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Review Article

Anti-inflammatory Metabolites and Allergenic Proteins from Green Lipped Mussel (*Perna canaliculus*)

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Abstract

Lipophilic extracts from the green-lipped mussel (*Perna canaliculus*) are known to have anti-inflammatory capacity, but allergenic proteins from Perna canaliculus were identified recently. This raises the question of the safety of the anti-inflammatory products of Perna canaliculus. The anti-inflammatory effects on symptoms of arthritis are reported for a lipid fraction, comprising inhibitors of cyclooxygenases (cox1 and cox2), histamine blockers and omega-3 fatty acids. The lipid fractions can be obtained by extracting mussel tissue using supercritical CO2 or organic solvents. To produce glycosaminoglycan-rich extracts, homogenates are delipidated, and the proteins are digested by proteases, leading to an enrichment of the carbohydrate fraction consisting primarily of glycosaminoglycans. Products for animal health care can also be prepared more cost-efficiently by simply homogenising mussel tissue and subsequent freeze-drying. These products are mainly applied as dietary supplements. We here review briefly the knowledge on the mode of action of the various supposed anti-inflammatory capacities of *Perna canalicus* associated with several classes of molecules and focus on the applied extraction protocols because the extraction methods define the potential risk of allergenic proteins, which were recently discovered.

Background

The Green Lipped Mussel (*Perna canaliculus*) is a bivalve mollusc from the family of Mytilidae and is found endemically in the sea around New Zealand. The mussels have been cultivated since the 1960s in large capacities by aqua farming and exported worldwide. *P. canaliculus* products are available as dietary supplements. They are promoted for therapy as well as for prevention of bone problems in humans as well as in animals.

Anti-inflammatory Activity of Lipid Fractions from *Perna canaliculus*

The anti-inflammatory potential of *Perna canalicus* was first reported about four decades ago [1]. The study by Couch et al. reported a positive effect in managing inflammatory joint disease [2], and Caughey et al. described a positive impact on treating rheumatoid arthritis [2]. The anti-inflammatory effects of *Perna canaliculus* were hypothesised to be caused by three different modes of action. First, there is evidence that *Perna canaliculus* extracts contain inhibitors of prostaglandin synthase, also known as cox-1 and cox-2 [3]; second, the histamine inhibitor lysolecithin was found in high abundance in *P. canaliculus* extracts [4], and thirdly also the relatively high content of Omega-3 fatty acids might exert an additional anti-inflammatory effect [5].The association of the prostaglandin level with auto-immune diseases is well documented for many auto-immune diseases like rheumatoid arthritis and osteoarthritis [6]. Cox-1 is constitutively expressed in many tissues, but the cox-2 gene is dramatically upregulated after inflammation [7]. Since the formation of prostaglandins is associated with inflammation and pain, many painkillers are cox-1 or cox-2 inhibitors. Due to its induction during inflammation, the cox-2 enzyme is a primary target for the therapy of auto-immune diseases [8-10]. Based on identifying cox-I inhibition by freeze-dried homogenates of *P. canaliculus* in different studies, the question was raised about the specific mode of action and the actively involved molecules. In the study of McPhee et al., the homogenate was saponified by KOH hydrolysis, which enormously increased the inhibition of cox-enyzmes [3]. The treatment of the homogenate with proteases and lipase also resulted in a substantial increase in the inhibitory capacity compared to the homogenate; please see Figure 1.

These results rule out the role of proteins and complex lipids and favour the involvement of the lipid fraction. Such a lipid fraction from *P. canaliculus* is also produced as the commercially available extract Lyprinol ®(Pharmalink International Ltd.), which is achieved by extracting the lipid fraction from the homogenate by supercritical CO2. Further Lyprinol free fatty acid fraction tests revealed that purified polyunsaturated fatty acids (PUFA) extracts seem to be competitive substrate inhibitors of prostaglandin synthase [11]. The effects of different types of molecules were summarised in the review of Grienke et al. [1]. Besides the inhibition of prostaglandin synthase, the blocking of histamine by lysolecithin might contribute to the anti-inflammatory effects of extracts from *P. canaliculus*. Lysolecithin was isolated from a methanol-based extraction from *Perna* homogenate by liquid-liquid extractions, further silica-based chromatography, and size-exclusion chromatography. The molecular analysis of a single spot from thin-layer chromatography by NMR and mass spectrometry yielded the identification of lysolecithin [4]. Because

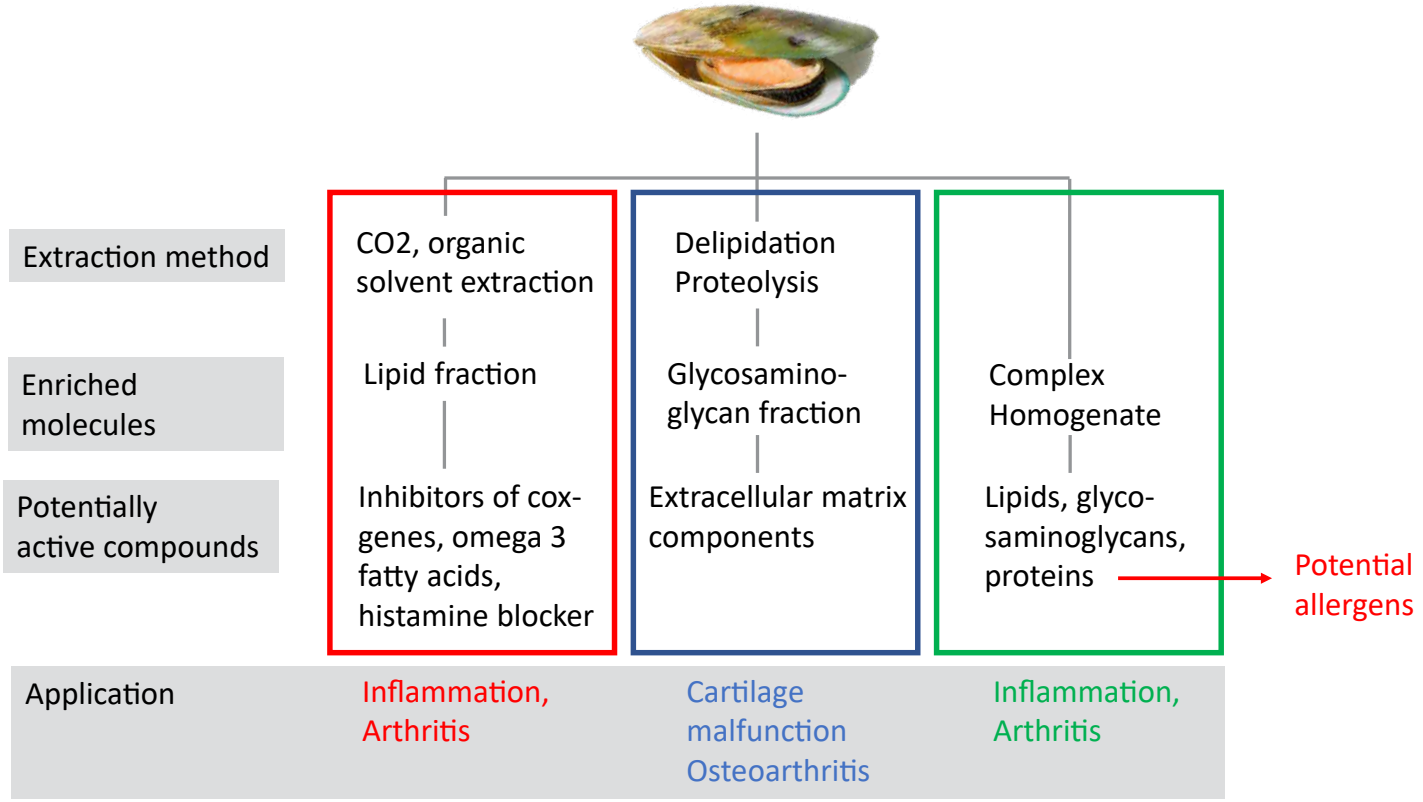

Figure 1: Overview of processes resulting in *P. canaliculus* products. The lipid fraction, glycosaminoglycans and whole homogenate require different extraction methods and are promoted by commercial providers for applications like inflammation, arthritis, cartilage malfunctions and osteoarthritis. The extracellular matrix comprises a wide range of glycosaminoglycans and collagens as the main protein content and associated proteins.

phosphatidylcholine is relatively small, it is soluble in methanol and assumingly also in CO2, which explains the enrichment by these extraction methods. The third potential anti-inflammatory activity within lipid extracts is omega-3 fatty acids, which have been found to inhibit cox-2 [12]. In the case of osteoarthritis, both the lipid fraction and whole extracts of *Perna canaliculus* have yielded therapeutic benefits for the included patients [13].

Effects of Glycosaminoglycans

Besides the anti-inflammatory capacity of *Perna* extracts, there is also experimental evidence for the effects of Perna extracts on cartilage function in the case of osteoarthritis [13,14]. In this disease, inflammation is supposed to be the primary starting point with secondary effects on the cartilage function. Here, the high content of sulphated glycosaminoglycans in *Perna canaliculus* extracts [15] might play a role since they first replace a disease-induced lack of glycosaminoglycans in affected joints and secondly interact with proteins involved in regulating the inflammatory processes [16]. The main cartilage components are proteoglycans, consisting of a protein core with covalently bound glycosaminoglycans (GAGs). The high content of chondroitin-sulfate (up to 12%) in *Perna canaliculus* [15] might supply the chondrocytes in the cartilage to synthesise an increased amount of proteoglycans. The increase in proteoglycans in the cartilage might also affect the binding of cytokines that control the inflammation processes and contribute to the healing process.

Application of Whole Homogenates in Animals and Detection of Allergens Therein

Perna canaliculus extracts have been used in studies on animals like dogs with a focus on osteoarthritis [17]. Besides osteoarthritis in dogs, studies about the effects of feline degenerative joint disease and lameness and joint pain in horses have been reviewed earlier [18]. For most of the cases, positive results were found. Still, since the more cost-effective whole homogenates were used for animals, there is less information about the effective molecule class or molecule. Recently, proteins from *Perna canaliculus* were identified as allergenic in humans [19]. The sole case of an allergic reaction to *Perna* proteins was a dog owner who fed freeze-dried homogenate to her arthritic dog. The affected person had dermal contact with the powder and assumingly inhaled small amounts. Prick tests confirmed the allergic symptoms, and the allergic proteins were identified by IgE-based western blotting with the patient's serum. The proteins in the IgE-positive bands were identified by mass-spectrometry as actin, tropomyosin, and paramyosin. All these proteins are highly abundant in all cells across the animal kingdoms. Actin is crucial in forming a part of the cytoskeleton, which is key for forming cells. Tropomyosin and paramoysin form fibres that are crucial for muscle contraction. The biggest part of the mussel is the muscle necessary to move the clamps, which leads to a very high abundance of these two proteins in extracts.Although these are the first allergens to be reported, they are closely related to allergens found in other mussels. For example, actin

is a significant allergen in *Paphia textile* and tropomyosin in *Haliotis discus* [20-22]. Further evidence stems from the free available software AllCatPro which predicts high potential allergenicity for humans [23-25]. The prediction is primarily based on the degree of homology distance to human proteins because the more significant the difference, the higher the allergenicity prediction. The same principle also applies to the potential allergenic reactions in pet animals like dogs. However, much less is known about allergic reactions in dogs than in humans, which raises concerns about protein-containing *Perna canaliculus* extracts for treating arthritis in dogs. However, reports also describe a strong antioxidant and ACE inhibitory activity of peptides derived from a proteolytic digest of the mussel proteome [2].

Conclusions

Despite a lack of successful clinical studies on the therapeutic efficiency of *Perna canaliculus* in humans, there is plenty of experimental evidence for an anti-inflammatory capacity of both the lipid fraction and the glycosaminoglycan fraction. These purified extracts lack the protein content and thus do not suppose a threat of any protein-based allergenicity for humans or pet animals.

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