Anti-Inflammatory Effects of Compounds from Echinoderms

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Chronic inflammation can extensively burden a healthcare system. Several synthetic anti-inflammatory drugs are currently available in clinical practice, but each has its side effect profile. The planet is gifted with vast and diverse oceans, which provide a treasure of bioactive compounds, the chemical structures of which may provide valuable pharmaceutical agents. Marine organisms contain various bioactive compounds, some of which have anti-inflammatory activity and have received considerable attention from the scientific community to develop anti-inflammatory drugs. Herein, it was described such bioactive compounds, as well as crude extracts (published during 2010–2022) from echinoderms: namely, sea cucumbers, sea urchins, and starfish. Moreover, their chemical structures were also included, evaluation models, and anti-inflammatory activities, including the molecular mechanism(s) of these compounds. Herein, it also highlights the potential applications of those marine-derived compounds in the pharmaceutical industry to develop leads for the clinical pipeline. In conclusion, here is a well-documented reference for the research progress on developing potential anti-inflammatory drugs from echinoderms against various chronic inflammatory conditions.

Keywords: anti-inflammatory activity ; inflammatory pathways ; marine drugs ; echinoderm ; sea cucumber

1. Inflammatory Pathways and Models

Multiple inflammatory pathways play a role in innate immunity and activate adaptive immunity to combat the cause of inflammation. Several class receptors initiate these pathways on leukocytes, known as pattern recognition receptors. Common examples of such receptors are (1) the toll-like receptor family (TLR), (2) C-type lectin receptors, (3) retinoic acid-inducible gene-I-like receptors, and (4) nucleotide-binding and oligomerization domain (NOD)-like receptors (NLR) [1][2]. Activating immune cells such as macrophages, neutrophils, and other immune cells leads to the secretion of cytokines, which sustain the inflammatory response. These cytokines bind to the immune cells and activate their function. The typical cytokine receptor families are the: (1) immunoglobulin superfamily, (2) class I cytokine receptor family, (3) class II cytokine receptor family, (4) tissue necrosis factor (TNF) receptor superfamily, and (5) chemokine receptor family. Ligand binding on the pattern recognition receptors or cytokine receptors activates several signaling pathways, which ultimately induces the transcription of several inflammation regulatory genes. There are four broad categories of signaling pathways activated during the inflammation process: (1) the mitogen-activated protein kinase (MAPK) pathway, (2) the phosphoinositide 3-kinase signaling pathway, (3) the Janus kinase (JAK) signal transducer and activator of transcription (STAT), and (4) I kappa B kinase (IκB)/nuclear factor kappa B (NF-κB) signaling pathways [3][4].

The sustained activation of these signaling pathways underlies the cause of several inflammatory diseases. For instance, the NF-kB signaling pathway is a classic pathway in regulating inflammation. The activation of NF-kB via IκBα increases the expression of various downstream inflammatory mediators, such as proinflammatory cytokines (interleukin 1β (IL-1β), IL-6, and TNFα); key proinflammatory enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2); and their derivatives nitric oxide (NO) and prostaglandin E2 (PGE2) [5][6]. Multiple experimental models are available to study the activation of inflammatory signaling and transcription for various inflammatory diseases. These experimental models are also widely used to evaluate potential anti-inflammatory compounds and to understand the mechanism(s) of their therapeutic effects. Different experimental models have been designed and implemented to study the preliminary efficacy of anti-inflammatory compounds. For example, carrageenan-induced paw edema in mice [7] and 12-O-tetradecanoylphorbol-13-acetate (TPA) mouse ear inflammation models [8]. Other specific experimental models are also available and have been used to assess chronic inflammatory diseases, including the dextran sodium sulfate (DSS)-induced colitis model [9], which has been widely used to screen the anti-inflammatory effects of marine drugs. For example, this model was recently used to study the anti-inflammatory effects of polysaccharides isolated from the mussel *Mytilus couscous* [10]. Another well-known model to explore cytokine-mediated inflammatory signaling pathways is TNFα-induced intestinal inflammation in colon cancer cell lines [11]. For example, krill oil was screened for its anti-inflammatory

effects by using this model in HT-29 and Caco-2 cells [12]. The free fatty acid (FFA)-mediated activation of inflammatory signaling in hepatocytes is a well-known model for nonalcoholic steatohepatitis [13]. Jiena et al. [14] demonstrated that fucoxanthin, a popular marine-derived compound, attenuated FFA-induced inflammation via the AMP-activated protein kinase/nuclear factor erythroid 2–related factor 2/TLR4 signaling pathway in normal human Chang liver cells.

2. Marine-Derived Anti-Inflammatory Drugs

Chronic inflammatory conditions pose a significant burden on the healthcare system, despite the availability of several synthetic compounds used for the management of these conditions. Over the past decade, the research and development of model systems and evaluation of the efficacy of various compounds have led to the identification of several anti-inflammatory compounds from natural origins [15][16][17]. Marine sources produce a vastly diverse range of bioactive compounds, several possessing anti-inflammatory potential. Indeed, anti-inflammatory compounds have been derived from marine microorganisms such as seaweeds, corals, and algae [18]. These fall into several classes of bioactive compounds with therapeutic potential for several chronic inflammatory conditions. For example, marine alkaloids from diverse marine organisms have been evaluated for their potential anti-inflammatory activity [19]. Another class of marine compounds acts as inhibitors of NF-κB, a mediator activated in the inflammation process [20]. Pigments from various marine organisms have been shown to have anti-inflammatory activity and can be used to manage chronic inflammation [21][22]. For instance, Echinochrome A (EchA, a pigment isolated from sea urchin), briaviodiol A (a cembranoid from a soft coral), and cucumarioside A2 (a triterpene glycoside from sea cucumbers) have been shown to suppress inflammation via the reprogramming of macrophages from M1 to M2 [23]. Seaweeds are classically used as food supplements and have great potential as a source of anti-inflammatory compounds [24][25]. Overall, because of the diversity of classes of bioactive compounds from marine sources with potential applications as anti-inflammatory agents, there is a need to catalog these resources comprehensively.

Over the past few decades, attempts have been made to isolate and purify biologically active compounds with potent anti-inflammatory activity from different marine sources. However, very few compounds have been selected for clinical trials, and even fewer have reached the market. Despite this low success rate, the hunt for new anti-inflammatory compounds from the diverse marine environment continues. Recently, Li et al. reviewed the anti-inflammatory metabolites from marine organisms such as sponges and corals but did not include larger organisms such as sea cucumbers, sea urchins, and starfish [18]. Herein, promising anti-inflammatory compounds and crude extracts isolated from echinoderms such as sea cucumbers, sea urchins, and starfish were described and their potential molecular mechanisms of action to shed light on the current state of the research on anti-inflammatory compounds from echinoderms are reviewed.

3. Application to the Pharmaceutical Industry

The drug discovery process is lengthy, time-consuming, and costly for the pharmaceutical industry, including target identification, lead compound discovery, the structure-activity relationship (SAR) study, in vitro and in vivo screening, and clinical trials on large human populations. More recently, the bioinformatics approach has been employed for target identification and the discovery of lead compounds, which has significantly reduced the length of the drug discovery process [26]. Lead compounds may come from combinational chemistry, computer-aided drug design, or natural products [27][28]. However, lead compounds often produce suboptimal biological responses and require chemical modifications to improve their efficacy and potency. The majority of drugs available clinically are derived from natural sources. Indeed, many of the small anticancer molecules available on the market are either natural products or derived from natural products [29]. The search for novel or lead compounds was previously limited to plant-based natural products but has now been expanded to marine-derived natural products. There have been reports of marine natural products with exploitable properties, including those that treat cancer and inflammation and neurological, immunological, and metabolic disorders [30][31][32]. The global preclinical marine pharmacology pipeline still produces significant preclinical data on numerous pharmacological classes and provides new leads [33]. Some pharmaceutical companies are focusing on marine natural product research.

However, there is a general trend that anticancer drugs have received more attention, resources, and efforts in pharmacological research, discovery, and development than other drug classes, such as anti-inflammatory drugs. For example, several marine organism-derived anticancer drugs (such as vidarabine (Ara-A) for Hodgkin's lymphoma and chronic large cell anaplastic lymphoma, cytarabine, Ara-C for acute non-lymphoblastic leukemia, and trabectedin vedotin for ovarian cancer and soft tissue sarcoma) have been approved by the FDA. Moreover, several anticancer molecules are in Phase I, II, or III clinical trials [34][35]. However, the discovery of several marine-derived anti-inflammatory molecules also has ignited the pharmaceutical industry's interest in developing them into lead compounds for the drug discovery process [36][37]. Unfortunately, to date, no marine-derived anti-inflammatory drug has been approved by the FDA. Still, a few

promising anti-inflammatory compounds are under various phases of clinical trials: for example, pseudopterosin A (a diterpene glycoside obtained from soft coral) and IPL-576092 (a polyhydroxylated steroid obtained from a sponge) [38]. This suggests the significant involvement of marine-derived natural products in the potential pharmaceutical industry and encourages the pursuit of new anti-inflammatory lead compound discoveries. Productive teamwork among researchers from various universities and institutes and the leadership of the pharmaceutical industry is required to ensure the development of future therapeutic entities that will significantly contribute to the treatment of various inflammatory disorders.

4. Research Prospects

Research into marine-derived anti-inflammatory lead compounds has received little consideration compared to anticancer leads; however, this is evolving rapidly. Herein, anti-inflammatory compounds isolated from various species of sea cucumbers, sea urchins, and starfish, including their chemical structures were presented. Many compounds, such as fucoidan, fucosylated chondroitin sulfate, eicosapentaenoic acid derivatives, and echinochrome A, have been investigated in detail for their anti-inflammatory activity and molecular mechanisms. Moreover, some novel compounds, such as glycosides from starfish, have been studied well in terms of their chemical structure and SAR with a target but only screened for preliminary anti-inflammatory activity (such as COX and 5-LOX inhibitory activity). These need further investigation to establish their molecular mechanisms. Marine pharmacology research faces many obstacles. For example, the isolation of bioactive compounds from marine organisms is extremely difficult, as they live in a complex and biodiverse environment, and it is difficult to mimic such an environment in the laboratory for their cultivation to obtain a large number of active substances. The prospects in marine pharmacology should focus on the following: (1) the reproduction of compounds by the chemical synthesis of established marine-derived anti-inflammatory leads to increase their production and overcome cultivation obstacles, (2) the chemical modification of existing marine-derived anti-inflammatory leads (analogs) to enhance their potency and efficacy, (3) develop lead compound libraries for large and rapid random high-throughput screening methods, (4) industry collaboration to translate preclinical leads into the clinical pipeline, and (5) establish comprehensive and efficient separation and purification techniques. The planet is gifted with vast and diverse coastlines by nature that is a treasure of bioactive compounds that have not been exploited. The scientific community should consider further research to find other potentially valuable marine drugs.

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