. Dietary supplementation with laminarin, a fermentable marine β (1–3) glucan, protects against hepatotoxicity induced by LPS in rat by modulating immune response in the hepatic tissue. *International Immunopharmacology* 7 (12):1497–506. doi:10.1016/j.intimp.2007.06.011.

Ng, S. K., J. P. Wood, G. Chidlow, G. Han, T. Kittipassorn, D. J. Peet, and R. J. Casson. 2015. Cancer-like metabolism of the mammalian retina: Mammalian retina metabolism. *Clinical & Experimental Ophthalmology* 43 (4):367–76. doi:10.1111/ceo.12462.

Nickells, R. W. 1996. Retinal ganglion cell death in glaucoma: The how, the why, and the maybe. *Journal of Glaucoma* 5 (5):345–56.

Nicolaeva, G. V., E. I. Sidorenko, and A. L. Iosifovna. 2015. Influence of the blood glucose level on the development of retinopathy of prematurity in extremely premature children. *Arquivos Brasileiros de Oftalmologia* 78 (4):232–5. doi:10.5935/0004-2749.20150060.

Nomura, T., M. Kikuchi, A. Kubodera, and Y. Kawakami. 1997. Proton-donative antioxidant activity of fucoxanthin with 1,1-diphenyl-2-picrylhydrazyl (DPPH). *IUBMB Life* 42 (2):361–70. doi:10.1080/15216549700202761.

Nucci, C., R. Tartaglione, L. Rombolà, L. A. Morrone, E. Fazzi, and G. Bagetta. 2005. Neurochemical evidence to implicate elevated glutamate in the mechanisms of high intraocular pressure (IOP)-induced retinal ganglion cell death in rat. *NeuroToxicology* 26 (5):935–41. doi:10.1016/j.neuro.2005.06.002.

Office of Health Assessment and Translation (2015). 2019. *OHAT risk of bias tool for human and animal studies. Office of health assessment and translation*. Research Triangle Park, NC: Division of the National Toxicology Program, National Institute of Environmental Health Sciences. Accessed July 26. https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html.

Oh, H., H. Takagi, C. Takagi, K. Suzuma, A. Otani, K. Ishida, M. Matsumura, Y. Ogura, and Y. Honda. 1999. The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. *Investigative Ophthalmology & Visual Science* 40 (9): 1891–8.

Ohata, T., K. Fukuda, M. Takahashi, T. Sugimura, and K. Wakabayashi. 1997. Suppression of nitric oxide production in lipopolysaccharide-stimulated macrophage cells by Ω3 polyunsaturated fatty acids. *Japanese Journal of Cancer Research* 88 (3):234–7. doi:10.1111/j.1349-7006.1997.tb00372.x.

Ohmes, J., X. Yuejun, W. Fanlu, M. D. Mikkelsen, T. T. Nguyen, S. Harald, S. Andreas, A. S. Meyer, and F. Sabine. 2020. Effect of enzymatically extracted fucoidans on angiogenesis and osteogenesis in primary cell culture systems mimicking bone tissue environment. *Marine Drugs* 18 (9):481. doi:10.3390/md18090481.

Oka, S., O. Mizuki, T. Daisuke, S. Kunihiko, F. Masato, and N. Yusaku. 2008. Two distinct pathways of cell death triggered by oxidative damage to nuclear and mitochondrial DNAs. *The EMBO Journal* 27 (2):421–32. doi:10.1038/sj.emboj.7601975.

Olivares-González, L., C. Martínez-Fernández de la Cámara, D. Hervás, M. P. Marín, A. Lahoz, J. María Millán, and R. Rodrigo. 2016. CGMP-phosphodiesterase inhibition prevents hypoxia-induced cell death activation in porcine retinal explants. *PLoS One* 11 (11): e0166717. doi:10.1371/journal.pone.0166717.

Olsen, R. L., J. Toppe, and I. Karunasagar. 2014. Challenges and realistic opportunities in the use of by-products from processing of fish and shellfish. *Trends in Food Science & Technology* 36 (2):144–51. doi:10.1016/j.tifs.2014.01.007.

Oltra, M., L. Vidal-Gil, R. Maisto, J. Sancho-Pelluz, and J. M. Barcia. 2020. Oxidative stress-induced angiogenesis is mediated by miR-205-5p. *Journal of Cellular and Molecular Medicine* 24 (2):1428–36. doi:10.1111/jcmm.14822.

Ostermann, A. I., A. L. West, K. Schoenfeld, L. M. Browning, C. G. Walker, S. A. Jebb, P. C. Calder, and N. H. Schebb. 2019. Plasma oxylipins respond in a linear dose-response manner with increased intake of EPA and DHA: Results from a randomized controlled trial in healthy humans. *The American Journal of Clinical Nutrition* 109 (5):1251–63. doi:10.1093/ajcn/nqz016.

Otrock, Z. K., J. A. Makarem, and A. I. Shamseddine. 2007. Vascular endothelial growth factor family of ligands and receptors: Review. *Blood Cells, Molecules, and Diseases* 38 (3):258–68. doi:10.1016/j.bcmd.2006.12.003.

Ozaki, H., A. Y. Yu, N. Della, K. Ozaki, J. D. Luna, H. Yamada, S. F. Hackett, N. Okamoto, D. J. Zack, G. L. Semenza, et al. 1999. Hypoxia inducible factor-1alpha is increased in ischemic retina: Temporal and spatial correlation with VEGF expression. *Investigative Ophthalmology & Visual Science* 40 (1):182–9.

Ozaki, T., N. Mitsuru, K. Takashi, H. Satoshi, S. Kaori, and I. Sei-Ichi. 2014. Protection of cone photoreceptor M-opsin degradation with 9-

cis-β-carotene-rich alga dunaliella bardawil in rpe65(-/-) mouse retinal explant culture. *Current Eye Research* 39 (12):1221–31. doi:10.3109/02713683.2014.907430.

Pamphlett, R., S. Cherepanoff, L. K. Too, S. Kum Jew, P. A. Doble, and D. P. Bishop. 2020. The distribution of toxic metals in the human retina and optic nerve head: Implications for age-related macular degeneration. *PLoS One.* 15 (10):e0241054. doi:10.1371/journal.pone.0241054.

Pangestuti, R., and S.-K. Kim. 2011. Neuroprotective effects of marine algae. *Marine Drugs* 9 (5):803–18. doi:10.3390/md9050803.

Park, C. H., Lee, S. Hyun Hong, J.-H. Kim, S.-K. Park, J.-W. Jeong, G.-Y. Kim, J. W. Hyun, S. J. Yun, B. W. Kim, et al. 2019. Protective effect of diphlorethohydroxycarmalol against oxidative stress-induced DNA damage and apoptosis in retinal pigment epithelial cells. *Cutaneous and Ocular Toxicology* 38 (3):298–308. doi:10.1080/15569527.2019.1613425.

Parness-Yossifon, R., and M. B. Mets. 2008. The electroretinogram in children. *Current Opinion in Ophthalmology* 19 (5):398–402. doi:10.1097/ICU.0b013e32830abf11.

Patel, S. 2018. Danger-associated molecular patterns (DAMPs): The derivatives and triggers of inflammation. *Current Allergy and Asthma Reports* 18 (11):63. doi:10.1007/s11882-018-0817-3.

Pawlik, D., R. Lauterbach, and E. Turyk. 2011. Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. *Pediatrics* 127 (2):223–8. doi:10.1542/peds.2010-2427.

Pawlik, D., R. Lauterbach, and J. Hurkała. 2011. The efficacy of fish-oil based fat emulsion administered from the first day of life in very low birth weight newborns. *Medycyna Wieku Rozwojowego* 15 (3):306–11.

Pawlik, D., R. Lauterbach, M. Walczak, J. Hurkała, and M. P. Sherman. 2014. Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: A prospective, randomized study. *Journal of Parenteral and Enteral Nutrition* 38 (6):711–6. doi:10.1177/0148607113499373.

Pe'er, J., D. Shweiki, A. Itin, I. Hemo, H. Gnessin, and E. Keshet. 1995. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. *Laboratory Investigation; A Journal of Technical Methods and Pathology* 72 (6):638–45.

Penn, J. S., A. Madan, R. B. Caldwell, M. Bartoli, R. W. Caldwell, and M. E. Hartnett. 2008. Vascular endothelial growth factor in eye disease. *Progress in Retinal and Eye Research* 27 (4):331–71. doi:10.1016/j.preteyeres.2008.05.001.

Pescosolido, N., A. Barbato, A. Stefanucci, and G. Buomprisco. 2015. Role of electrophysiology in the early diagnosis and follow-up of diabetic retinopathy. *Journal of Diabetes Research* 2015:319692. doi:10.1155/2015/319692.

Peters, S., P. Heiduschka, S. Julien, F. Ziemssen, H. Fietz, K. U. Bartz-Schmidt, U. Schraermeyer, and Tübingen Bevacizumab Study Group. 2007. Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. *American Journal of Ophthalmology* 143 (6):995–1002. doi:10.1016/j.ajo.2007.03.007.

Poli, G., G. Leonarduzzi, F. Biasi, and E. Chiarpotto. 2004. Oxidative stress and cell signalling. *Current Medicinal Chemistry* 11 (9):1163–82. doi:10.2174/0929867043365323.

Pomin, V. H. 2015. Sulfated glycans in inflammation. *European Journal of Medicinal Chemistry* 92:353–69. doi:10.1016/j.ejmech.2015.01.002.

Pomin, V. H. 2016. Dual and antagonic therapeutic effects of sulfated glycans. *Bioorganic & Medicinal Chemistry* 24 (18):3965–71. doi:10.1016/j.bmc.2016.07.037.

Ponce, N. M. A., and C. A. Stortz. 2020. A comprehensive and comparative analysis of the fucoidan compositional data across the phaeophyceae. *Frontiers in Plant Science* 11:556312. doi:10.3389/fpls.2020.556312.

Pozharitskaya, O. N., Alexander, N. Shikov, N. M. Faustova, E. D. Obluchinskaya, V. M. Kosman, H. Vuorela, and V. G. Makarov. 2018. Pharmacokinetic and tissue distribution of fucoidan from fucus vesiculosus after oral administration to rats. *Marine Drugs* 16 (4):132. doi:10.3390/md16040.

Qi, H., X. Ji, S. Liu, D. Feng, X. Dong, B. He, J. Srinivas, and C. Yu. 2017. Antioxidant and anti-dyslipidemic effects of polysaccharidic extract from sea cucumber processing liquor. *Electronic Journal of Biotechnology* 28:1–6. doi:10.1016/j.ejbt.2017.04.001.

Querques, G., P. Benlian, B. Chanu, C. Portal, G. Coscas, G. Soubrane, and E. H. Souied. 2009. Nutritional AMD treatment phase I (NAT-1): Feasibility of oral DHA supplementation in age-related macular degeneration. *European Journal of Ophthalmology* 19 (1):100–6. doi:10.1177/112067210901900115.

Radi, R., J. S. Beckman, K. M. Bush, and B. A. Freeman. 1991. Peroxynitrite-induced membrane lipid peroxidation: The cytotoxic potential of superoxide and nitric oxide. *Archives of Biochemistry and Biophysics* 288 (2):481–7. doi:10.1016/0003-9861(91)90224-7.

Ramchani-Ben Othman, K., C. Cercy, M. Amri, M. Doly, and I. Ranchon-Cole. 2015. Dietary supplement enriched in antioxidants and omega-3 protects from progressive light-induced retinal degeneration. *PloS One* 10 (6):e0128395. doi:10.1371/journal.pone.0128395.

Rana, T., P. Kotla, R. Fullard, and M. Gorbatyuk. 2017. TNFa knockdown in the retina promotes cone survival in a mouse model of autosomal dominant retinitis pigmentosa. *Biochimica et Biophysica Acta - Molecular Basis of Disease* 1863 (1):92–102. doi:10.1016/j.bbadis.2016.10.008.

Rangasamy, S., P. G. McGuire, C. Franco Nitta, F. Monickaraj, S. R. Oruganti, and A. Das. 2014. Chemokine mediated monocyte trafficking into the retina: Role of inflammation in alteration of the blood-retinal barrier in diabetic retinopathy. *PLoS One* 9 (10):e108508. doi:10.1371/journal.pone.0108508.

Rangel-Huerta, O. D., C. M. Aguilera, M. D. Mesa, and A. Gil. 2012. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomakers: A systematic review of randomised clinical trials. *British Journal of Nutrition* 107 (S2):S159–S70. doi:10.1017/S0007114512001559.

Rao, N. A., L. G. Thaete, J. M. Delmage, and A. Sevanian. 1985. Superoxide dismutase in ocular structures. *Investigative Ophthalmology & Visual Science* 26 (12):1778–81.

Rathnasamy, G., W. S. Foulds, E. A. Ling, and C. Kaur. 2019. Retinal microglia - A key player in healthy and diseased retina. *Progress in Neurobiology* 173:18–40. doi:10.1016/j.pneurobio.2018.05.006.

Ravi Kumar, S., B. Narayan, and B. Vallikannan. 2008. Fucoxanthin restrains oxidative stress induced by retinol deficiency through modulation of Na + Ka+-ATPase and antioxidant enzyme activities in rats. *European Journal of Nutrition* 47 (8):432–41. doi:10.1007/s00394-008-0745-4.

Renard, J.-P., J.-F. Rouland, A. Bron, E. Sellem, J.-P. Nordmann, C. Baudouin, P. Denis, M. Villain, G. Chaine, J. Colin, et al. 2013. Nutritional, lifestyle and environmental factors in ocular hypertension and primary open-angle glaucoma: An exploratory case-control study. *Acta Ophthalmologica* 91 (6):505–13. doi:10.1111/j.1755-3768.2011.02356.x.

Renju, G. L., G. M. Kurup, and C. H. Saritha Kumari. 2014. Effect of lycopene from chlorella marina on high cholesterol-induced oxidative damage and inflammation in rats. *Inflammopharmacology* 22 (1):45–54. doi:10.1007/s10787-013-0178-4.

Ridge, K. D., and K. Palczewski. 2007. Visual rhodopsin sees the light: Structure and mechanism of G protein signaling. *The Journal of Biological Chemistry* 282 (13):9297–301. doi:10.1074/jbc.R600032200.

Rinninella, E., M. C. Mele, N. Merendino, M. Cintoni, G. Anselmi, A. Caporossi, A. Gasbarrini, and A. Maria Minnella. 2018. The role of diet, micronutrients and the gut microbiota in age-related macular degeneration: New perspectives from the gut¯retina axis. *Nutrients* 10 (11):1677. doi:10.3390/nu1011.

Ristau, T., L. Ersoy, M. Hahn, A. I. den Hollander, B. Kirchhof, S. Liakopoulos, and S. Fauser. 2014. Nongenetic risk factors for neovascular age-related macular degeneration. *Investigative Opthalmology & Visual Science* 55 (8):5228–32. doi:10.1167/iovs.14-14299.

Rivera, J., Carlos, R. Dabouz, B. Noueihed, S. Omri, H. Tahiri, and S. Chemtob. 2017. Ischemic retinopathies: Oxidative stress and

inflammation. *Oxidative Medicine and Cellular Longevity* 2017:1–16. doi:10.1155/2017/3940241.

Rivera, J. C., M. Holm, D. Austeng, T. S. Morken, T. E. Zhou, A. Beaudry-Richard, E. M. Sierra, O. Dammann, and S. Chemtob. 2017. Retinopathy of prematurity: Inflammation, choroidal degeneration, and novel promising therapeutic strategies. *Journal of Neuroinflammation* 14 (1):165. doi:10.1186/s12974-017-0943-1.

Rivera, J. C., N. Sitaras, B. Noueihed, D. Hamel, A. Madaan, T. Zhou, J.-C. Honoré, C. Quiniou, J.-S. Joyal, P. Hardy, et al. 2013. Microglia and interleukin-1β in ischemic retinopathy elicit microvascular degeneration through neuronal semaphorin-3A. *Arteriosclerosis, Thrombosis, and Vascular Biology* 33 (8):1881–91. doi:10.1161/atvbaha.113.301331.

Rodríguez-Muela, N., A. M. Hernández-Pinto, A. Serrano-Puebla, L. García-Ledo, S. H. Latorre, E. J. de la Rosa, and P. Boya. 2015. Lysosomal membrane permeabilization and autophagy blockade contribute to photoreceptor cell death in a mouse model of retinitis pigmentosa. *Cell Death and Differentiation* 22 (3):476–87. doi:10.1038/cdd.2014.203.

Rogero, M., and P. Calder. 2018. Obesity, inflammation, toll-like receptor 4 and fatty acids. *Nutrients* 10 (4):432. doi:10.3390/nu10040432.

Rohwer, K., S. Neupane, K. S. Bittkau, M. G. Pérez, P. Dörschmann, J. Roider, S. Alban, and A. Klettner. 2019. Effects of crude fucus distichus subspecies evanescens fucoidan extract on retinal pigment epithelium cells-implications for use in age-related macular degeneration. *Marine Drugs* 17 (9):538. doi:10.3390/md17090.[10.3390/md17090538]

Rotenstreich, Y., M. Belkin, S. Sadetzki, A. Chetrit, G. Ferman-Attar, I. Sher, A. Harari, A. Shaish, and D. Harats. 2013. Treatment with 9-cis β-carotene-rich powder in patients with retinitis pigmentosa: A randomized crossover trial. *JAMA Ophthalmology* 131 (8):985–92. doi:10.1001/jamaophthalmol.2013.147.

Rózanowska, M., J. Jarvis-Evans, W. Korytowski, M. E. Boulton, J. M. Burke, and T. Sarna. 1995. Blue light-induced reactivity of retinal age pigment. in vitro generation of oxygen-reactive species. *The Journal of Biological Chemistry* 270 (32):18825–30. doi:10.1074/jbc.270.32.18825.

Russo, R., G. P. Varano, A. Adornetto, C. Nucci, M. T. Corasaniti, G. Bagetta, and L. A. Morrone. 2016. Retinal ganglion cell death in glaucoma: Exploring the role of neuroinflammation. *European Journal of Pharmacology* 787:134–42. doi:10.1016/j.ejphar.2016.03.064.

Saccà, S., C. Cutolo, D. Ferrari, P. Corazza, and C. Traverso. 2018. The eye, oxidative damage and polyunsaturated fatty acids. *Nutrients* 10 (6):668. doi:10.3390/nu10060668.

Sachindra, N. M., E. Sato, H. Maeda, M. Hosokawa, Y. Niwano, M. Kohno, and K. Miyashita. 2007. Radical scavenging and singlet oxygen quenching activity of marine carotenoid fucoxanthin and its metabolites. *Journal of Agricultural and Food Chemistry* 55 (21):8516–22. doi:10.1021/jf071848a.

Saint-Geniez, M., T. Kurihara, E. Sekiyama, A. E. Maldonado, and P. A. D'Amore. 2009. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. *Proceedings of the National Academy of Sciences of the United States of America* 106 (44):18751–6. doi:10.1073/pnas.0905010106.

Saint-Geniez, M., A. S. Maharaj, T. E. Walshe, B. A. Tucker, E. Sekiyama, T. Kurihara, D. C. Darland, M. J. Young, and P. A. D'Amore. 2008. Endogenous VEGF is required for visual function: Evidence for a survival role on Müller cells and photoreceptors. *PLoS One* 3 (11):e3554. doi:10.1371/journal.pone.0003554.

Sakai, S., T. Sugawara, K. Matsubara, and T. Hirata. 2009. Inhibitory effect of carotenoids on the degranulation of mast cells via suppression of antigen-induced aggregation of high affinity IgE Receptors. *Journal of Biological Chemistry* 284 (41):28172–9. doi:10.1074/jbc.M109.001099.

Sala-Vila, A., A. Díaz-López, C. Valls-Pedret, M. Cofán, A. García-Layana, R.-M. Lamuela-Raventós, O. Castañer, V. Zanon-Moreno, M. A. Martinez-Gonzalez, E. Toledo, et al. 2016. Dietary marine ω-3 fatty acids and incident sight-threatening retinopathy in middle-aged and older individuals with type 2 diabetes: Prospective investigation from the PREDIMED trial. *JAMA Ophthalmology* 134 (10):1142–9. doi:10.1001/jamaophthalmol.2016.2906.

Salom, D., M. Diaz-Llopis, S. GarcíA-Delpech, P. Udaondo, M. Sancho-Tello, and F. J. Romero. 2008. Aqueous humor levels of vascular endothelial growth factor in retinitis pigmentosa. *Investigative Opthalmology & Visual Science* 49 (8):3499–502. doi:10.1167/iovs.07-1168.

SanGiovanni, J., Paul, E. Y. Chew, T. E. Clemons, M. D. Davis, F. L. Ferris, G. R. Gensler, and N. Kurinij. 2007. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS Report No. 20. *Archives of Ophthalmology* 125 (5):671–9. doi:10.1001/archopht.125.5.671.

Sayadi, J., A. Miere, E. H. Souied, and S. Y. Cohen. 2017. Type 3 neovascularization associated with retinitis pigmentosa. *Case Reports in Ophthalmology* 8 (1):245–9. doi:10.1159/000471790.

Schmidt-Erfurth, U., V. Chong, A. Loewenstein, M. Larsen, E. Souied, R. Schlingemann, B. Eldem, J. Mones, G. Richard, F. Bandello, et al. 2014. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *The British Journal of Ophthalmology* 98 (9):1144–67. doi:10.1136/bjophthalmol-2014-305702.

Ścieszka, S., and E. Klewicka. 2019. Algae in food: A general review. *Critical Reviews in Food Science and Nutrition* 59 (21):3538–47. doi:10.1080/10408398.2018.1496319.

Seddon, J. M., G. Gensler, M. L. Klein, and R. C. Milton. 2006. C-Reactive protein and homocysteine are associated with dietary and behavioral risk factors for age-related macular degeneration. *Nutrition (Burbank, Los Angeles County, Calif.)* 22 (4):441–3. doi:10.1016/j.nut.2005.12.004.

Seddon, J. M., S. George, B. Rosner, and N. Rifai. 2005. Progression of age-related macular degeneration: Prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. *Archives of Ophthalmology* 123 (6):774–82. doi:10.1001/archopht.123.6.774.

Senate and House of Representatives of the United States of America. 1994. Dietary Supplement Health and Education Act of 1994. https://ods.od.nih.gov/About/DSHEA_Wording.aspx#sec8.

Senger, C., R. Moreto, S. E. S. Watanabe, A. G. Matos, and J. S. Paula. 2020. Electrophysiology in glaucoma. *Journal of Glaucoma* 29 (2):147–53. doi:10.1097/IJG.0000000000001422.

Shadel, G. S., and T. L. Horvath. 2015. Mitochondrial ROS signaling in organismal homeostasis. *Cell* 163 (3):560–9. doi:10.1016/j.cell.2015.10.001.

Shan, X., X. Liu, J. Hao, C. Cai, F. Fan, Y. Dun, X. Zhao, X. Liu, C. Li, and G. Yu. 2016. In vitro and in vivo hypoglycemic effects of brown algal fucoidans. *International Journal of Biological Macromolecules* 82:249–55. doi:10.1016/j.ijbiomac.2015.11.036.

Sharkey, S. J., P. A. Harnedy-Rothwell, P. J. Allsopp, L. E. Hollywood, R. J. FitzGerald, and F. P. M. O'Harte. 2020. A narrative review of the anti-hyperglycemic and satiating effects of fish protein hydrolysates and their bioactive peptides. *Molecular Nutrition & Food Research* 64 (21):2000403. doi:10.1002/mnfr.202000403.

Shaw, P. X., T. Stiles, C. Douglas, D. Ho, W. Fan, H. Du, and X. Xiao. 2016. Oxidative stress, innate immunity, and age-related macular degeneration. *AIMS Molecular Science* 3 (2):196–221. doi:10.3934/molsci.2016.2.196.

Shen, W., Y. Gao, B. Lu, Q. Zhang, Y. Hu, and Y. Chen. 2014. Negatively regulating TLR4/NF-KB signaling via PPARα in endotoxin-induced uveitis. *Biochimica et Biophysica Acta* 1842 (7):1109–20. doi:10.1016/j.bbadis.2014.03.015.

Sher, I., A. Tzameret, S. Peri-Chen, V. Edelshtain, M. Ioffe, A. Sayer, L. Buzhansky, E. Gazit, and Y. Rotenstreich. 2018. Synthetic 9-cis-beta-carotene inhibits photoreceptor degeneration in cultures of eye cups from rpe65rd12 mouse model of retinoid cycle defect. *Scientific Reports* 8 (1):6130. doi:10.1038/s41598-018-24439-3.

Shevalye, H., M. S. Yorek, L. J. Coppey, A. Holmes, M. M. Harper, R. H. Kardon, and M. A. Yorek. 2015. Effect of enriching the diet with menhaden oil or daily treatment with resolvin D1 on neuropathy in a mouse model of type 2 diabetes. *Journal of Neurophysiology* 114 (1):199–208. doi:10.1152/jn.00224.2015.

Shoda, C., Y. Miwa, K. Nimura, K. Okamoto, S. Yamagami, K. Tsubota, and T. Kurihara. 2020. Hypoxia-inducible factor inhibitors derived from marine products suppress a murine model of neovascular retinopathy. *Nutrients* 12 (4):1055. doi:10.3390/nu1204.

Sidhu, K. S. 2003. Health benefits and potential risks related to consumption of fish or fish oil. *Regulatory Toxicology and Pharmacology: RTP* 38 (3):336–44. doi:10.1016/j.yrtph.2003.07.002.

Siemerink, M. J., I. Klaassen, C. J. F. Van Noorden, and R. O. Schlingemann. 2013. Endothelial tip cells in ocular angiogenesis: Potential target for anti-angiogenesis therapy. *The Journal of Histochemistry and Cytochemistry: Official Journal of the Histochemistry Society* 61 (2):101–15. doi:10.1369/0022155412467635.

Silveira, R. C., J. B. Fortes Filho, and R. S. Procianoy. 2011. Assessment of the contribution of cytokine plasma levels to detect retinopathy of prematurity in very low birth weight infants. *Investigative Ophthalmology & Visual Science* 52 (3):1297–301. doi:10.1167/iovs.10-6279.

Sivakumar, V., W. S. Foulds, C. D. Luu, E.-A. Ling, and C. Kaur. 2011. Retinal ganglion cell death is induced by microglia derived pro-inflammatory cytokines in the hypoxic neonatal retina. *The Journal of Pathology* 224 (2):245–60. doi:10.1002/path.2858.

Skowronska-Krawczyk, D., and D. L. Chao. 2019. Long-chain polyunsaturated fatty acids and age-related macular degeneration. *Advances in Experimental Medicine and Biology*. 1185:39–43. doi:10.1007/978-3-030-27378-1_7.

Škrha, J., J. Šoupal, J. Škrha, and M. Prázný. 2016. Glucose variability, HbA1c and microvascular complications. *Reviews in Endocrine & Metabolic Disorders* 17 (1):103–10. doi:10.1007/s11154-016-9347-2.

Sohal, R. S., and W. C. Orr. 2012. The redox stress hypothesis of aging. *Free Radical Biology & Medicine* 52 (3):539–55. doi:10.1016/j.freeradbiomed.2011.10.445.

Solebo, A. L., L. Teoh, and J. Rahi. 2017. Epidemiology of blindness in children. *Archives of Disease in Childhood* 102 (9):853–7. doi:10.1136/archdischild-2016-310532.

Somasundaran, S., I. J. Constable, C. B. Mellough, and L. S. Carvalho. 2020. Retinal pigment epithelium and age-related macular degeneration: A review of major disease mechanisms. *Clinical & Experimental Ophthalmology* 48 (8):1043–56. doi:10.1111/ceo.13834.

Song, J., M. Hu, C. Li, B. Yang, Q. Ding, C. Wang, and L. Mao. 2018. Dose-dependent effects of fish oil on cardio-metabolic biomarkers in healthy middle-aged and elderly Chinese people: A double-blind randomized controlled trial. *Food & Function* 9 (6):3235–43. doi:10.1039/C7FO01566F.

Souied, E. H., T. Aslam, A. Garcia-Layana, F. G. Holz, A. Leys, R. Silva, and C. Delcourt. 2015. Omega-3 fatty acids and age-related macular degeneration. *Ophthalmic Research* 55 (2):62–9. doi:10.1159/000441359.

Souied, E. H., C. Delcourt, G. Querques, A. Bassols, B. Merle, A. Zourdani, T. Smith, P. Benlian, and Nutritional AMD Treatment 2 Study Group. 2013. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: The nutritional AMD treatment 2 study. *Ophthalmology* 120 (8):1619–31. doi:10.1016/j.ophtha.2013.01.005.

Spencer, B. G., J. J. Estevez, E. Liu, J. E. Craig, and J. W. Finnie. 2020. Pericytes, inflammation, and diabetic retinopathy. *Inflammopharmacology* 28 (3):697–709. doi:10.1007/s10787-019-00647-9.

Stitt, A. W., T. M. Curtis, M. Chen, R. J. Medina, G. J. McKay, A. Jenkins, T. A. Gardiner, T. J. Lyons, H.-P. Hammes, R. Simó, et al. 2016. The progress in understanding and treatment of diabetic retinopathy. *Progress in Retinal and Eye Research* 51:156–86. doi:10.1016/j.preteyeres.2015.08.001.

Su, X., Q. Chen, W. Chen, T. Chen, W. Li, Y. Li, X. Dou, Y. Zhang, Y. Shen, H. Wu, et al. 2014. Mycoepoxydiene inhibits activation of BV2 microglia stimulated by lipopolysaccharide through suppressing NF-KB, ERK 1/2 and toll-like receptor pathways. *International Immunopharmacology* 19 (1):88–93. doi:10.1016/j.intimp.2014.01.004.

Subhapradha, N., V. Shanmugam, and A. Shanmugam. 2017. Chitosan nanoparticles from marine squid protect liver cells against N-diethylnitrosoamine-induced hepatocellular carcinoma. *Carbohydrate Polymers* 171:18–26. doi:10.1016/j.carbpol.2017.04.097.

Sugawara, T., K. Matsubara, R. Akagi, M. Mori, and T. Hirata. 2006. Antiangiogenic activity of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. *Journal of Agricultural and Food Chemistry* 54 (26):9805–10. doi:10.1021/jf062204q.

Sung, C.-H., and J.-Z. Chuang. 2010. The cell biology of vision. *The Journal of Cell Biology* 190 (6):953–63. doi:10.1083/jcb.201006020.

Supartini, A., T. Oishi, and N. Yagi. 2018. Changes in fish consumption desire and its factors: A comparison between the United Kingdom and Singapore. *Foods (Basel, Switzerland)* 7 (7). doi:10.3390/foods7070097.

Tang, J., and T. S. Kern. 2011. Inflammation in diabetic retinopathy. *Progress in Retinal and Eye Research* 30 (5):343–58. doi:10.1016/j.preteyeres.2011.05.002.

Tangvarasittichai, O., and S. Tangvarasittichai. 2019. Oxidative stress, ocular disease and diabetes retinopathy. *Current Pharmaceutical Design* 24 (40):4726–41. doi:10.2174/1381612825666190115121531.

ten Berge, J. C., Z. Fazil, L. I. Born, R. C. W. Wolfs, M. W. J. Schreurs, W. A. Dik, and A. Rothova. 2019. Intraocular cytokine profile and autoimmune reactions in retinitis pigmentosa, age-related macular degeneration, glaucoma and cataract. *Acta Ophthalmologica* 97 (2):185–92. doi:10.1111/aos.13899.

Tezel, G. 2006. Oxidative stress in glaucomatous neurodegeneration: Mechanisms and consequences. *Progress in Retinal and Eye Research* 25 (5):490–513. doi:10.1016/j.preteyeres.2006.07.003.

Tezel, G., X. Yang, C. Luo, A. D. Kain, D. W. Powell, M. H. Kuehn, and H. J. Kaplan. 2010. Oxidative stress and the regulation of complement activation in human glaucoma. *Investigative Opthalmology & Visual Science* 51 (10):5071–82. doi:10.1167/iovs.10-5289.

The European Parliament and the Council of the European Union. 2007. Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on Nutrition and Health Claims Made on Foods. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32006R1924&from=DE#d1e756-9-1.

The European Parliament and the Council of the European Union. 2010. Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on Food Additives. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32008R1333&from=DE.

Tischer, E., R. Mitchell, T. Hartman, M. Silva, D. Gospodarowicz, J. C. Fiddes, and J. A. Abraham. 1991. The human gene for vascular endothelial growth factor. multiple protein forms are encoded through alternative exon splicing. *Journal of Biological Chemistry* 266 (18):11947–54. doi:10.1016/S0021-9258(18)99049-6.

Titos, E., B. Rius, A. González-Périz, C. López-Vicario, E. Morán-Salvador, M. Martínez-Clemente, V. Arroyo, and J. Clària. 2011. Resolvin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macrophage polarization toward an M2-like phenotype. *Journal of Immunology* 187 (10):5408–18. doi:10.4049/jimmunol.1100225.

Torgalkar, R., S. Dave, J. Shah, N. Ostad, K. Kotsopoulos, S. Unger, and P. S. Shah. 2019. Multi-component lipid emulsion vs soy-based lipid emulsion for very low birth weight preterm neonates: A pre-post comparative study. *Journal of Perinatology* 39 (8):1118–24. doi:10.1038/s41372-019-0425-7.

Totan, Y., R. Yağcı, Y. Bardak, H. Özyurt, F. Kendir, G. Yılmaz, Ş. Şahin, and U. Şahin Tığ. 2009. Oxidative macromolecular damage in age-related macular degeneration. *Current Eye Research* 34 (12):1089–93. doi:10.3109/02713680903353772.

Tu, C.-F., C.-H. Lee, H.-N. Chen, L.-Y. Tsao, J.-Y. Chen, and C.-C. Hsiao. 2020. Effects of fish oil-containing lipid emulsions on retinopathy of prematurity in very low birth weight infants. *Pediatrics & Neonatology* 61 (2):224–30. doi:10.1016/j.pedneo.2019.11.010.

Turner, J. M., Y. Sauvé, M. Suh, P. W. Wales, P. Wizzard, S. Goruk, and C. J. Field. 2016. A third-generation lipid emulsion that contains n-3 long-chain PUFAs preserves retinal function in parenterally fed neonatal piglets. *The Journal of Nutrition* 146 (11):2260–6. doi:10.3945/jn.116.237669.

Unal, S., N. Demirel, S. Erol, D. U. Isik, F. Kulali, F. Iyigun, and A. Y. Bas. 2018. Effects of two different lipid emulsions on morbidities and oxidant stress statuses in preterm infants: An observational study. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 31 (7):850–6. doi:10.1080/14767058.2017.1300644.

Ustyuzhanina, N. E., M. I. Bilan, N. A. Ushakova, A. I. Usov, M. V. Kiselevskiy, and N. E. Nifantiev. 2014. Fucoidans: Pro- or antiangiogenic agents? *Glycobiology* 24 (12):1265–74. doi:10.1093/glycob/cwu063.

van Leeuwen, E. M., E. Emri, B. M. J. Merle, J. M. Colijn, E. Kersten, A. Cougnard-Gregoire, S. Dammeier, M. Meester-Smoor, F. M. Pool, E. K. de Jong, et al. 2018. A new perspective on lipid research in age-related macular degeneration. *Progress in Retinal and Eye Research* 67:56–86. doi:10.1016/j.preteyeres.2018.04.006.

Verbakel, S. K., R. A. C. van Huet, C. J. F. Boon, A. I. den Hollander, R. W. J. Collin, C. C. W. Klaver, C. B. Hoyng, R. Roepman, and B. Jeroen Klevering. 2018. Non-syndromic retinitis pigmentosa. *Progress in Retinal and Eye Research* 66:157–86. doi:10.1016/j.preteyeres.2018.03.005.

Viera, I., A. Pérez-Gálvez, and M. Roca. 2018. Bioaccessibility of marine carotenoids. *Marine Drugs* 16 (10):397. doi:10.3390/md16100397.

Wachtmeister, L. 1998. Oscillatory potentials in the retina: What do they reveal. *Progress in Retinal and Eye Research* 17 (4):485–521. doi:10.1016/S1350-9462(98)00006-8.

Waern, M., E. Rubenowitz, B. Runeson, I. Skoog, K. Wilhelmson, and P. Allebeck. 2002. Burden of illness and suicide in elderly people: Case-control study. *BMJ* 324 (7350):1355. doi:10.1136/bmj.324.7350.1355.

Wali, A. F., S. Majid, S. Rasool, S. B. Shehada, S. K. Abdulkareem, A. Firdous, S. Beigh, S. Shakeel, S. Mushtaq, I. Akbar, et al. 2019. Natural products against cancer: Review on phytochemicals from marine sources in preventing cancer. *Saudi Pharmaceutical Journal: SPJ: The Official Publication of the Saudi Pharmaceutical Society* 27 (6):767–77. doi:10.1016/j.jsps.2019.04.013.

Wan, T. T., X. F. Li, Y. M. Sun, Y. B. Li, and Y. Su. 2015. Recent advances in understanding the biochemical and molecular mechanism of diabetic retinopathy. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 74:145–7. doi:10.1016/j.biopha.2015.08.002.

Wang, J. J., G. H. S. Buitendijk, E. Rochtchina, K. E. Lee, B. E. K. Klein, C. M. van Duijn, V. M. Flood, S. M. Meuer, J. Attia, C. Myers, et al. 2014. Genetic susceptibility, dietary antioxidants, and long-term incidence of age-related macular degeneration in two populations. *Ophthalmology* 121 (3):667–75. doi:10.1016/j.ophtha.2013.10.017.

Wang, J. J., E. Rochtchina, W. Smith, R. Klein, B. E. K. Klein, T. Joshi, T. A. Sivakumaran, S. Iyengar, and P. Mitchell. 2009. Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. *American Journal of Epidemiology* 169 (5):633–41. doi:10.1093/aje/kwn358.

Wang, S. K., Y. Xue, and C. L. Cepko. 2020. Microglia modulation by TGF-B1 protects cones in mouse models of retinal degeneration. *Journal of Clinical Investigation*. doi:10.1172/JCI136160.

Wang, W., A. Kini, Y. Wang, T. Liu, Y. Chen, E. Vukmanic, D. Emery, Y. Liu, X. Lu, L. Jin, et al. 2019. Metabolic deregulation of the blood-outer retinal barrier in retinitis pigmentosa. *Cell Reports* 28 (5):1323–34.e4. doi:10.1016/j.celrep.2019.06.093.

Wang, Y.-Q., and Z.-H. Miao. 2013. Marine-derived angiogenesis inhibitors for cancer therapy. *Marine Drugs* 11 (3):903–33. doi:10.3390/md11030903.

Whatham, A. R., V. Nguyen, Y. Zhu, M. Hennessy, and M. Kalloniatis. 2014. The value of clinical electrophysiology in the assessment of the eye and visual system in the era of advanced imaging. *Clinical & Experimental Optometry* 97 (2):99–115. doi:10.1111/cxo.12085.

Wheaton, D. H., D. R. Hoffman, K. G. Locke, R. B. Watkins, and D. G. Birch. 2003. Biological safety assessment of docosahexaenoic acid supplementation in a randomized clinical trial for X-linked retinitis pigmentosa. *Archives of Ophthalmology* 121 (9):1269–78. doi:10.1001/archopht.121.9.1269.

WHO. 2019. *World report on vision*. Geneva: World Health Organization.

Wiggs, J. L. 2015. Glaucoma genes and mechanisms. *Progress in Molecular Biology and Translational Science* 134:315–42. doi:10.1016/bs.pmbts.2015.04.008.

Witmer, A. N., G. F. J. M. Vrensen, C. J. F. Van Noorden, and R. O. Schlingemann. 2003. Vascular endothelial growth factors and angiogenesis in eye disease. *Progress in Retinal and Eye Research* 22 (1):1–29. doi:10.1016/S1350-9462(02)00043-5.

Wong, F., and S. Y. Kwok. 2016. The survival of cone photoreceptors in retinitis pigmentosa. *JAMA Ophthalmology* 134 (3):249–50. doi:10.1001/jamaophthalmol.2015.5490.

Wong, M. Y. Z., R. E. K. Man, E. K. Fenwick, P. Gupta, L.-J. Li, R. M. van Dam, M. F. Chong, and E. L. Lamoureux. 2018. Dietary intake and diabetic retinopathy: A systematic review. *PLoS One* 13 (1):e0186582. doi:10.1371/journal.pone.0186582.

Wooff, Y., S. M. Man, R. Aggio-Bruce, R. Natoli, and N. Fernando. 2019. IL-1 family members mediate cell death, inflammation and angiogenesis in retinal degenerative diseases. *Frontiers in Immunology* 10:1618. doi:10.3389/fimmu.2019.01618.

WoRMS Editorial Board. 2021. *World Register of Marine Species*. Available from http://www.marinespecies.org at VLIZ. Accessed 2021-04-29. doi:10.14284/170.

Wu, J., E. Cho, E. L. Giovannucci, B. A. Rosner, S. M. Sastry, W. C. Willett, and D. A. Schaumberg. 2017. Dietary intakes of eicosapentaenoic acid and docosahexaenoic acid and risk of age-related macular degeneration. *Ophthalmology* 124 (5):634–43. doi:10.1016/j.ophtha.2016.12.033.

Xi, M., and L. O. Dragsted. 2019. Biomarkers of seaweed intake. *Genes & Nutrition* 14:24. doi:10.1186/s12263-019-0648-4.

Xie, P., I. Fujii, J. Zhao, M. Shinohara, and M. Matsukura. 2012. A novel polysaccharide compound derived from algae extracts protects retinal pigment epithelial cells from high glucose-induced oxidative damage in vitro. *Biological and Pharmaceutical Bulletin* 35 (9):1447–53. doi:10.1248/bpb.b110706.

Yadav, U. C. S., N. M. Kalariya, and K. V. Ramana. 2011. Emerging role of antioxidants in the protection of uveitis complications. *Current Medicinal Chemistry* 18 (6):931–42. doi:10.2174/092986711794927694.

Yamada, S., T. Koyama, H. Noguchi, Y. Ueda, R. Kitsuyama, H. Shimizu, A. Tanimoto, K.-Y. Wang, A. Nawata, T. Nakayama, et al. 2014. Marine hydroquinone zonarol prevents inflammation and apoptosis in dextran sulfate sodium-induced mice ulcerative colitis. *PLoS One* 9 (11):e113509. doi:10.1371/journal.pone.0113509.

Yang, W., X. Yu, Q. Zhang, Q. Lu, J. Wang, W. Cui, Y. Zheng, X. Wang, and D. Luo. 2013. Attenuation of streptozotocin-induced diabetic retinopathy with low molecular weight fucoidan via inhibition of vascular endothelial growth factor. *Experimental Eye Research* 115:96–105. doi:10.1016/j.exer.2013.06.011.

Yao, J., Y. Qiu, E. Frontera, L. Jia, N. W. Khan, D. J. Klionsky, T. A. Ferguson, D. A. Thompson, and D. N. Zacks. 2018. Inhibiting autophagy reduces retinal degeneration caused by protein misfolding. *Autophagy* 14 (7):1226–38. doi:10.1080/15548627.2018.1463121.

Yee, P., A. E. Weymouth, E. L. Fletcher, and A. J. Vingrys. 2010. A role for omega-3 polyunsaturated fatty acid supplements in diabetic neuropathy. *Investigative Ophthalmology & Visual Science* 51 (3):1755–64. doi:10.1167/iovs.09-3792.

Yuzbasioglu, E., O. Artunay, R. Rasier, A. Sengul, and H. Bahcecioglu. 2009. Intravitreal bevacizumab (avastin) injection in retinitis pigmentosa. *Current Eye Research* 34 (3):231–7. doi:10.1080/02713680802710692.

Zaragozá, M. C., D. López, M. P. Sáiz, M. Poquet, J. Pérez, P. Puig-Parellada, F. Màrmol, P. Simonetti, C. Gardana, Y. Lerat, et al. 2008. Toxicity and antioxidant activity in vitro and in vivo of two *Fucus vesiculosus* extracts. *Journal of Agricultural and Food Chemistry* 56 (17):7773–80. doi:10.1021/jf8007053.

Zerbib, J., C. Delcourt, N. Puche, G. Querques, S. Y. Cohen, J. Sahel, J.-F. Korobelnik, M. L. Goff, and E. H. Souied. 2014. Risk factors for exudative

age-related macular degeneration in a large French case-control study. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes. Archiv Fur Klinische Und Experimentelle Ophthalmologie* 252 (6):899–907. doi:10.1007/s00417-013-2537-7.

Zhang, K., Q. Zhong, S. Chen, C. Guo, Y. Xu, Y. Liu, W. Sun, Y. Yan, and P. Zhao. 2018. An epidemiological investigation of age-related macular degeneration in aged population in China: The Hainan study. *International Ophthalmology* 38 (4):1659–67. doi:10.1007/s10792-017-0639-7.

Zhang, Y., H. Fang, Q. Xie, J. Sun, R. Liu, Z. Hong, R. Yi, and H. Wu. 2014. Comparative evaluation of the radical-scavenging activities of fucoxanthin and its stereoisomers. *Molecules (Basel, Switzerland)* 19 (2):2100–13. doi:10.3390/molecules19022100.

Zhang, Y., and C. Liang. 2016. Innate recognition of microbial-derived signals in immunity and inflammation. *Science China. Life Sciences* 59 (12):1210–7. doi:10.1007/s11427-016-0325-6.

Zhao, D., J. Cho, M. H. Kim, D. S. Friedman, and E. Guallar. 2015. Diabetes, fasting glucose, and the risk of glaucoma. *Ophthalmology* 122 (1):72–8. doi:10.1016/j.ophtha.2014.07.051.

Zheng, J., M. J. Piao, Y. Sam Keum, H. S. Kim, and J. W. Hyun. 2013. Fucoxanthin protects cultured human keratinocytes against oxidative stress by blocking free radicals and inhibiting apoptosis. *Biomolecules & Therapeutics* 21 (4):270–6. doi:10.4062/biomolther.2013.030.

Zhu, C. L., Y. Ji, E.-J. Lee, and N. M. Grzywacz. 2013. Spatiotemporal pattern of rod degeneration in the S334ter-line-3 rat model of retinitis pigmentosa. *Cell and Tissue Research* 351 (1):29–40. doi:10.1007/s00441-012-1522-5.

Zhu, W., W. Yan, M. Yi-Fang, X. Qian, T. Jian-Jun, and L. Jiong. 2016. Fish consumption and age-related macular degeneration incidence: A meta-analysis and systematic review of prospective cohort studies. *Nutrients* 8 (11):743. doi:10.3390/nu8110743.

Zirpoli, H., C. L. Chang, Y. A. Carpentier, A. T. Michael-Titus, V. S. Ten, and R. J. Deckelbaum. 2020. Novel approaches for omega-3 fatty acid therapeutics: Chronic versus acute administration to protect heart, brain, and spinal cord. *Annual Review of Nutrition* 40 (1):161–87. doi:10.1146/annurev-nutr-082018-124539.