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Review

Greenshell Mussel Products: A Comprehensive Review of Sustainability, Traditional Use, and Efficacy

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Abstract: Greenshell™ mussels (GSMs), *Perna canaliculus*, are Aotearoa/New Zealand's most important aquaculture species and is sold as a variety of food products worldwide. GSMs are a traditional and culturally valuable food of the Māori people. Following the development of a series of nutraceutical products (dried powders and extracted oils) by the GSM aquaculture industry in the 1960s, there has been an increased scientific interest in the clinical health benefits of GSM products. Omega-3 polyunsaturated fatty acids in GSMs have exhibited significant anti-inflammatory activity, and the clinical evidence has led to GSM powders and oils being extensively promoted as treatments for rheumatoid arthritis and osteoarthritis. This review defines the nutritional composition of GSMs and describes the sustainability of GSMs and their traditional uses. The review also details the health benefits of GSMs in clinical applications and identifies potential mechanisms and molecular pathways initiated by the various bioactive components of GSMs.

Keywords: green-lipped mussel; greenshell mussel; marine bioactive; arthritis; omega-3 polyunsaturated fatty acids

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1. Introduction

Green-lipped mussels, trademarked as Greenshell™ mussels (GSMs), *Perna canaliculus*, are a bivalve mollusc indigenous to the inshore coastlines of Aotearoa/New Zealand (NZ). GSMs are Aotearoa/NZ's most important aquaculture species and are characterised by a green colouration of the shell and a larger size than other major commercial mussel species, such as the blue mussel (*Mytilus galloprovincialis*). The annual revenue from GSMs exported to the international food market was worth over NZD 303 M in 2021 [1]. GSMs are commercially farmed for food as well as for nutraceutical products in the form of oil extracts and powders [2].

GSMs have been a long-established kaimoana (seafood) in Aotearoa/NZ, traditionally eaten by Māori after intertidal collection. Mātaitai (seafood, shellfish, fish or other food collected from the approximate intertidal zone of the sea) was a prized taonga (treasure) to Māori people. Traditional indigenous uses and practices of preparing kūkū (GSMs) have been recorded as far back as the 1700s throughout Aotearoa/NZ and the Pacific. The kūkū (also known as kūtai and kūkūtai) was regarded as a staple part of the diet of coastal Māori people. Its benefits were traditionally recognised, and more recently, scientists have attempted to understand its effectiveness in supporting health and preventing disease. In the accounts of Sydney Parkinson, the artist aboard Captain Cook's vessel *Endeavour*, wrote in 1769, "We traded with them [the Māori] for cloth, crayfish, and mussels" [3]. In 1777, William Anderson, the surgeon aboard Cook's vessel *Resolution*, wrote, "The rocks

are abundantly furnished with great quantities of excellent mussels" [3]; thus, GSMs were one of the first internationally traded products from NZ.

The GSM aquaculture industry was developed during the 1960s and established in 1969 following the collapse of dredge fisheries; initially, the industry met local demand but has since grown to become a major exporter. GSMs are now an established export product with frozen half-shell products successfully selling in the competitive and cost-sensitive food service sector. GSMs are also used to produce high-value nutraceuticals, including oil extracts and mussel powders, which are sold worldwide. Furthermore, GSMs have become a key ingredient in pet foods, particularly for companion animals [4]. In the last decade, several unique mussel powder and oil products based on different extraction and drying technologies have come onto the market.

The earliest clinical studies focused on the potential of GSMs in the treatment of arthritis [5–7] before more broadly assessing its anti-inflammatory effects [8–10]. The potential health benefits and biological activity of GSMs are generally accepted to be derived from lipid and some carbohydrate components. The long-chain omega-3 polyunsaturated fatty acids (PUFAs) present in GSMs include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These PUFAs can effectively compete with arachidonic acid (AA) as a substrate for cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO) enzymes due to their structural similarity. However, they produce fewer inflammatory prostaglandins, broncho-constricting agents (leukotrienes) and tumour-promoting agents, such as 5-hydroxyeicosatetraenoic acid (5-HETE), in various immune cell types [11]. Instead, EPA and DHA generate potent anti-inflammatory E-series resolvins [12]. There are relatively few reports on the bioactivity of other lipid components of GSMs; for example, the furan fatty acids (FuFA) [13] or the novel anti-inflammatory omega-3 PUFAs, such as 5,9,12,15-octadecatetraenoic acid, 5,9,12,16-nonadecatetraenoic acid, 7,11,14,17-eicosatetraenoic acid and 5,9,12,15,18-heneicosapentaenoic acid [14,15]. In addition, glucosamine and chondroitin, which are a monosaccharide and polysaccharide, respectively, are found in GSMs as a component of glycosaminoglycans (GAGs) [16]. Due to their role as matrix components of cartilage tissue, they have generally been studied in the context of osteoarthritis (OA) treatment. Some studies indicated the promotion of chondrocyte proliferation, proteoglycan production and inhibition of cartilage degradation by these components [17].

Whole-GSM powder contains a mixture of proteins, lipids and carbohydrates with a complex profile of omega-3 PUFAs, sterols, GAGs and several vitamins and minerals. It appears that the combination of these compounds acts additively, or perhaps even synergistically, providing additive bioactivity. To support this observation, a clinical trial demonstrated that a combination of both omega-3 PUFAs and glucosamine provided a greater response in terms of improving the OA symptoms than glucosamine alone [18]. Further in vitro studies are needed to clarify the mechanisms by which the whole-GSM extract acts at the cellular and molecular levels.

This review comprehensively examines the production, composition and function of GSMs and explores their traditional use by the indigenous Māori population and communities. The Section 1 of the review covers the GSM content and nutritional composition and is followed by a description of its sustainability and traditional uses. The Section 2 identifies its bioactive components, their bioavailability and the details of the health benefits of GSMs in clinical applications. The Section 5 highlights the potential mechanisms and molecular pathways of each bioactive component in the context of the discovered health benefits.

2. Greenshell™ Mussel Industry, Traditional Use, Sustainability and Products

The GSM nutraceutical industry has grown significantly since its small beginnings in the 1970s, exporting NZD 13.4 M (368 tonnes) of dried powder and NZD 46.0 M (21.6 tonnes) of extracted oil in 2021 [1]. The industry consists of a number of differently sized businesses that use a variety of techniques to produce a range of products, which are primarily oils, dried powders and defatted powders. It is vital that the highest quality mussels are used to produce nutraceutical products.

GSMs are opened with physical, steam or pressure assistance to release the meat from the shell. The GSM meat is then frequently homogenised and dried by either freeze-drying or bead-assisted flash drying. Extracting the lipids from GSMs creates challenges, as the lipid content is low, being approximately 6–10% of the dried product, and consists of a mixture of lipid types. The majority are polar lipids, including phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylglycerol (PG) and phosphatidylserine (PS), ceramides, acyl carnitines, their lysophospholipid precursors, and plasmanyl and plasmenyl orthologues. The fatty acid profile of the polar lipid fraction of mussel oil also has moderate levels (approximately 5–10% of the fatty acids profiles) of dimethylacetals of aliphatic aldehydes, a methylated component of a plasmalogen [19]. In addition, the mixture contains non-polar fats, such as triacylglycerols, diacylglycerols, sterols and free fatty acids [20]. Extraction techniques have been developed using solvents such as ethanol or super-critical CO_2 extraction (SCO_2) to isolate the lipid fraction from the protein and carbohydrate fractions. Each business has developed its own systems to produce nutraceutical products, which are often highly dissimilar to each other. The active components in GSM powder include the well-known omega-3 PUFAs, an array of bioactive lipids and GAGs, but they also include components such as glycogen, selenium, iron, iodine, phosphorus, niacin and vitamin B_{12} [21].

GSM powders and oils are sold under a broad range of brand names. GSM lipid extract, trademarked as PCSO-524™ (Lyprinol®), is produced by MacLab (Nelson, Aotearoa/NZ) in partnership with Pharmalink International Ltd., headquartered in Hong Kong. MacLab has been producing GSM nutraceutical products since 1973, and its products are sold under the trade names OmegaXL®, BioLex™, Biolane® and Seatone®. GlycOmega™ PLUS is marketed by Aroma NZ Ltd. (Christchurch, Aotearoa/NZ). Enzaq, an extraction company based in Blenheim, Aotearoa/NZ, has commercially produced mussel powders since its first GSM concentrate in 1967. Enzaq and its facility were purchased by the fishing and aquaculture company Sanford Limited in 2017. Recently, Sanford introduced two new brands, the mussel powder product PernaUltra™ and the lipid extract product PernaGold™. CFARMX, based in Motueka, Aotearoa/NZ, produces mussel powders as well as peptide and oil products and is partnered with the privately-owned Aotearoa/NZ-based seafood and agribusiness company Talley's Group Ltd. Based in Christchurch, Aotearoa/NZ, Waitaki Biosciences produces mussel powder and oil under the brand name PernaTec®. United Fisheries, also based in Christchurch, is a family-owned fishing company that produces GSM powders under the brand Nutri Zing. There are also several other companies in Aotearoa/NZ, including DryFoods in Havelock and Kōrure and Bio-Mer in Christchurch, producing mussel-based nutraceutical products.

2.1. Traditional Use of Greenshell™ Mussels 'Ka Whakangotea Ki Te Wai o Te Kākahi . . . ' (It Was Suckled on the Juice of the Freshwater Shellfish...)

This Māori proverb (whakataukī) references the cultural child-rearing practice of feeding the kākahi to young infants as an acceptable means of food to prime an infant's stomach in its formative years. Research conducted by Whaanga, Wehi [22] considered how whakataukī, such as the proverb cited above, were informed by oral traditions relating to the marine and freshwater practices of Māori.

A century ago, Best [23] observed and documented the traditional preparation methods of the Māori to cook shellfish in a steam earth oven (umu) or preserve them through a drying process. This drying method involved both curing and dehydrating the kūkū before storage in a pātaka, a raised storehouse [23]. Later, the kūkū were re-steamed prior to eating. This method sought to lock in the nutritional quality of mussels whilst extending the shelf life of the kai and embellishing its mana, which encapsulates prestige, authority, status and spiritual power as both an important and lasting food source and a tradeable asset. Kūkū and many other types of seafood were prepared this way, and these methods are still practised in some hapū (subtribe or sections of a large kinship group in traditional Māori communities) of Aotearoa/NZ.

Many of these Māori practices are similar to native Hawaiian culture, which also has a rich traditional mātauranga (the modern term for the traditional knowledge of the Māori people) base pertaining to kūkū and other marine food sources that encompasses their appropriate nutritional context, uses and values. A similar steaming method was specifically used to prepare pipi (oysters) and kio-nahawele (common mussels) for chiefs and children in pre-European Hawaii. The meat was removed from the shell, salted and placed in a nest of fibres from 'ahu'awa, a sedge plant, to drain overnight. The next morning, the pipi were wrapped in clean leaves and then placed in an umu or on a fire for cooking before eating or drying [24]. These cultural practices of early pacific communities indicate a very nuanced knowledge of the nutritional value and methods required to enhance the durability of kūkū.

The authors acknowledge that Te Ao Māori is a culture whose knowledge is recorded and transferred through oral and practical traditions as opposed to written traditions. Therefore, academic literature is not an accurate measure of recorded mātauranga Māori. It is also important to recognise that although researchers such as Best [23] recorded vast traditional content, knowledge and practices, the nature of their recording was abstract and translative through the English language. It is a mere glimpse of the totality of the knowledge base and knowledge of hapū-specific oral traditions such as te reo, tikanga, kawa and whakarite, which encompass "what we say, what we do, how we do it and how we regulate it," is required to further unlock the potential of the information found in this review.

Toroi–The Traditional Method of Fermentative Preservation

Toroi is the Māori term that describes a fermentation process that is a traditional method of preserving seafood. It is commonly known as preserved pickled kūkū or mussels, and the usual ingredients are mussels and pūhā (*Sonchus oleraceus*), a native leafy green vegetable, or watercress (*Nasturtium officinale*) as an alternative. Traditionally, toroi is a method used to preserve fish and other shellfish in addition to kūkū (both marine and freshwater), and it used a variety of traditional vegetables in the pickling process, including pūhā, pikopiko (bush asparagus-*Gastro obscura*) and tī kōuka (cabbage tree-*Cordyline australis*); watercress, dandelion and other vegetables were also used following their introduction to Aotearoa/NZ [25]. These preserved foods were a common delicacy favoured by central inland hapū, who had limited access to fresh marine resources. Fish and shellfish were traditionally packed into kono or oko, which are woven baskets and wooden bowls, respectively, and stored in pātaka or other traditional food storage areas. These were used both as a food source and as a commodity for trade. Toroi is now often prepared using glass preserving jars.

A common method of preparation is as follows: boil chopped pūhā for 30–60 min; drain; mix in chopped mussels that have been steamed open [25–27]. The pūhā and mussel mixture is then packed into preserving jars. Retained mussel juice and plant juice are added to the jar, and the jar is then overlain with fat or topped with a screwcap lid to seal the mixture airtight. The toroi mixture is then stored under cool, dry conditions. Kūkū preserved using the process of toroi is suggested to use lactic acid fermentation, which changes the pH of the food to reduce microbial growth [28]. As a means of ensuring food safety, the toroi should be made with mussels sourced from reputable and regulated sources, and, as an extra precaution, the storage of toroi should be maintained at chilled temperatures (<5 °C) until it is consumed.

2.2. Sustainability of GSM Production

Shellfish aquaculture is considered one of the most sustainable forms of aquaculture, as it has little to no negative effect on the environment [29,30]. Shellfish and GSMs are extractive species that filter nutrients from the water column; therefore, they do not require any feed inputs during cultivation. These species can also provide important coastal ecosystem functions by contributing to habitat and removing accumulated nitrogen and

phosphorous from the ambient environment when harvested [31]. Each mussel can filter up to 350 L of water per day [32], and in doing so, they remove suspended solids, bioremediate land run-off and aquaculture outputs; the improvements to water clarity allow light to penetrate, which enables the growth of algae and sea grass, and thus the key primary producers of the marine food chain can thrive [33].

The aquaculture production of extractive species, including molluscs and algae, has doubled in volume since the year 2000 [30]. A recent life cycle assessment (LCA) of Aotearoa/NZ mussels commissioned by the country's Ministry for Primary Industries (MPI) modelled that farmed mussels in Aotearoa/NZ have a lower carbon footprint per 100 g of protein than all other animal protein sources in the country, which is comparable to producing tofu (Figure 1) [34]. Although the industry has the potential to further reduce its carbon footprint, a core reason for its low impact is that it does not have to source, produce and ship feed for these animals. Instead, their filter feeding from the surrounding marine ecosystem of phytoplankton, microalgae and other particulates, including macroalgae detritus and particulate matter, allows for rich and diverse sources of essential macro- and micro-nutrients. For example, GSMs obtain long-chain (carbon length $\geq$ 20 -LC)-PUFAs directly from ocean-sourced microalgae rather than bioaccumulation lower trophic levels of the food chain, as is the case for many commercial fish species. This, in turn, ensures a rich and diverse lipid profile in GSMs. Recently a non-targeted lipidomic study of a GSM lipid fraction identified over 750 individual lipids species (data not shown; manuscript in preparation by M Miller et al.). As consumers eat the whole GSM, including the digestive gland, they also consume the contents of the mussels' last meals as well as their microbiome. Therefore, part of the nutritional benefit of the GSM comes directly from the phytoplankton and other particulates they consume.

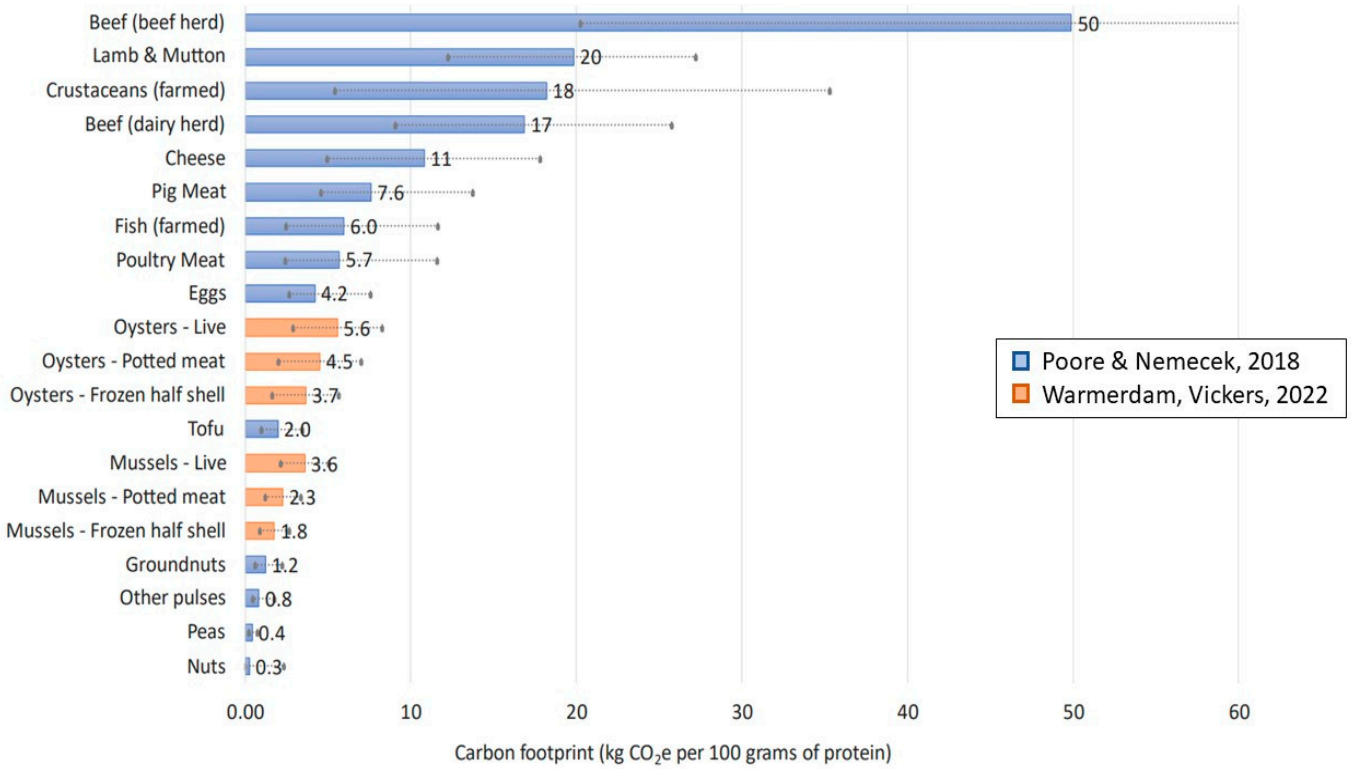

Figure 1. 'Cradle-to-retail' carbon footprint of high proteins food sources (domestic markets) from Warmerdam, Vickers [34] and data from Poore and Nemecek [35]. Taken with permission from Warmerdam, Vickers [34].

The sustainability of nutraceuticals from GSMs is superior compared to other marine resources primarily because of the sustainability and low-carbon nature of the raw

material [34]. However, producing oils and powder products does add environmental and carbon costs. The drying of marine products is an energy-intensive process [36]. Drying can cost approximately 20–30% of the total energy consumed to produce the various products [37,38]. Freeze drying has two energy-intensive stages, the freezing time and the vacuum drying time; however, it is the best technique in terms of preventing oxidative stress and protecting the bioactivity of the raw material due to low processing temperatures, which range from −2 to −10 °C, and the virtual absence of air/oxygen during processing [39]. Spray drying is potentially more energy efficient than freeze drying, as it removes the freezing stage and is much faster [40]. The extraction of lipid fractions has a further impact on the carbon footprint. Supercritical CO_2 (SCO_2) extraction of lipids has many benefits because it is highly selective, highly efficient and uses a short extraction time compared with other extraction methods. CO_2 as a solvent is inert, cheap, available, odourless, tasteless and partially recyclable. However, there are higher energy costs associated with creating the high pressures involved in SCO_2 extraction [41]. The solvent extraction of lipids has lower energy costs, but solvents such as ethanol need to be removed from the product to ensure consumer safety, although they can be recycled through the process.

2.3. Nutritional Composition of GSM

The composition of fresh, whole GSM is comprised of approximately 12–14% protein, 3–6% carbohydrate, 2–3% ash, 1.6–2.2% fat and 76–82% moisture (Figure 2) [19]. The composition of dried whole meat is comprised of approximately 36–67% protein, 10–25% carbohydrate, 2–25% ash, 6–12% fat and 0–5% moisture (Figure 2) [42]. These proportions vary across GSM and GSM nutraceutical products and depend on the season of harvest, aquaculture location, mussel diet and the procedure used to produce the powder [19]. The content of carbohydrates, fats and proteins in GSMs show major fluctuations across the season, with the lowest levels occurring during the winter and the higher levels occurring in the other seasons. Notably, fat content undergoes a 3.4-fold change over the calendar year, varying from 0.6 to 2.6 g/100 g wet weight [19]. This seasonal variation in the proximate composition of GSMs is mainly related to their reproductive cycle and controlled by water temperature, which is linked to food availability in their habitat; food availability is critical to maintaining energy requirements for spawning [19]. In addition, GSMs contain significant amounts of minerals, including iron, zinc, magnesium, calcium and iodine, making it a food rich in micronutrients [2].

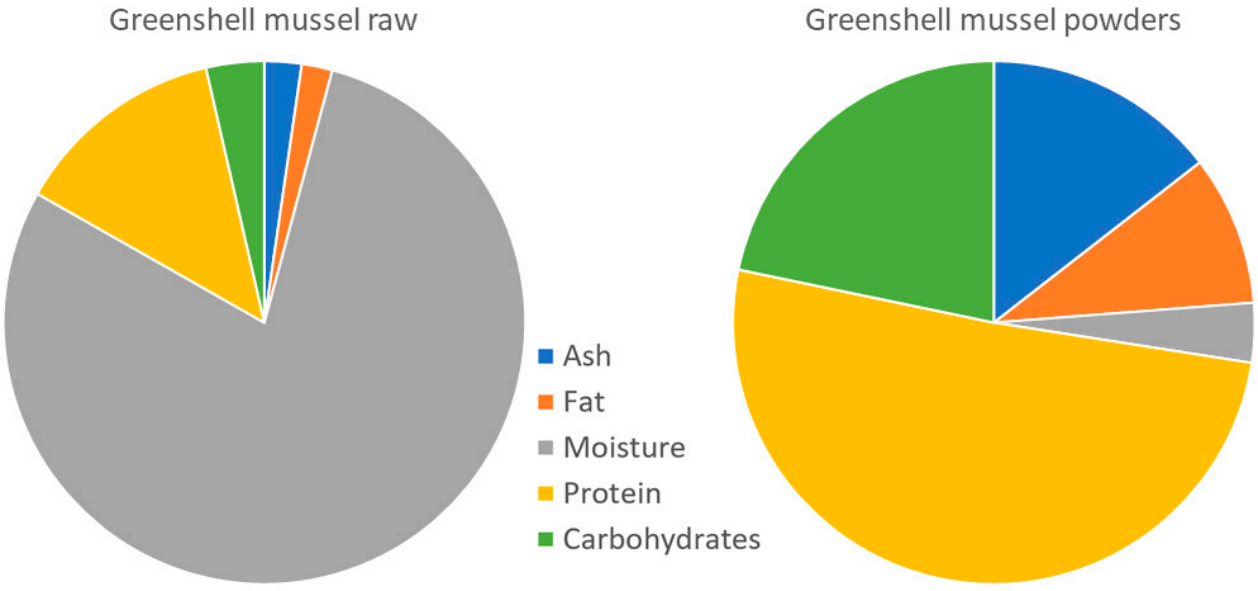

Figure 2. The composition of fresh, whole Greenshell mussels (GSMs) and GSM powders. Data taken from Miller and Tian [19] and Miller [42].

There is a strong industry and research focus on the lipid fraction of GSMs. It contains unique anti-inflammatory omega-3 PUFAs that have four double bonds and carbon chain lengths of 18, 19, 20 or 21 carbon atoms; respectively, these are 5,9,12,15-octodecatetraenoic acid (OTA, C18:4), 5,9,12,16-nonadecatertraenoic acid (C19:4), 7,11,14,17-eicosatetraenoic acid (ETA, C20:4) and 5,9,12,15,18-heneicosapentaenoic acid (C21:5). These four PUFAs have been detected in GSM lipid extracts, but not often reported in fish oil or other marine sources [14]. ETA, a structural isomer of arachidonic acid (AA), is the predominant type of PUFA detected in the lipid extract [18]. It has been shown that the COX inhibition activity of GSM oil extract is predominantly due to the free fatty acid fraction, with the greatest activity residing in the PUFA class [24]. Other fatty acids such as non-methylene interrupted (NMI), particularly 20:2 NMI and 22:2 NMI, are present in minor amounts of 1–3 g/100 g of total lipid extract, but they have potential novel biological mechanisms and bioactivity [43]. Plasmalogens, a subclass of phospholipids that include a vinyl–ether bond at the sn-1 position and polyunsaturated fatty acid at the sn-2 position, are common in GSM oil fractions, making up approximately 3–12% of total lipids [19,44]. Plasmalogens have potential health benefits for Alzheimer's and respiratory diseases. Furan fatty acids (FuFA) are another potent antioxidant and anti-inflammatory fatty acid class detected in a GSM product in one study [17], although the product in that study contained olive oil, which is a known source of FuFA [26]. Recently, FuFA were not detected when screening the extracts or raw products of GSMs (unpublished data).

2.4. Bioavailability of Bioactive Components in GSM Products

The components of GSMs that have clearly and consistently demonstrated bioactivity are omega-3 PUFAs in the lipid portion of the mussel and glucosamine and chondroitin sulphate in the carbohydrate portion of the mussel. The latter is primarily in the form of polysaccharides and are sometimes bound to polypeptides, forming a glycoprotein [45]. Glucosamine is a monosaccharide and forms one of the building blocks of GAGs, including chondroitin sulphate. Because of its large size, chondroitin sulphate is poorly bioavailable in its intact form when consumed orally. Its low bioavailability of 5–15% in the small intestine results in approximately 90% remaining unabsorbed; the remaining unabsorbed portion must be degraded by the gut bacteria in order to be absorbed [46]. Thus, degradation by gut microbiota plays a vital role in the bioavailability of chondroitin sulphate in the host [47].

The bioavailability of long-chain omega-3 PUFAs is affected by many factors. Following oral intake of omega-3 PUFAs in food or nutraceuticals, they are initially emulsified in the stomach; omega-3 PUFAs then enter the small intestine, where they are cleaved off from their TG bond to form free fatty acids and 2-monoacylglyceride (2-MAG). Free omega-3 fatty acids and 2-MAG are taken up by enterocytes and then re-esterified to form TGs, which are incorporated into chylomicrons; omega-3 PUFAs are then transferred to the lymphatic system and finally to the blood circulation, where they reach target tissues and become incorporated into cell membranes [48]. In general, EPA and DHA that are bound to triglycerides (TGs) are more effectively absorbed than the free forms bound to ethyl esters. Moreover, the fat content of food plays an important role in the absorption rate [48]. Therefore, the delivery format of a GSM product influences intestinal absorption of its omega-3 PUFAs. A study by Miller et al. [49] established the bioavailability of EPA and DHA in four orally administrated GSM products: phospholipid-rich oil, half-shell unprocessed whole mussel, TAG-rich powder and a food ingredient. Although the EPA content was consistent and all four formats were incorporated into identical whole meals of leek and potato soup, the half-shell whole mussel and powder formats resulted in a 20% greater increase in plasma EPA concentration compared to the oil format. In contrast, DHA and total n-3 LC PUFA plasma exposure parameters were not statistically different across the four GSM products. It is likely that lipid class has an impact on EPA bioavailability, but other factors, such as processing and extraction methods, may also play a role. The

bioavailability of the other components of GSMs (other lipids, vitamins, minerals and bioactive peptides) is yet to be determined.

3. The GSM Health Benefits: Evidence from Clinical Studies

The potent anti-inflammatory bioactivity of GSM lipids has made it an attractive nutraceutical treatment for various inflammatory conditions, including arthritis. Glucosamine and chondroitin sulphate from GSMs and other sources have also been marketed for decades as treatments for arthritic conditions and joint health. There are a number of potential mechanisms underlying the protective effect of the bioactive compound present in GSM (Figure 3). The following sections describe the established GSM health benefits and the cellular and molecular mechanisms by which these compounds exert their bioactive properties.

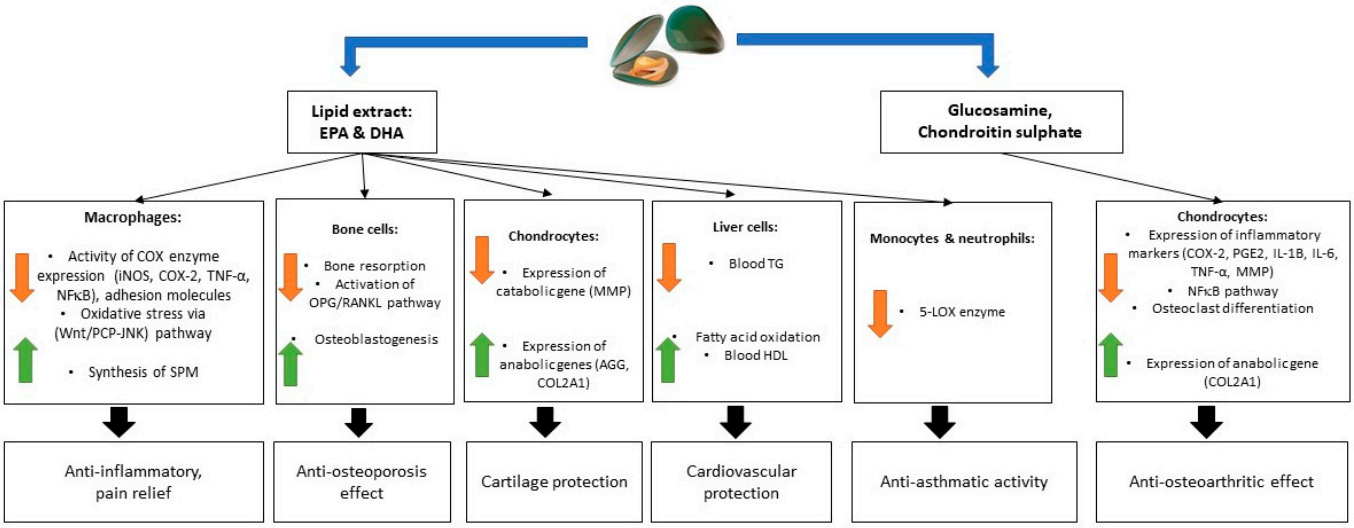

Figure 3. Potential mechanisms underlying the protective effect of bioactive compounds present in Greenshell™ mussels. AGG, aggrecan; COX, cyclooxygenase; COL2A1, collagen Type II alpha 1 chain; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; IL-1B, interleukin-1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LOX, lipoxygenases; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; TNF-α, tumour necrosis factor alpha; OPG, osteoprotegerin; PGE2, prostaglandin E2; RANKL, receptor activator of NF-κB ligand; SPM, specialised pro-resolving mediators; TG, triglycerides; Wnt/PCP-JNK, Wnt/planar cell polarity-c-Jun N-terminal kinase.

3.1. Osteoarthritis, Rheumatoid Arthritis and Osteoporosis

The early clinical trials [7,50] and the majority of the subsequent studies found in the published literature have established the efficacy of GSM extract on arthritis symptoms, with the assumption being that the anti-inflammatory PUFAs in GSM reduced chronic inflammation and, thus, joint pain [7,50]. Freeze-dried GSM powder at a dose of 3 g/day for 3 months improved OA symptoms [51] and was equally effective as glucosamine sulphate at the same dose [52]. Similarly, the GSM oil extract Lyprinol at four capsules per day (200 mg of GSM oil extract/day) resulted in OA pain relief in several studies [53,54], with higher efficacy compared to fish oil [55]. BioLex, a dose of four capsules per day (600 mg/day) for 3 months, showed no effect, possibly because of the high severity of symptoms in the participants, and furthermore, this formula contains fewer bioactive lipids than Lyprinol [56]. Based on our recent systematic review and an earlier study, both GSM oil and the powder format have proven to be equally effective in reducing OA symptoms [50,57].

In studies of rheumatoid arthritis (RA), GSM powder supplementation (300–1180 mg/day) resulted in no improvement [6,58,59], whereas Lyprinol combined with fish oil (140 and

1832 mg/day, respectively) reduced RA symptoms. The improvement of RA symptoms with the oil extract but not with the powder [60] is probably due to RA patients' higher requirements of omega-3 PUFAs to modify their autoimmune-related inflammation [61]. In addition, GSM oil and powder have shown promise as protective agents against proteoglycan and collagen degradation in animal studies. For example, GSM oil (PCSO-524) fed to dogs with OA at 5mg/kg body weight once daily reduced cartilage degradation and the release of WF6, an epitope of chondroitin sulphate; in contrast, fish oil fed at 1000 mg/dog twice daily had no significant protective effect [62]. More recently, GSM powder administrated at 5% of the diet, providing 1% of the total dietary fat and 33% of dietary protein, was shown in an obese rat model of metabolic OA to reduce both the production of C-telopeptide collagen type II (CTX-II), a biomarker of type II collagen degradation, and the severity of cartilage damage in knee joints [63]. Similarly, oral supplementation of whole GSM powder at 3 g/day demonstrated a reduction in degradation of type II collagen in overweight and obese postmenopausal women and demonstrated a clinical benefit on overall joint pain as self-reported by the Visual Analogue Scale (VAS) [64]. However, in this study and in the above-mentioned study using the obese rat model of metabolic OA [63], no significant decreases in inflammatory cytokines were observed. This suggests that GSMs may act within the joint microenvironment rather than at the systemic level [64].

Animal and human studies indicate that omega-3 PUFAs can also influence bone health. Clinical trials have demonstrated that treatment with EPA and DHA decreased bone turnover markers [65], inhibited bone resorption [66] and protect against bone mineral density loss in postmenopausal women [67]. Dietary intake of omega-3 and -6 PUFAs affects the fatty acid composition of the bone, thus modulating the synthesis of PGE2, a potent stimulator of bone resorption [68]. In murine models of high-fat diet-induced obesity [69] and senile osteoporosis [70], supplementation with fish oil prevented adipose tissue expansion in the bone marrow as well as hematopoietic bone marrow atrophy and, ultimately, bone loss.

The bioactivities of glucosamine and chondroitin sulphate in promoting joint health and cartilage protection have been documented in human studies. In studies in athletes such as soccer players and cyclists, the administration of glucosamine at 1.5 or 3 g/day for 3 months reduced the urinary level of the cartilage degradation marker CTX-II in a dose-dependent fashion, but these doses had no effect on bone formation and bone resorption markers [71,72]. Glucosamine may have potential benefits in the treatment of osteoporosis and bone maintenance; however, to date, positive results in bone health and osteogenesis have been limited to experimental models. For example, a study in a rat model of combined ovariectomy-induced osteoporosis and OA induced by anterior cruciate ligament transection showed that supplementation with a mixture of glucosamine and chondroitin sulphate effectively protected both cartilage and bone. The mixture was administered at 140 or 175 mg/kg/day, which would equate to a very achievable dose of 1200–1500 mg/day for the average adult human. In this rat model, the treatment significantly reduced cartilage and proteoglycan depletion by 80%. The bone microarchitecture, assessed by micro-computed tomography (microCT), exhibited positive improvements in bone structure, and these correlated with an increased ratio of osteoprotegerin (OPG): receptor activator for nuclear factor kappa B ligand (RANKL) [73]. The OPG/RANKL system is a critical molecular pathway that induces osteoclast bone resorption and bone loss. OPG neutralises the effect of RANKL and suppresses bone resorption; therefore, an increase in the ratio of OGP:RANKL reduces the rate of bone resorption [74].

3.2. Metabolism, Chronic Inflammation and Cardiovascular Disease

There is evidence that GSM extracts effectively modulate the metabolism associated with obesity in rodent models. Increased lean mass and decreases in fat mass gain, body weight and visceral fat were observed in obese rats fed with GSM powder or oil [63,75]. Similarly, blue mussel powder improved metabolic parameters in rats [76]. In a recent study, a lipid-lowering effect was reported when GSM powder comprised 25–45% of the

basal diet of rats; this dietary intervention reduced low-density lipoprotein cholesterol (LDL-C) and lipid peroxidation in liver tissue and increased glutathione and glutathione peroxidase antioxidant activities [77]. The same study also revealed an increase in antithrombotic activity and prolonged coagulation time, which could be beneficial for patients who need to take blood thinners, such as warfarin, to prevent the formation of intravascular thromboses. These highly promising data will undoubtedly generate interest for further investigation into whole and fractionated GSMs; future studies should identify its potential uses in humans for the treatment or prevention of cardiovascular disease and numerous other disorders related to oxidative stress and inflammation.

It is well documented that a diet rich in EPA and DHA, which are the most abundant types of fatty acid in GSM, lowers the risk of cardiovascular disease, which is a leading cause of death in Western countries [78]. A previous intervention study showed intake of blue mussels (75 g/day) as a meal elevated EPA and DHA in red blood cells and plasma, which correlates with a lower risk of cardiovascular disease [79]. Habitual intake of fish oil and marine foods rich in omega-3 PUFAs has also been associated with reduced systemic inflammation [78,80]. Daily doses of EPA and DHA at 0.7 or 1.8 g/day for 8 weeks have been shown to clinically reduce blood pressure, which plays a role in lowering the risk of cardiovascular disease [81]. In addition to omega-3 PUFAs, the GAG components of GSM have been shown to provide protective cardiovascular health benefits. For example, long-term intake of glucosamine was associated with decreased cardiovascular mortality [82] and a reduction in C-reactive protein (CRP) [83], which is a biomarker for systemic inflammation.

3.3. Asthma and Airway Inflammation

Lyprinol, a GSM oil product rich in EPA and DHA, has been investigated in asthma and airway inflammation in four studies, and two of these studies showed positive outcomes. Lyprinol improved asthma symptoms and airway inflammation in asthmatic adults when taken at a dose of 4 to 8 capsules per day (each capsule contained 50 mg of GSM oil extract and 100 mg of olive oil) for 8 and 3 weeks, respectively [84,85]. However, children with moderate to severe asthma showed no significant difference between Lyprinol and olive oil treatments (4 capsules daily), although children with moderate asthma did improve with Lyprinol treatment [86]. Lyprinol taken at eight capsules per day for 12 weeks did not improve respiratory muscle function in non-asthmatic runners [87]. Due to the limited number of studies, it is likely but not conclusively proven that Lyprinol is effective in the treatment of asthmatic adults and children with mild to moderate symptoms. No other components of GSMs have been studied for bioactivity in asthma and airway inflammation.

3.4. Exercise-Induced Muscle Damage and Inflammation

There are four published clinical studies assessing the effects of Lyprinol on muscle damage induced by exercise, of which three reported a beneficial effect. Lyprinol administrated to nonprofessional runners at 400 mg/day for 11 weeks resulted in less soreness after running, with a greater effect observed in less well-trained runners [88]. Lyprinol, taken at 1200 mg/day for 26 days after muscle damage had occurred resulted in reductions in a circulating biomarker of muscle damage and inflammation, muscle pain, loss of strength, range of motion in the knee and peripheral fatigue in untrained men [89]. ESPO-572, a mixture of 75% Lyprinol and 25% krill oil, taken at 600 mg/day for 26 days prior to conducting physical exercise, was equally effective as Lyprinol at a matching dose in reducing physical symptoms of muscle damage in untrained men [90]. However, Lyprinol at a lower dose of 200 mg/day for 8 weeks provided no observable benefits in male athletes [91]. Similarly, several intervention studies have demonstrated the positive effects of EPA and DHA on delaying muscle soreness and decreasing the elevation in muscle damage markers [92–94]. In contrast, clinical trials using non-lipid components of GSM, specifically glucosamine and chondroitin sulphate, did not reduce muscle soreness, a muscle damage biomarker, or inflammation related to exercise even when provided at 1500–3600 mg/day; in fact,

glucosamine increased muscle pain [95,96]. In general, the current evidence supports the effectiveness of GSM in mitigating exercise-induced muscle damage in untrained individuals, with the bioactive factors likely being EPA and DHA lipids.

3.5. Dysbiosis and Colorectal Cancer

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of inflammatory diseases. The mechanism of action of NSAIDs is based on the inhibition of prostaglandin biosynthesis via inhibiting COX enzyme activity. There are two isoforms of this enzyme: COX-1 is responsible for the protection of gastric mucosa [97], while COX-2 is induced by cell damage and produces proinflammatory prostaglandins. NSAID-induced gastropathy, such as gastric ulcers, is caused by the inhibition of COX-1 [98,99]. Freeze-dried GSM powder orally administered to rats on NSAIDs with carrageenan-induced paw oedema, which is used as a model of arthritis, produced anti-inflammatory effects and reduced gastric ulcer formation [100]. This is explained by the fact that GSM lipids have stronger inhibitory effects on COX-2 (25%) compared to COX-1 (12%), and thus their overall effect protects the gastric mucosal lining [101]. Two clinical studies showed that GSM powder reduced the required dose of NSAIDs and improved gastrointestinal symptoms associated with NSAIDs in patients with knee OA [52,102]. In addition, GSM powder and glucosamine supplementation positively altered gut microbiome profiles that correlated with decreases in inflammation and OA symptoms [52].

These findings suggest that the anti-inflammatory and pain-reducing effects of GSM and glucosamine may be partially due to their effect on gut microbiota. Supplementation with GSM powder and glucosamine sulphate (3 g/day for 12 weeks) notably reduced the abundance of *Clostridium* and increased short-chain fatty acid-producing bacteria such as *Lactobacillus*, *Streptococcus* and *Eubacterium* species in the gut. Specifically, supplementation with GSM in particular increased *Bifidobacterium* and *Enterococcus* and decreased yeast species [52]. The matching effects of GSM and glucosamine on gut microbes imply that glucosamine or other indigestible compounds in GSM powder provide a substrate for gut bacteria and promote prebiotic activity. This could lead to the protection of the gut barrier [103] and increase the bioavailability of chondroitin sulphate and glucosamine, which may add to the therapeutic efficacy of GSMs and alleviate OA symptoms [104]. How intestinal microbiota metabolise GSM powder has not been fully investigated; however, in vitro [105] and in vivo [106] studies have confirmed that omega-3 PUFAs and GAG compounds present in GSM can alter the profile of the microbiome. For example, supplementation with EPA and DHA has been shown to promote the abundance of commensal and short-chain fatty acid-producing bacteria such as *Bifidobacterium* and *Lactobacillus* in healthy middle-aged people [107].

It is important to note that gut microbiota has been implicated in colorectal carcinogenesis. There is evidence that the use of glucosamine and chondroitin sulphate supplements lowers the risk of colorectal cancer [108]. Recently, an animal study using low-molecular-weight chondroitin sulphate effectively prevented the growth of colorectal tumour cells by inhibiting cell proliferation and inducing apoptosis [109]. Increasing the abundance of short-chain fatty acid-producing bacteria via supplementation with whole GSM or an isolate of its prebiotic components may be the mechanism by which it provides a beneficial effect in protecting against colorectal cancer.

3.6. Attention Deficit Hyperactivity Disorder (ADHD)

One published study provided Lyprinol (200 mg of GSM oil per day via three to four capsules) to children with ADHD in a 14-week trial. The data from this study identified a promising effect of GSM oil in treating inattention and hyperactivity, particularly in children with less severe symptoms [110]. The marine omega-3 PUFA EPA, alone or combined with DHA in the form of fish oil, has also shown benefits in children and adults with ADHD [111]. The findings of these two studies show insufficient evidence to determine the benefit of GSM in treating ADHD, and further research is warranted in this field.

4. Potential Mechanisms and Molecular Pathways of GSM Components

4.1. Cellular and Molecular Mechanisms of Lipid Components of GSM

The lipid fraction of GSM, particularly EPA and DHA, are the major components that are assumed to be responsible for GSM's anti-inflammatory and other beneficial effects observed in patients with arthritis, asthma and cardiovascular disease [2,112]. To date, the role of GSM lipid extracts or fractions has not been directly investigated for a cardioprotective effect. However, there are data from several in vitro studies using individual omega-3 PUFAs, and in particular, EPA, which support this hypothesis. EPA has shown anti-inflammatory effects in macrophages via the inhibition of the expression of adhesion molecules and monocyte chemoattractant protein 1 (MCP-1), a molecule that regulates the migration and infiltration of monocytes and macrophages, as well as the inhibition of the synthesis of metalloproteinases, which are enzymes that accumulate in and promote the formation of atherosclerotic plaques [113]. Another potential mechanism to explain the cardioprotective role of EPA is through its influence on the Wnt/planar cell polarity-c-Jun N-terminal kinase (Wnt/PCP-JNK) pathway in macrophages, which is involved in oxidative stress and inflammation [114]. Furthermore, dietary EPA and DHA reduce fasting and postprandial plasma TG levels and are approved for the treatment of hypertriglyceridemia, as they reduce very-low-density lipoprotein (VLDL)-TG production by increasing hepatic fatty acid oxidation, which reduces the TG content in liver cells. The reduction in postprandial plasma VLDL-TG concentrations is explained by an increase in lipoprotein lipase activity and enhanced chylomicron clearance [115]. Data from studies on omega-3 PUFAs treatment in patients with non-alcoholic fatty liver disease suggest that the resultant reduction in liver fat content was related to changes in DHA intake, while the reduction in fasting plasma TG concentration was mainly associated with EPA intake [116].

EPA and DHA have been positively associated with high-density lipoprotein (HDL) functionality by improving HDL size and altering their lipid content, antioxidant capacity and enzyme composition [117]. EPA and DHA can reduce blood pressure and increase vasodilation. The vasodilatory effects of EPA and DHA on vascular smooth muscle cells are largely facilitated through the opening of conductance calcium-activated potassium channels (BKCa), ATP-sensitive potassium channels (KATP) and members of the Kv7 family of voltage-activated potassium channels, leading to vasodilation and relaxation [118]. In addition, these fatty acids can protect vascular cells by mitigating the proinflammatory reactions that occur with hypertension [119].

The main mechanism of action underpinning the anti-asthmatic activity of GSM lipids is their ability to reduce leukotrienes, such as the bronchiole constrictor eicosanoid, by inhibiting 5-lipoxygenase (5-LOX) in monocytes and neutrophils [14]. With respect to muscle recovery, GSM oil contains an ample amount of fatty acids bound to phospholipids (approximately 77–82%), which gives it anabolic properties that have been shown to enhance muscle recovery by facilitating muscle protein synthesis [120]. Due to limited data, the mechanism of action by GSM lipids in reducing ADHD symptoms is still unknown; however, it has been proposed that its anti-inflammatory activity and ability to decrease the ratio of AA to EPA may lead to improvement in associated symptoms [121].

There are several mechanisms proposed for the anti-arthritic effects of GSM oil. Its lipids are well documented as having an inhibitory effect on COX-2 and the 5-LOX cascade to suppress the inflammatory response [101]. Specialised pro-resolving mediators (SPMs) are compounds enzymatically derived from EPA and DHA when they are metabolised by LOX. These novel anti-inflammatory molecules, which include resolvins, maresins and protectins, promote the resolution of inflammation, tissue healing and relief of chronic pain in rheumatic diseases [122,123]. Another mechanism for the anti-inflammatory effect of GSM lipids is the suppression of gene expression of inducible nitric oxide synthase (iNOS) and COX-2, resulting in reduced levels of nitric oxide (NO) and prostaglandin E2 (PGE2), two mediators of the inflammatory response. GSM lipids also down-regulate the expression of the proinflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β and suppress the nuclear factor kappa B (NF-kB) signalling pathway and

phosphorylation of mitogen-activated protein kinases (MAPKs) in macrophage cells [124]. The enhanced expression of these proinflammatory cytokines and activation of NF-kB signalling in macrophages that reside in synovial membranes have both been associated with the development of OA [125]. Thus, inhibiting the NF-kB pathway in macrophages by GSM lipids is another likely mechanism by which they modify OA disease incidence and progression.

Plasmalogens are a class of glycerophospholipids found in GSMs and other marine bivalves, accounting for 10–35% of their total lipids [126,127]. Plasmalogens are unique phospholipids, being characterised by a vinyl ether at the sn-1 position attached to saturated and monounsaturated fatty acids (C16:0, C18:0 and C18:1), while PUFAs, specifically DHA (C22:6 omega-3) or arachidonic acid (C20:4 omega-6), are found in the sn-2 position [128,129]. Plasmalogens are present in cell membranes where they serve as endogenous antioxidants due to their vinyl ether double bond, protecting the PUFAs in the sn-2 position from oxidative stress [130]. Low levels of plasma ethanolamine plasmalogens have been linked with Alzheimer's disease and cognition deficit, and there is growing interest in clinical interventions using plasmalogens as potential therapeutics for Alzheimer's [131].

The treatment of chondrocytes, the cells that produce cartilage, with omega-3 PUFAs from GSM oil versus krill oil and versus fish oil demonstrated overall down-regulation in the expression of the catabolic genes matrix metalloproteinase (MMP)-1, MMP-3 and MMP-13, which code for enzymes that degrade collagen; the data showed up-regulation in the expression of anabolic genes that produce aggrecan (AGG) and the alpha-1 subunit of collagen type II (COL2A1), which are components of healthy cartilage [132]. The PUFAs also reduced the release of sulfated glycosaminoglycans (s-GAGs); however, for this effect, fish oil and krill oil were superior to GSM oil, a variation that is likely due to the differences in their forms of lipid classes. In krill and GSMs, the omega-3 PUFAs are mainly in the form of phospholipids, while in fish oil, these are in the form of either triacylglycerols or fatty acid esters. With respect to individual fatty acids, EPA was more effective than DHA in promoting anabolic activity and reducing catabolic activity. However, omega-3 PUFAs were unable to reduce the expression of inflammatory cytokines IL-1β and TNF-α in chondrocytes.

A non-polar lipid fraction of GSM oil, which is rich in free fatty acids, was shown to possess potent anti-osteoclastogenic activity. Osteoclasts are cells that degrade and resorb bone. In an in vitro study using the murine macrophage cell line RAW 264.7 stimulated with RANKL to induce osteoclastogenesis, cells treated with the non-polar GSM lipid extract significantly inhibited osteoclast differentiation, the production of tartrate-resistant acid phosphatase (TRAP) enzyme that degrades bone, and the number of TRAP-containing cells, which in vivo would equate to a decrease in osteoclast activity and bone resorption [133]. The non-polar lipids also diminished the formation of actin rings in osteoclasts, which is an important element of bone resorption. In addition, this treatment down-regulated mRNA expression of several genes related to osteoclast function and bone digestion, including cathepsin K, carbonic anhydrase II (CA II), MMP-9 and nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), which is a master transcription factor of osteoclast differentiation. DHA and EPA in the form of free fatty acids are likely responsible for this anti-osteoclastogenic effect. Further studies are needed to confirm this bioactivity of non-polar GSM lipids on bone metabolism in humans.

EPA and DHA from marine sources have been shown to positively affect bone metabolism. The osteoprotegerin (OPG)/RANKL signaling pathway is the main mediator of osteoclastogenesis. AA and its metabolite PGE2 are the main stimulators of RANKL expression, leading to enhanced bone resorption. Krill oil, which contains abundant omega-3 EPA and DHA, suppresses the osteoclastogenesis-related OPG/RANKL pathway by decreasing the secretion of PGE2 and its receptor EP4 [134]. Moreover, omega-3 PUFAs can regulate bone formation and the differentiation of osteoblasts. In vitro evidence from bone marrow mesenchymal stem cells treated with krill oil showed an increase in osteogenesis via increasing Runx2 expression, a transcription factor that promotes osteoblastogenesis, as

well as in vivo evidence of krill oil downregulating PPARγ and adipogenesis in a mouse model of postmenopausal osteoporosis [135]. There is also evidence that omega-3 PUFAs can act as PPAR ligands and modulate osteoclast formation. In a study by Kasonga, Kruger [136], DHA and EPA activated PPARα and PPARγ to a larger extent than PPAR β/σ in the human CD14+ osteoclast cell line. This study showed that PPAR activation exerted an inhibitory effect on osteoclastogenesis via the modulation of RANKL signaling [136].

4.2. Cellular and Molecular Mechanisms of Glucosamine and Chondroitin Sulphate and Bioactive Peptides

Whole GSM powder typically contains 3% GAGs [2]. There is only one in vivo study in which glycogen isolated specifically from GSMs produced an anti-inflammatory effect in rats with induced footpad oedema; however, the anti-inflammatory effect disappeared with further hydrolysis of protein, suggesting that a protein component of glycogen was responsible for the effect [137]. The existing in vitro studies on glucosamine and chondroitin sulphate used samples obtained from bovine and other marine sources; there are no data available specifically on GAGs derived from mussels. Nevertheless, as the origin of GAGs has not been shown to impact their bioactivity, GAGs present in mussels are likely to possess similar bioactivity to bovine GAGs.

As the main component of the extracellular matrix in cartilage, GAGs have been widely studied for joint and cartilage protective properties [138]. The potential anti-inflammatory and chondroprotective effects of glucosamine on human osteoarthritic chondrocytes and the possible mechanisms have been investigated. Glucosamine sulphate reduced chondrocyte expression and the release of COX-2, PGE2, IL-1β, IL-6, TNF-α and MMPs, while it up-regulated COL2A1 [139,140]. It also reduced apoptosis and promoted both chondrocyte proliferation and proteoglycan production [140,141]. The effects of glucosamine sulphate are mediated through the inhibition of NF-kB activity [142]. However, chondrocyte and synoviocyte cell cultures treated with glucosamine at physiologically relevant concentrations found in serum and synovial fluid did not show the same impact on proteoglycan production or MMP-13 synthesis; however, the results showed a decrease in the production of PEG2 in chondrocytes, suggesting that oral supplementation with glucosamine at clinically relevant concentrations may reduce inflammation in joint disease [143]. In an in vitro study using human primary osteoclasts cultured in a dynamic three-dimensional system to resemble the in vivo bone microenvironment, treatment with glucosamine sulphate decreased osteoclast cell differentiation and function; in addition, osteoclasts isolated from patients with OA were more sensitive and responsive to glucosamine compared to osteoclasts from healthy donors [144].

In a clinical trial, participants regularly taking a glucosamine supplement or a chondroitin sulphate supplement, or both, were found to have lower biomarkers of systemic inflammation compared to non-users [145]. In addition to possessing chondroprotective and anti-inflammatory activities, the GAGs present in GSMs may have health benefits in preventing sarcopenia, a state of high-fat mass and relatively low muscle mass that commonly occurs with ageing. Several studies have shown an association and comorbid interaction of sarcopenia with musculoskeletal diseases such as OA and osteoporosis [146,147]. The mechanisms of action of GAGs on the pathophysiology of sarcopenia have been partially identified. These compounds inhibit the proinflammatory NF-kB that is activated in muscle atrophy. Furthermore, they supply building blocks for the regeneration of connective tissue surrounding myocytes [148].

The proteins from mussels have also been investigated to identify bioactive peptides. Antioxidant, antimicrobial and angiotensin-converting enzyme (ACE)-inhibitory activities are the main bioactive features that have been found for mussel peptides [149]. ACE is the enzyme that converts angiotensin I into angiotensin II, which constricts blood vessels and increases blood pressure; therefore, inhibiting ACE is a target for hypertension treatment [150]. To date, only one published study has characterised bioactive peptides from GSMs [151]. This study singled out one bioactive peptide isolated from enzymatic hydroly-

sis by pepsin after 30 min. Named GPH, the peptide possessed the highest antioxidant and ACE inhibitory activities but no antimicrobial activity. Other peptides demonstrated both antioxidant and antihypertensive bioactivities, but to a lesser degree than GPH. This study also showed that the antioxidant and ACE inhibitory activities were predominantly in peptides with a molecular weight of less than 5 kD. Analysis of the amino acid composition for these peptides showed that hydrophobic amino acids, such as glycine, valine, lysine, isoleucine and alanine, were present in higher quantities compared to polar and charged amino acids; in addition, the hydrophobic amino acids appeared to have contributed to the observed bioactivity. In this study, GSM peptides did not show any antimicrobial activity; the authors suggest potential antimicrobial peptides from GSMs are more likely to be present in the haemolymph and would best be extracted using organic solvents. Bioactive peptides with potent antioxidant or ACE inhibitory activity have enormous potential for the treatment of cardiovascular diseases, and it would be of interest to confirm the in vitro findings with GPH by conducting further investigations in vivo.

5. Conclusions

Greenshell™ mussels, kūkū, a kaimoana species endemic to Aotearoa/NZ, have for centuries been consumed, either fresh, dried or pickled, for their health-promoting bioactivity as well as for their nutritive content. GSMs are the basis of the country's highly sustainable aquaculture industry and a major export product. Although GSMs are low in fat and carbohydrates and high in protein, it is their non-protein components that are of the most value due to their bioactivity. The lipid fraction of GSMs is rich in omega-3 PUFAs, including DHA and EPA, which have been shown to provide protection against inflammation, osteoarthritis, osteoporosis and cardiovascular disease by modulating well-defined cellular signaling pathways. GSM lipid products, such as Lyprinol, have been proven in multiple clinical trials to be efficacious and have been marketed primarily to osteoarthritis patients for decades; in recent years, research has focused on the lipids' bioactive effects in asthma and muscle damage. Glucosamine and chondroitin sulphate have also been shown to protect against osteoarthritis and other joint disorders by providing the building blocks needed to produce new cartilage and by modulating cellular functions. GSMs contain other unusual components, including plasmalogens and unique lipids, which are likely to have novel bioactivities as well as at least one novel peptide with antioxidant and antihypertensive bioactivity. Further investigations will likely identify additional bioactive components and health benefits of GSM.

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Abbreviations

2-monoacylglyceride (2-MAG); 5,9,12,15-octodecatetraenoic acid (OTA); 5-hydroxyeicosatetraenoic acid (5-HETE); 5-lipoxygenase (5-LO); 7,11,14,17-eicosatetraenoic acid (ETA); Aggrecan (AGG); Alpha-1 subunit of collagen type II (COL2A1); Angiotensin-converting enzyme (ACE); Aotearoa—New Zealand (NZ); Arachidonic acid (AA); ATP-sensitive potassium channels (KATP); Attention deficit hyperactivity disorder (ADHD); Calcium-activated potassium channels (BKCa); Carbonic anhydrase II (CA II); Collagen Type II alpha 1 chain (COL2A1); C-reactive protein (CRP); C-telopeptide collagen

type II (CTX-II), Cyclooxygenase (COX); Docosahexaenoic acid (DHA); Eicosapentaenoic acid (EPA); Furan fatty acids (FuFA); Glycosaminoglycans (GAGs); GreenshellTM mussel (GSM); High-density lipoprotein (HDL); Inducible nitric oxide synthase (iNOS); Interleukin 6, IL-6; Interleukin-1 beta, IL-1B; Lipoxygenases; LOX; Low-density lipoprotein cholesterol (LDL-C); Matrix metalloproteinase (MMP); Ministry for Primary Industries (MPI); Non-methylene interrupted (NMI); Nonsteroidal anti-inflammatory drugs (NSAIDs); Nuclear factor kappa B (NFkB); Nuclear factor of activated T-cells cytoplasmic 1 (NFATc1); Osteoarthritis (OA); Osteoprotegerin (OPG); Phosphatidylcholine (PC); Phosphatidylethanolamine (PE); Phosphatidylglycerol (PG); Phosphatidylinositol (PI); Phosphatidylserine (PS); Polyunsaturated fatty acids (PUFAs); Prostaglandin E2 (PGE2); Receptor activator of NF-kB ligand (RANKL); Rheumatoid arthritis (RA); Specialised pro-resolving mediators (SPM); Sulfated glycosaminoglycans (s-GAGs); Supercritical CO2 (SCO2); Tartrate-resistant acid phosphatase (TRAP); Triglycerides (TGs); Tumour necrosis factor alpha (TNF-α); Very-low-density lipoprotein (VLDL); Visual Analogue Scale (VAS); Wnt/planar cell polarity-c-Jun N-terminal kinase (Wnt/PCP-JNK).

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