MINI REVIEW

Anti-inflammatory Compounds from the Hydrolysate of Indian Marine Green Mussel (*Perna viridis* L)

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DOI: 10.18811/ijpen.v7i02.8

Abstract

Natural products offer a great hope in identifying bioactive compounds and their development into drugs to treat several diseases including inflammatory problems. Ocean has been considered as a rich source of such compounds with novel structures and important biological activities. Traditional medicine is widespread and natural compounds represent a large source of naturally occurring secondary metabolites that might lead to novel drugs. The ocean also offers the potential for producing metabolites, which may be different from the terrestrial organisms. Due to the complex nature and dynamic system in the ocean, the marine organisms have developed unique metabolic and physiologic capabilies that ensure their survival in extreme variations of pressure, salinity and temperature. Marine organisms, including mussel, have produced a variety of chemically interesting and biologically significant secondary metabolites. Some are expected to serve as lead compounds for drug development or pharmacological tools for basic life science studies. Marine animals can survive in an inimical environment surrounded by various pathogenic organisms, including human pathogens. They are also potential sources for bioactive compounds as observed in edible bivalves, such as *Meretrix casta* (Chemnitz), *Polymesod*a (*Geloina*) *Polymesoda erosa* (Solander), *Perna viridis* (Linnaeus), *Crassostrea gryphoides* (Schlothim), and *Villorita cyprinoides* (Grey). Recent studies conducted have shown that green mussels are an inexpensive source of protein for human consumption and possess some important complex potential bioactive compounds useful as medicines. Isolation of bioactive compounds like anti-inflammatory from marine sources has been receiving special attention among natural bioactive compounds because of their economic significance effectiveness and the increasing incidents of drug resistance lead to difficulties in the pharmacological field.

The present study reviewed the anti-inflammatory compounds from the hydrolysate prepared from green mussel which will be identified and characterized for commercial use.

Keywords: Anti-inflamatory, Green Mussel, Hydrolysate, Marine Algae.

International Journal of Plant and Environment (2021); **ISSN:** 2454-1117 (Print), 2455-202X (Online)

Introduction

Mussels contribute substantially to the total marine fish catch of the world as they are nutritious with high protein and thus, they are consumed generally as raw or cooked, canned, smoked and even small quantities are frozen. The majority of the mussels are collected from the fishing stakes, fish cages, and jetties and sold in the local consumption market—the Russians for the first time designed a pilot plant for the extraction of the mussel hydrolysate. Initially, the basic component in hydrolysate showed antiviral properties as such mussel hydrolysate marketed in Russian markets as antiviral drug (Cheng, 2009). Most of the testes carried out in these laboratories showed that the mussel hydrolysate, besides having an immune-modulating effect, helps greatly build organisms' resistance against various types of toxins, ultra violet rays, and ionizing radiation. Hydrolysate has also been found effective in stimulating rhe restoration of blood production and radiotherapy of tumors.

Cyclosporine is isolated from the fungus *Tolypocladium inflatum* in Norway which is a natural product successfully developed as first-line of immunosuppressive medicine in treatment of transplant rejection and treatment of inflammatory diseases like rheumatoid arthritis and psoriasis. There have been numerous anti-inflammatory pharmacologically active compounds identified from marine organisms like sponges, molluscs, bryozoans, sea combs, algae, echinoderms, ascidians and bacteria (Chatterji *et al*., 2002). Similarly, astaxanthin, the main carotenoid pigment found in marine algae and aquatic animals, has anti-inflammatory properties. Several publications are available on natural anti-inflammatory compounds with other particular targets like COX-1 and -2, lipoxygenases (LOXs), nitric oxide (NO), phopholipases, A2(PLA2s) pathway etc. The pro-inflammatory mediators have also been considered as potential targets in anti-inflammatory drug discovery. The anti-inflammatory and anti-proliferative properties of scytonemin, an extracellular sheath pigment originally isolated from the cyanobacterium (*Stigonema* spp.) have also been reported (Abad 2008, Breton *et al*. 1997). Many new anti-inflammatory cembranolides have recently been identified from different soft coral (*eq* Lobophytum).

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How to cite this article: Kumari, B. & Solanki, H. (2021). Anti-inflammatory Compounds from the Hydrolysate of Indian Marine Green Mussel (*Perna viridis* L). International Journal of Plant and Environment, 7(2), 170-174.

Conflict of Interest: None

Submitted: 31/03/2021 **Accepted:** 30/05/2021 **Published:** 15/07/2021

It took few years for the scientists to standardize the process of extraction of the mussel hydrolysate. Finally, the scientists achieved considerable success in developing a new drug Viramid from the mussels. The drug was patented as a product in Russia. Elaborate studies were carried out at the Pasteur Institute, St. Petersburg, Russia, which showed that the drug was more effective than remantadin used for curing patients suffering from herpes I and II viruses with no side effects. The drug has further undergone various clinical tests at Vishnevsky Surgery Institute, Russia, where the scientists found that the drug effectively stimulated the immune system and resistant to inflammation. It also intensifies the regeneration process in burn wounds. Based on these results, the drug has also been recommended as an anti-burn tonic. Herpes ointment and antiviral toothpaste are the other products made out of the mussel hydrolyzate. It has been confirmed that the use of mussel hydrolyzate by people suffering from acute and chronic virus hepatitis A, B, C and D, quickness the recovery (Dang 2008). The extracts prepared by enzyme–acid hydrolysis of the meat and mantle fluid of commercially important Indian green mussels showed a high antiviral activity in both *in vitro* and *in vivo* models (Daun *et al*., 2006, D Orazio, 2012). Two compounds identified and characterized from the Indian green mussel displayed significant biological activity against the malarial parasite (mouse and human tested).

Both the compounds exhibited activity against *P. falciparum* for *in-vitro* culture assay. Importantly, both compounds act by directly killing parasites rather than just causing inhibition in their growth. No effect of these compounds has been seen on the host cell showing non-toxic nature of the compounds. One of the compounds also displayed activity against the chloroquine-resistant strain-W2Mef. Another compound has also been identified and isolated from the Indian green mussels that could be used as an effective drug for the prevention and treatment of osteoporosis, osteoarthritis, rheumatoid arthritis, prevention of bone loss in bone metastasis, Paget's disease, and other bone disorders of clinical importance (Folmer, 2010). A compound has also been characterized from Indian green mussels for tuberculosis, displaying no detectable growth of the bacteria up to 40 days after initiation of the culture.

During hydrolyzing for extraction of mussel hydrolysate from green mussels, only a portion was considered useful as a drug, and the rest was discarded. But, recently, Russian scientists have found a protein-vitamin-rich compound in the discarded part (by-product), which is very useful for animals. This particular substance is useful in removing the toxins from the animal's body, providing resistance against different viral strains, enhancing protein synthesis, stimulating tissue regeneration, animal growth, and normal development (Gautam *et al*., 2008). The Russian scientists have got a patent on a new drug called Midivet, recommended for use in animals. It took almost ten years for scientists to confirm its use on animals, especially poultry, piggery, and other animals and pets like cats and dogs.

Types of Mussels

There are many different types of mussels around the world. A mussel is much like a clam; it lives in a shell and thrives in salt or fresh water rivers, streams, tidal water and lakes (Fig. 1). Various mussel species are also favorite dishes among many shellfish lovers and a hated pest in lakes and rivers.

Zebra Mussels (*Dreissena ploymorpha*)

The zebra mussel is a freshwater mussel species found in the lakes and rivers of America. They are small, but some can grow up to 2 inches and live four to five years.

The zebra mussel is a pest to lakes due to its prodigious consumption of phytoplankton and zooplankton. The younger mussels freely swim through the rivers and lakes, riding along the water currents from one place to another. The older mussels are stationary, attaching themselves to rocks, boats, pipes, turtles, or other mussels.

Blue Mussels (*Mytilus edulis*)

Blue mussels are found around the world in temperate and polar waters. They attach themselves to pilings and rocks along the beach in tidal areas. Their hard-hinged shells vary in color, such as blue, purple, and brown. The inside of the shell is pearl-white with a blue or purple lined border around the edges.They grow up to 10 centimeters in length and some can grow up to 20 centimeters.

Rabbitsfoot Mussels (*Quadrula cylindrical*)

The Rabbitsfoot mussel is a freshwater mollusk and gets its name from its shell shape; the shape of a rabbit's foot. Their shells are hinged, thick, rectangular and elongated with a ridges and knobs along the outside. The shell's inside is white and the outside is yellowish brown or an olive color that can grow up

Fig. 1: Showing different varieties of Mussels

to 4 inches in length. The Rabbitsfoot mussel is an endangered species and found in clear running streams.

Snuffbox Mussels (*Epioblasma triquetra*)

The Snuffbox mussel is a medium-sized mussel, only growing up to 2 inches in size. They have a triangular-shaped shell that is yellow and very thick. Their shells have solid and broken dark green stripes along its width, and one end is hinged. The Snuffbox mussel is an endangered species and is legally protected. They are found in fast-moving rivers with cobble, sand or gravel substrates to bury themselves deep within the sediment of the riverbed.

Horse Mussel (*Modiolus modiolus*)

The Horse mussel can grow up to 20 centimeters, much larger than other types of mussels. They live 10 to 25 meters deep in the water; some have been discovered to be as far as 280 meters deep underwater. They attach themselves to hard surfaces like rocks, turtles and other mussels.

Global Research on Hydrolysate of Indian Marine Green Mussel (*Perna viridis* L)

It is now globally accepted that natural products play a dominant role in discovering leads for the development of drugs for treating human diseases. Natural products offer great hope in identifying bioactive compounds and their development into drugs for the treatment of inflammatory diseases. Cyclosporine isolated from the fungus *T. inflatum* was approved for use in 1983 to treat inflammatory diseases like rheumatoid arthritis and psoriasis. The drug has numerous immunosuppressive activities, but the main action is a selective inhibitory effect on IL-2 and IL-4 gene transcription. This example highlights the significant role of natural products as a source of drug discovery. Recently, there have been identified numerous anti-inflammatory pharmacologically active compounds from marine organisms. These compounds have been purified from many different marine sources, including sponges, molluscs, bryozoans, sea combs, algae, echinoderms, ascidians and bacteria. The Red alga *Gracilaria verrucosa* have possessed anti-inflammatory activities by inhibiting lipopolysaccharide (LPS)-induced nitric oxide (NO) production, TNF-αand IL-6.Earlier studies have suggested that lipid extract of the blue-green alga Nostoc commune repressed expression of pro-inflammatory mediators, such as TNF-α,COX-2, IL-6and IL-1β, by inhibiting the activation of NF-κB pathway in RAW 264.7 macrophages. Astaxanthin, the main carotenoid pigment found in algae and aquatic animals' marine world, has shown anti-inflammatory properties. Several reviews have been published on natural anti-inflammatory compounds with other particular targets like COX-1 and -2, lipoxygenases (LOXs), nitric oxide (NO), phopholipases. A2(PLA2s) pathway etc. These pro-inflammatory mediators have also been considered as potential targets in anti-inflammatory drug discovery (Lowery *et al*., 1951, Nile *et al*., 2013). The anti-inflammatory and anti-proliferative properties of scytonemin, an extracellular sheath pigment originally isolated from the cyanobacterium *Stigonema* spp. have been reported. Many new anti-inflammatory cembranolides have recently been identified from different soft coral Lobophytum.

Role of Marine Green Mussel (*P. viridis* L) Responsible for Anti-inflammatory Activities

The enormous ecological resources in the diversified environment with different oceanic zones have been exploited since ancient times. They have been used for various purposes and include marine animals like fish and other invertebrates and algae for many drugs. Marine organisms also provide a rich source of nutraceuticals and potential candidates for treating several human diseases. The marine environment is an exceptional storehouse of novel bioactive natural products, with structural and chemical features generally not found in the terrestrial natural products. Green mussels are one of the important bivalve molluscs useful in biomedical science. Extract prepared by enzyme–acid hydrolysis of the meat and mantle fluid of Indian green mussels showed a high antiviral activity *in vitro* and *in-vivo* models. Several important compounds have been identified and characterized from the Indian green mussel, and most of them displayed significant biological activity against the malarial parasite, treatment of osteoporosis, osteoarthritis, and rheumatoid arthritis, prevention of bone loss in bone metastasis (Park, 2008, Pedro *et al*., 2006), Paget's disease and other bone disorders of clinical importance, tuberculosis and diabetes. There is still an opportunity for an advanced scale of research and investigation to discover new potential in hydrolysate of green mussel with an ultimate aim to produce novel drugs. This current proposed work will help provide new bioactive agents that could overcome the limitations of the current arsenal of drugs to treat inflammatory disorders (Chao *et al*., 2008). This study will also ensure the production of the bioactive compound on a scale using advanced bioprocessing synthetic techniques without ecological exploitation of green mussel.

International Status

Considering green mussels as a source of several important compounds, attempts have been made in countries like Japan, the Netherlands, Italy, France, New Zealand, and India to identify and extract several bioactive compounds. These studies also showed that the extract prepared from the mussels could effectively be used to cure the patients suffering from viral diseases and prevent the spread of viral diseases to others. Scientists of Denmark extracted an anti-rheumatic drug. New Zealanders have prepared a new drug useful against arthritis and nervous problems (Sreekumar *et al*., 2007). A team of Russian scientists, in 1969, discovered an antiviral compound in the tissue of blue mussels that opened a new chapter in this field. An extract prepared from the brown mussel (*M. edulis*), a sister species of green mussel, has been both prophylactic and therapeutic properties. It is useful for curing viral diseases such as influenza, *Herpes simplex, Herpes zooster*, hepatitis, flu, and even respiratory syncytial virus (RSV). The extract is commonly called mussel hydrolysate. The mussel hydrolysate has immunomodulation properties, and as such, it has been approved by the Drug and Food Controller in Russia, after all, clinical, toxicological, and pharmacological trials (Chatterji *et al*., 2002, Villa *et al*., 2010). The mussel hydrolysate in a drug is now available in the Russian market for human use. The drug is more effective in people living under conditions of the high background of nuclear radiation, unfavorable ecological

conditions, and thickly populated areas such as factories, schools, institutes, and army divisions. Russian scientists have isolated mytilin, a carbohydrate-rich protein complex, which helps provide more body resistance and fighting power against the dreaded TB bacteria but also against the toxins produced by them. The treatment of toxicogenic influenza-infected mice with the extract prepared from blue mussel in both intranasal and oral mice gave significant protective effects. The maximum prophylactic effect has been observed in mice when a dose of mussel extract was given 5 hours before inoculation of virus, and the mice showed 100% survivals.

National Status

In India, attempts were also made to demonstrate the use of hydrolysate prepared by the enzyme-acid hydrolysis process that initially showed a high antiviral activity in both *in vitro* and *in vivo* models. The mussel hydrolysate has been found to reduce the infection of influenza virus types A and B. Two compounds were identified and characterized by the Indian scientists from the green mussel, those displayed significant biological activity against the malarial parasite (mouse and human tested). Both the compounds exhibited activity against *P. falciparum* for *in vitro* culture assay. Importantly, both compounds act by directly killing parasites rather than just causing inhibition in their growth. No side effect of these compounds has been seen on the host cell showing the non-toxic nature of the compounds. One of the compounds also displayed activity against the chloroquine-resistant strain-W2Mef. Another compound has also been identified and isolated from the Indian green mussels that could be used as an effective drug for the prevention and treatment of osteoporosis, osteoarthritis, rheumatoid arthritis, prevention of bone loss in bone metastasis, Paget's disease, and other bone disorders of clinical importance (Shaughressy 2007, Rao *et al*. 2006). A compound has also been characterized from Indian green mussels for tuberculosis, displaying no detectable growth of the bacteria up to 40 days after initiation of the culture. The chemical composition of the mussel hydrolysate showed the presence of albumen (22%), mineral salts (22%), microelements (iodine, copper, silver), macro-elements (phosphorous, calcium, ferrum), vitamins (B, B2, PP, AE), lipids, melanoidins and oligo-peptides. In the albumen, taurin (2 amino-sulfanilic acid) is the most important component. Taurine has also been found as an effective drug for encephalitic syndrome, cataract, and glaucoma. It is also useful as a neuro-modulator and neuro-inhibitor of the central nervous system. As such, it could be effectively used as an anti-convulsion drug. The presence of taurin in mussel hydrolysate helped in the proper regulation of heart function and osmotic processes with glycosides intoxication at the cellular level (Roshak, 1997).

The amino acid content in mussel hydrolysate is also very high compared to chicken egg that has been considered to have the highest concentration of amino acids so far. Lysine, methionine, and tryptophan are the main components present in the mussel hydrolysate, and they are considered highly nutritional compounds. The other important amino acids in mussel hydrolysate are gistodine, tirozin, and arginine, which maintain human vitality. The polyunsaturated fatty acids with low fatness are also found in mussel hydrolysate. (Saima *et al.,* 2003) The microelements reported in mussel hydrolysate are 10 times higher in concentration than in fish and meat. It has also been reported that a gram of fresh green mussel meat contains approximately 35 mg of donamin, a substitute for adrenaline, which has toning up effect on the cardiovascular system in humans. All studies done by Indian scientists have been patented, whereas one of them also licensed to a pharmaceutical company.

Scope of the Application

Disease ailments are changing the patterns daily where new diseases are emerging due to continual environmental changes. The enormous growth of the world population has overburdened the existing resources for drugs. Hence, drug manufacturers are always searching for new resources to develop effective and safe drugs for the increasing demands of the world population. Seventy-five percentage of the earth's surface is covered by water, but research into the pharmacology of marine organisms is limited, and most of it remains unexplored (Lowry *et al*., 1953). The marine environment represents countless and diverse resources for new drugs to combat major diseases like cancer or malaria. It also offers an ecological resource comprising a variety of aquatic plants and animals. These aquatic organisms are screened for the presence of antibacterial, immune-modulator, anti-fungal, anti-inflammatory, anti-cancer, anti-microbial, neuroprotective, analgesic, and anti-malarial compounds (Kevzers *et al*., 2005). They all are used for new drug developments extensively across the world. The marine environment is an exceptional storehouse of novel bioactive natural products with structural and chemical features generally not found in terrestrial natural products. Marine organisms also provide a rich source of nutraceuticals and potential candidates for treating several human diseases (Shaughney *et al*., 2001). The modern-day focus of marine pharmacology is on the discovery of new pharmaceuticals from marine organisms. Green mussel is one such marine organism considered to be a model for many biomedical scientific studies. The present project aims to identify, isolate and characterize potential and effective anti-inflammatory compounds from the hydrolysate prepared from the green mussel. In the future, these compound/s could then be chemically synthesized after characterizing it, which could be used as a medical drug.

Application of Mussels

Mussel plays an important role in many modern fractures, dental and pain therapies. In most cases, the life activity is based on mussel adhesive protein. The proteins of Mussels are considered to be an alternative to metal plate fixtures. Besides, mussels are also actively utilized in dental adhesives which undergo etching in the presence of phosphoric acid derivatives to maximize the bonding strength and adapt thiol chemistries to minimize shrinkage stress (Cha *et al*., 2009). Mussel-inspired 3, 4-dihydroxyphenyl-L-alanine acrylamide–polycaprolactone (L-DMA–PCL) hydrogels served as a strain sensor for biometrics and healthcare monitoring, and this proved to be competent as it can easily stick to human skin. To abet this problem, mussels were used to control the propensity of DOPA for oxidation (Chen *et al.,* 2011). Given the similarities between dental and underwater mussel adhesives, we employ several studies to confirm the strategy of mussel adhesion—the combination of

DOPA and thiol chemistry with acid etching—to one of the most critical issues in dentin bonding.

Conclusion

An attempt was made to review the study on mussel hydrolysate showing immune-modulatory properties. The present investigation may help develop a most potent and wide spectrum bioactive compound with anti-inflammatory properties that could be used as a potential drug in the field of medicine. Considering the presence of various biological activities in mussel hydrolysate, Russia's Drug and Food Controller approved the crude mussel hydrolysate for human use, after Various clinical, toxicological, and pharmacological trials. In the same effort, the most active fraction in the crude mussel hydrolysate will be isolated and characterized for commercial use.

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