

ANTI-INFLAMMATORY METABOLITES FROM MARINE ORGANISMS

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ABSTRACT

Inflammation is a complex reaction by the body against any self-created infection or foreign particle invasion causing body cell and tissue injury. The inflammation can heal these injuries but sometimes it can turn aggressive causing severe chronic pain such as different arthritis, retinitis and much multiple sclerosis. To combat the effect of inflammation synthetic anti-inflammatory agents (steroids and NSAIDS) are widely used. Many NSAIDS drugs like diclofenac, aspirin, indomethacin etc. are effective with lesser side effect. These drugs are effective but it does not eradicate the disease from the body and its regular consumption may lead to renal ulcers, gastrointestinal diseases etc. Thus in recent years the researchers are more focused in finding the metabolites to produce natural drugs for combating inflammation. The different metabolites from plants are mostly and widely exploited for natural inflammation drugs which are much effective and safe. It is also observed that many commonly found marine organisms produce some effective metabolites. These metabolites from marine sources are comparatively as effective as the synthetic anti-inflammatory agents. This review showcases the possible effective metabolites from marine organism in inhibiting the inflammation and how this discovery can bring sustainable global change.

Keywords: NSAIDS, marine, inflammation, metabolites

1. INTRODUCTION

Inflammation is a host defense mechanism of the body and is essential immune response that enables the body to survive during infection. Inflammation is a normal response of the body to any noxious stimulus that threatens the host. The defined role of inflammation is for restorative process as well as its aggressive role. Due to its due role the response may vary from being specific to generalize [1]. The process of inflammation in body has a wide variety of pathological and physiological responses. The inflammation can be acute or chronic in conditions. The acute inflammation is the immediate response to any pathogen or foreign material generally termed as

inflammatory agents or can be necrotic cells caused by cell death/ injuries. During acute inflammation the site undergoes several vascular changes to increase the amount of antibodies and leukocytes for recovery, leading to destroying the foreign particle [2]. When the body fails to fight against the foreign body or any other acute inflammation it leads to chronic inflammation. The chronic condition can even be generated due to failure of body's self-defense system. The chronic conditions include some of the major painful and non-treated disorders such as rheumatoid arthritis, osteoarthritis, axial spondylitis arthritis, retinitis, psoriasis, atherosclerosis, inflammatory bowel diseases etc.

Therefore, the inflammation process may be lifesaving as well as it can develop chronic state may last the life of the individual [3].

Since ages many studies are conducted to overcome the chronic problem but with safe and effective activity. The scientists are still trying to find the solution for absolute removal for inflammation but somehow only available with anti-inflammatory agents. The property of any substance to treat or reduce swelling or inflammation is known as anti-inflammatory agents [4, 5]. These anti-inflammatory agents can be natural and synthetic drugs are widely used as a source of therapeutic tools for the prevention or treatment of many diseases [6, 7]. Though, the anti-inflammatory drugs are widely used for relieving pain as due to their quick response at the site of inflammation. The major used anti-inflammatory drugs are categorized as Non-Steroidal Anti-Inflammatory medications (NSAIDs) and steroids. Both these drugs actively repress the effect of prostaglandins, which promote inflammation, fever, and pain in the body. But out of both these drugs, NSAIDs are the most prescribed for the treatment of major chronic conditions such as different arthritis. Although at current scenario the steroidal drugs and NSAIDs are majorly used to treat acute inflammatory conditions. As both these drugs are entirely not proved successful in curing the chronic inflammatory disorders [8]. But it is observed that NSAIDs are safe to use, provide quick relief and even helps in lowering fevers and preventing blood from clotting [9]. There are some successes of NSAIDs in treating various chronic inflammatory conditions such as rheumatoid arthritis, inhibiting prostaglandin H synthase (PGHS) enzyme [10] or cyclooxygenase (COX) [11]. However, the use of NSAID for long term therapy may lead to gastrointestinal (GI) associated toxicities [12]. In addition, NSAIDs alleviate the symptoms of the

disease without actual treatment or prevention of the inflammation [13].

The various metabolites from medicinal plants have wide variety of biopotential active compounds since centuries. The plants and used crudely or parts are extracted to compounds for treating various disease conditions [11]. Apart from plants the metabolites from different marine organisms are proven to be potent activities and are curing much different disease. But in spite of having great potential with safer effect these metabolites are always sidelined due to various reasons.

2. The Action Mechanism of NSAIDS

In early times, the salicylates obtained from natural sources were used for medicinal purpose. Later, salicylic acid was chemically synthesized and was used as antiseptic, antipyretic and ant-rheumatic. Almost 40 years, aspirin an anti-inflammatory drug was developed as a more palatable form of salicylate [14]. Since after its successful effect, other similar drugs action were discovered and later termed as non-steroidal anti-inflammatory drugs (NSAIDs) [16]. The action mechanism of NSAIDS was discovered in the year 1971 by Vane *et al.* 1998 where he proved that NSAIDs inhibit the activity of the enzyme cyclooxygenase which caused inflammation, swelling, pain and fever [16]. This discovery helped other scientists to discovery of COX-2 and other rapid development this enzyme [16]. NSAIDs also inhibit the NF-B and activator protein-1 (AP-1) [11], IL-6 and TNF [17, 18]. Some NSAIDs affects the response of T-cells, IL-2 [19]. It also inhibit the synthesis of prostaglandins, prostacycline and thromboxane by inhibiting the activities of COX-1 and COX-2. Inhibition of COX explains both the therapeutic effects and side effects of NSAIDs. The inhibition of COX-2 results in for physiological functions like healing inflammation whereas the inhibition of COX-1 leads to various side effects. It is

observed that the NSAIDs which selectively inhibited the COX-2 enzymes retain maximal anti-inflammatory activity and less toxicity [20]. According various studies, drugs like celecoxib, meloxicam and rofecoxib as posses higher COX-2 selectivity, followed by ibuprofen, piroxicam and diclofenac whereas drugs like aspirin, indomethacin and ketorolac have the lower COX-2 selectivity [21].

The salicylate inhibits the TNF induction of the NF- κ B/IB signaling pathway at the activity level of IB kinase and cAMP-response element binding protein (CREB) [22]. Studies show that, the signalling pathways of NF- κ B/IB or MAP kinases may have subsequent inhibition of mRNAs expression and the proteins of COX-2, iNOS and PLA2 when inhibited by NSAIDS [22, 23]. These drugs may activate the glucocorticoid receptors leading to down-regulation of cytokines, COX-2, iNOS, metalloproteinase enzymes and PLA2 [17]. The effects of PGE2 reduce due to production blockage of prostanoid which may form a component of their immuno-regulatory effects [23, 24]

Apart from treatment, recent finding have exposed the fatal side effects associated with NSAIDs. The studies prove that several NSAIDs affect the production of cytokines or may increase the production of IL-6 or TNF, inhibits the biological relevant targets like NF- κ B and Jak/STAT signaling pathways [25]. These inhibitory effects for longer term can develop bleeding gastrointestinal ulcers [26-28] and kidney failure [29].

3. Anti-inflammatory compounds from marine organisms

Natural compounds are used as foods, fragrances, pigments, insecticides, medicines, etc. Due to their easy accessibility and safer activity, terrestrial plants are majorly looked up as the major source of medicines especially for traditional or folk medicine. According to Joffe, 1989[30], about 25% of total

pharmaceutical sales are generated from drugs derived from plant and additional 12% sales are based on microbial produced products. A wide nutrient range is found in the extensive photic and non-photoc zones of marine environment. But it is observed that marine being major resource of earth, very less bio potential exploitation of marine organism is performed till date. This may be due to the lack of ethno-medical history and collection method of marine organisms [31] which creates ignorance towards it. However in recent year exploitation of marine organisms for their bio potential activities has accelerated with the growing recognition of their importance in human life [32]. In last few decades, it is seen that with help of developed new techniques and advance machines over 5000 novel compounds are isolated from shallow water ranging to 900-m depths of the sea [33].

4. Metabolites from Marine Organisms

The nature has provided us with vast variety of terrestrial and marine organisms. The marine organisms are becoming great interest for the researches due to their wide variety of bioactive compounds. In recent decades, there is an has been increase in pharmacological research on metabolites from marine organism for anti-inflammation activity. The biomolecules are classified into different chemical classes, encompassing sesquiterpenoids, diterpenes, steroids, polysaccharides, alkaloids, fatty acids, proteins etc. These generally target the neutrophils and macrophages and successfully shows pharmacological studies in both *in-vitro* and *in-vivo* conditions [34]. Most of the marine organisms showcase anti-inflammatory activity and can prove effective at large drug production scale. The metabolities actively show anti-inflammatory property are:

Sesquiterpenoids:

The anti-inflammatory activity is usually associated with inhibition of iNOS and COX-2 expression in macrophages [35], the generation of superoxide anion, and release of elastase in neutrophils [36]. *Lemnalium cervicornis* (soft coral), with anti-inflammatory and analgesic actions, mitigated intra-articular monosodium urate-induced gouty arthritis in rats. It is observed that lemnalol relieves knee swelling, mechanical allodynia, and paw edema, infiltration of inflammatory cells, and repress depression of COX-2, iNOS, and c Fos.

Diterpenes:

Diterpenes are often found in soft corals and possess anti-inflammatory property. These diterpenes are when regulates the immune response are sometimes classified as NF- κ B signaling pathway modulators [34, 37]. They exhibit their anti-inflammatory property by inhibiting the activation of the pathway at different sites [38].

Diterpene pentoside:

Cnidarians comprise of old, diverse and bio active animal phylum, and possess a wide variety of biopotent substances. The Pseudopetrocin-E, a tricyclic diterpenepentoside from gorgonians of the genus *Pseudopterogorgia*, shows anti-inflammatory and analgesic activities almost similar in potency to industrial standard indomethicine (NSAIDS) [39]

Steroids/ sterols:

Marine organisms like sponges are rich source of steroids with potent anti-inflammatory property. They attenuate the activity of the immune system and suppress the inflammation. In recent studies, steroidal compounds are isolated from sponges can modulate the farnesoid X receptor (FXR) and pregnane X receptors (PXR) [40]. The pregnane X receptor agonist are effective in reducing intestinal inflammation and NF- κ B activity, which is responsible

for the production of pro-inflammatory cytokines [40]. Therefore, their discovery holds promise in the treatment of inflammation-driven intestinal disorders.

Polysaccharides:

The sulfated polysaccharides from algae, have been demonstrated to express anti-inflammatory activity both in vitro and in vivo since ages [41-43] which is attributed to their structure and physicochemical characteristics [44]. Leiro *et al.* showed that the sulfate content was important in stimulation of macrophages due to the participation of the sulfate moiety in the interaction between polysaccharide and cell surface receptors [45]. The polysaccharides from *Nostoc* species also gave positive results for anti-inflammatory activity [46].

Alkaloids

Alkaloids are group of cyclic compounds which are an assemblage of pharmacological activities. They are majorly found in higher terrestrial plants, but many marine organisms like sponges, algae also contain alkaloids [47, 48]. Due to their structural diversity, there is no regular classification for alkaloids. The neoechinulins A and B, two diketopiperazine (DKP) type of indole alkaloids, from the marine fungus *Eurotium sp.* expressed *in-vitro* anti-inflammatory action on RAW264 [49].

Fatty acids:

The fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil possess inflammatory property in *in-vivo* disorders models [50]. Clinical evidence indicates that these fatty acids are beneficial as a dietary supplement in several inflammatory diseases including rheumatoid arthritis [51, 52] inflammatory bowel disease [53] and child asthma [54]

Terpenoids:

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The sponges dominate the presence of secondary metabolites by terpenoid compounds. The anti-inflammatory activity of sponges is also dominated by isoprenoid derived metabolite called sesterterpenes [55].

5. Future prospect of anti-inflammation from marine organism

Over the last few decades, the ocean has been identified as a sustained source for the medicinally requirements. The marine biodiversity has enormous potential for different scientific applications. Among the various potentials, the pharmaceutical perspective has been identified as having the utmost important and substantial role for future therapeutic. The various secondary metabolites derived from marine resources are becoming a promising source for the design and development of natural drugs.

The marine source has got plenty of metabolites and this is attracting researchers who are finding biomedical metabolites from living organisms. The major marine organism which possess biomedical activities are different sponges (37%), coelenterates (21%) and marine microorganisms (18%) followed by different algae and seaweeds (9%), echinoderms (6%), tunicates (6%), molluscs (2%) bryozoans (1%), etc [57]. The recent trends in drug discovery from natural sources have emphasized on investigation of different marine ecosystem and helps in exploring numerous complex with novel chemical entities. These entities are the source of a new lead for treatment of many diseases including some deadly diseases like autoimmune diseases and HIV-AIDS [58, 59].

Now a days people are aware about the drugs chemistry and its various side effect. The people's interest and faith shifted towards natural drugs hence creating huge demand. This is creating a pressure on pharmaceutical industry and researchers to carry out the researches and develop the drugs. The use and

demand of marine natural products can be clearly felt, which can be fulfilled but there should be sustainable use of all the resources.

6. Conclusion

Inflammation is very common and frequent action of our body. We are having wide variety of drugs to get rid of inflammation at our doorstep but at a cost of our health. The steroidal and NSAIDs are widely available to us and with limited efficacy. But we cannot overlook the fact that these NSAIDs are having adverse effect on the patient's body. Therefore, the use of herbal plants in drug industry have increased. The herbal plants have many different metabolites which shows bioactive compounds. Not only plants but metabolites from marine organisms also showed great achievement in the field of drugs. So from all the data and reports it can be concluded that the use of marine organism's metabolite can be great use and benefit. The world's pain can be healed naturally and without any adverse effect with nature's gift. But there should be proper care and control of natural resource, as there deterioration can cause great loss to mankind.

7. Reference

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