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Marine soft corals as source of lead compounds for anti-inflammatories

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ABSTRACT

Marine soft corals are known to produce a wide array of secondary metabolites, particularly diterpenoids and steroids, and often characterized by uncommon structural features and potent bioactivities. The remarkable abundance and diversity of bioactive small molecule which have been isolated from soft corals have made these organisms an important source of new drug candidates for human diseases, particularly for their anti-inflammatory activity. In this paper, the authors reported anti-inflammatory marine natural products isolated from diverse species of soft corals determined *in vitro* by their inhibition of lipopolysaccharide-induced expression of inducible NO synthase and cyclooxygenase-2 in murine macrophage cells (RAW 264.7).

1. Introduction

Natural products have been proven to be rich sources of novel compounds exhibiting many different biological activities. Their chemical structures are diverse and complex, and they have often demonstrated selective activities in various biological systems[1]. Compared to the terrestrial environment, which was the focus of the pharmaceutical industry for more than 50 years, marine habitats have remained virtually unexplored for their ability to yield pharmacological metabolites[2]. In the last several decades, researches have expanded from the land to the ocean in order to find new leads for drug candidates and more than 30 000 unique bioactive natural products have been isolated from marine organisms[3]. It has been estimated that the percentage of new metabolites discovered from soft corals represented up to 22% of the total new marine natural products reported from 2010 to 2011[4,5].

Soft corals belonging to the family of Alcyoniidae are characterized by a great variety of colours, shapes, and sizes and they are by far the most dominant reef dwelling octocorals in the Indo-West Pacific. These organisms are known to produce a wide array of secondary metabolites, particularly diterpenoids, sesquiterpenoid and steroids, and often characterized by uncommon structural features. A number of natural products isolated from soft corals have demonstrated that they are of great biomedical interests having antiviral, anti-tumor, anti-inflammatory and antifouling properties[4,6].

Inflammation is a pathological condition in which highly reactive species are produced[7]. Increasing evidence suggests a critical link between inflammation and the chronic promotion/progression of various human diseases, including atherosclerosis, diabetes, arthritis, inflammatory bowel disease, cancer and alzheimer[5]. The mechanisms and mediators involved in painful and inflammatory processes have been the targets of several studies in recent years[8]. During the process of inflammation, different cell types are recruited, including monocytes which differentiate locally into macrophages. This leads to the regulated production of various pro- and anti-inflammatory mediators including cytokines, such as tumor necrosis factor-α, chemokines and inducible enzymes [cyclooxygenase-2 (COX-2) and inducible NO synthase (iNOS)] which play critical roles in controlling the inflammatory processes[9]. Several natural products from marine organisms, including soft coral, sponges and algae, with anti-inflammatory effects have attracted researchers' attention in the

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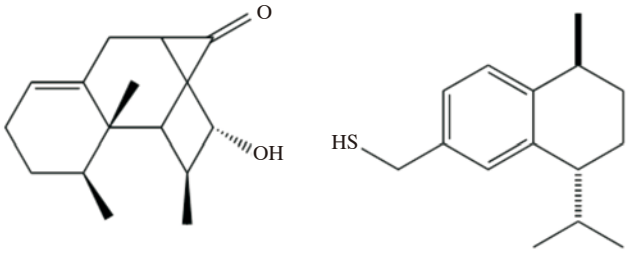
past few years.

2. Anti-inflammatory activity

During 2005–2012, 19 studies reported anti-inflammatory marine natural products isolated from diverse species of soft corals such as *Sinularia, Paralemnalia, Lobophytum, Nephthea, Klyxum and Sarcophyton*. In this paper, we reported anti-inflammatory activities of natural products from soft corals determined *in vitro* by their inhibition of lipopolysaccharide (LPS)-induced expression of iNOS and COX-2 in murine macrophage cells (RAW 264.7). Information from the year 2005 to 2012 was obtained from existing reviews and relevant articles[5,10-15].

2.1. Sesquiterpenoid

Huang *et al*. described a novel sesquiterpenoid isoparalemnone (1) from the Formosan soft coral *Paralemnalia thyrsoides* which significantly inhibited inflammatory iNOS protein expression (70% at 10 μmol/L) in activated RAW 264.7 cells[16]. Cheng *et al*. isolated a new sesquiterpenoid erectathiol (2) from *Nephthea erecta*. *In vitro* anti-inflammatory activity of (2) significantly reduced the levels of the iNOS protein [(58.0 ± 6.5)%] and COX-2 protein [(108.7 ± 4.5)%] (Figure 1)[17].



Isoparalemnone (1) Erectathiol (2)

Figure 1. Sesquiterpenoid from soft corals.

2.2. Diterpenoid

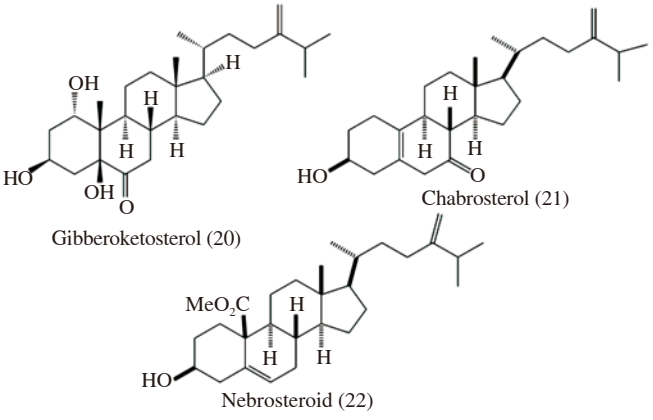
Chao *et al*. identified the new cembranolides crassumolides A and C (3, 4) from the soft coral *Lobophytum crassum* which inhibited the expression of iNOS and COX-2 (apparently IC_{50} was less than 10 μmol/L)[18]. Similarly, from the same university, Cheng *et al.* found that new cembranolides from the soft coral *Lobophytum durum*, durumolides A–C (5, 6, 7) inhibited both the iNOS and COX-2 proteins in LPS-activated RAW 264.7 cells *in vitro* (apparently IC_{50} was less than 10 μmol/L) suggesting that the α-methylene-γ-lactone moiety of these compounds was necessary for the observed activity[19]. Cheng *et al.* also isolated durumhemiketalolides A-C (8, 9, 10) and durumolide F (11) from the soft coral *Lobophytum durum* with anti-inflammatory activity[20,21]. Both compounds 8 and 10 reduced the levels of iNOS to (11.0 ± 1.3)% and (0.0 ± 0.0)%, respectively, and of COX-2 to (66.7 ± 6.4)% and (34.7 ± 4.2)%, respectively. The compound 9 reduced iNOS protein expression (6.4 ± 0.2%), but did not inhibit COX-2 protein expression. The anti-inflammatory activity of the compound 11 (10 μmol/L) significantly reduced the levels of the iNOS protein to (0.8 ± 0.6)% and COX-2 protein to (47.8 ± 9.0)%. Two new *Lobophytum crassum* diterpenes (12, 13) isolated by Wanzola *et al*. showed significant inhibitory effect of NO production, and their IC_{50} values were less than 10 μmol/L without any cytotoxic effect[22]. The inhibitory mechanism of these cembranoids was confirmed by the inhibition of iNOS expression via the suppression of a transcription factor nuclear factor κB.

Klysimplexin sulfoxide C (14) and simplexin E (15) were isolated from the soft coral *Klyxum simplex*[23,24]. The compound 14 at a concentration of 10 μmol/L significantly reduced the levels of iNOS protein to (11.3 ± 1.5)% and COX-2 expression [(7.2 ± 2.5)%]. At a concentration of 10 μmol/L, compound 15 was found to significantly reduce the levels of iNOS and COX-2 proteins to (4.8 ± 1.8)% and (37.7 ± 4.7)%, respectively, which was relative to the control cells stimulated with LPS only.

Lin *et al.* isolated sarcocrassocolides C (16) and D (17) from soft coral *Sarcophyton crassocaule*[25]. Compounds 16 and 17 were shown to exert significant *in vitro* anti-inflammatory activities in LPS-stimulated RAW 264.7. Cheng *et al*. also found gyrosanolides B (18) and C (19) from *Sinularia gyrosa*[26]. Compounds 18 and 19 at concentration of 10 μmol/L did not inhibit the COX-2 protein expression, but significantly reduced the levels of the iNOS protein (55.2% ± 14.6%, 10.6% ± 4.6%, respectively) by LPS stimulation (Figure 2).

2.3. Steroid

Ahmed *et al.* reported that the known steroid gibberoketosterol (20) isolated from the Formosan soft coral *Sinularia gibberosa* significantly reduced pro-inflammatory iNOS and COX-2 proteins in LPS-stimulated murine macrophages at a concentration of 10 μmol/L to 44.5% and 68.3% of control values, respectively[27]. Cheng *et al.* isolated chabrosterol (21) and nebrosteroid I (22) from the soft coral *Nephthea chabroli* which significantly reduced the levels of the iNOS protein (12.4% ± 2.9% and 20.2% ± 2.6%) and COX-2 protein (45.2% ± 5.4% and 75.3% ± 3.3%) (Figure 3)[17].



Gibberoketosterol (20) Chabrosterol (21)

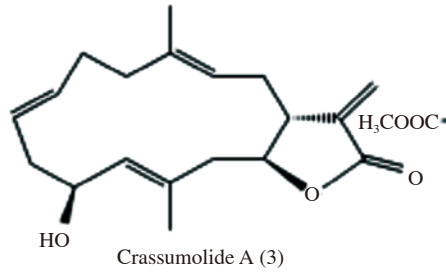
Nebrosteroid (22)

Figure 3. Steroid from soft corals.

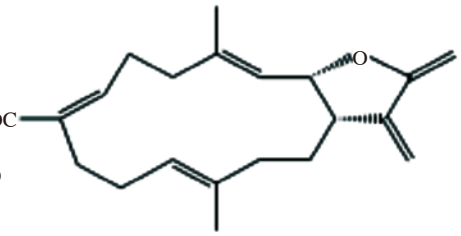
2.4. Glycolipid

Sarcoehrenosides A (23) and B (24) were isolated from *Sarcophyton ehrenbergi*. Compounds 23 and 24 reduced iNOS

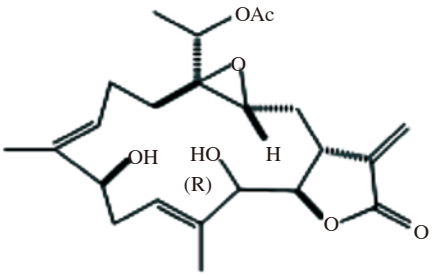
protein expression (47.3% ± 7.1%, 46.5% ± 5.3%, respectively), but did not inhibit COX-2 protein expression (Figure 4)[28].



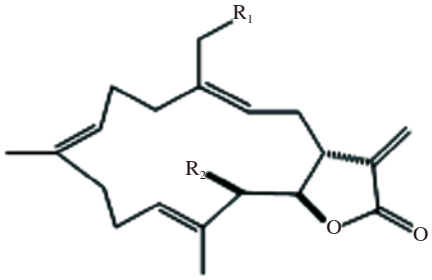
Crassumolide A (3)



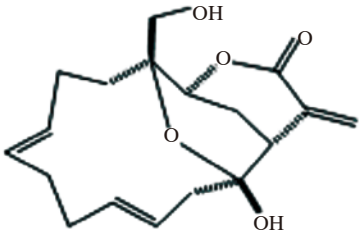
Crassumolide C (4)



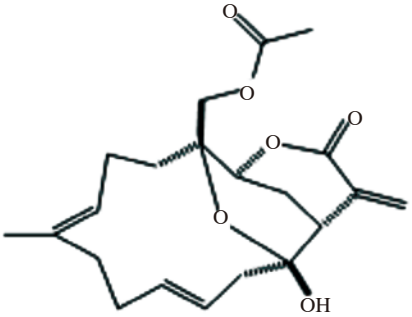
Durumolide A (5)



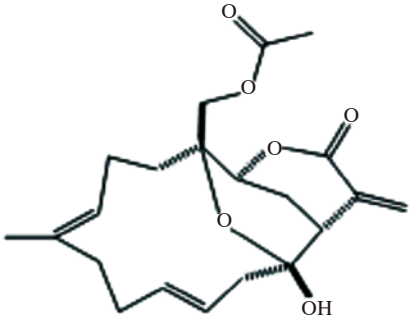
Durumolide B (6) R_1 = OAc R_2 = OH
Durumolide C (7) R_1 = OH R_2 = OH



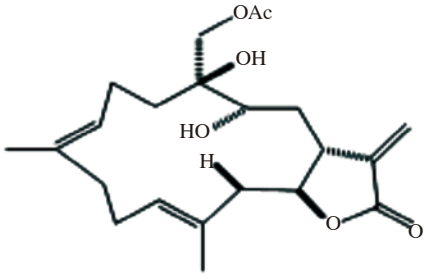
Durumhemiketalolide A (8)



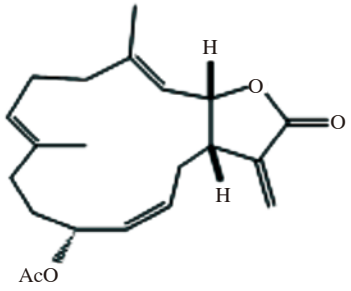
Durumhemiketalolides B (9)



Durumhemiketalolides C (10)



Durumolide F (11)



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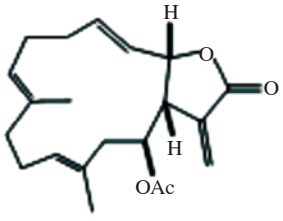
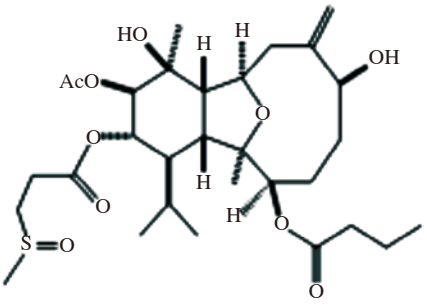
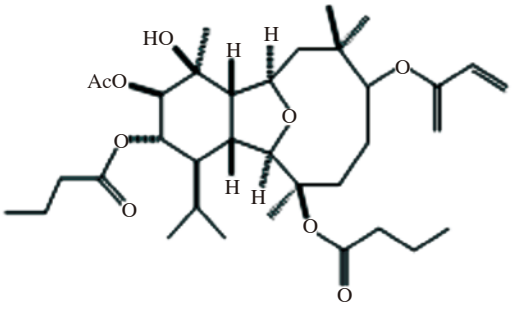


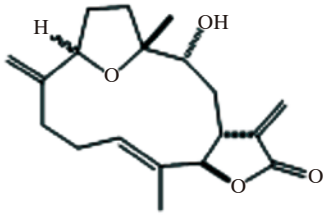
(13)



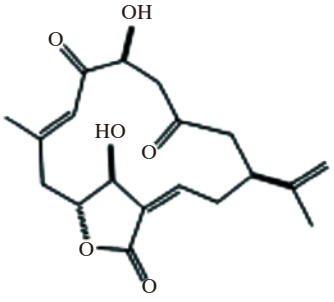
Klysimplexin sulfoxide C (14)



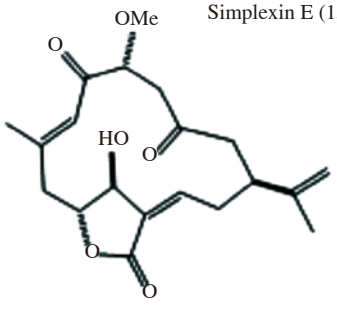
Simplexin E (15)



Sarcocrassocolide C (16)
Sarcocrassocolide D (17)

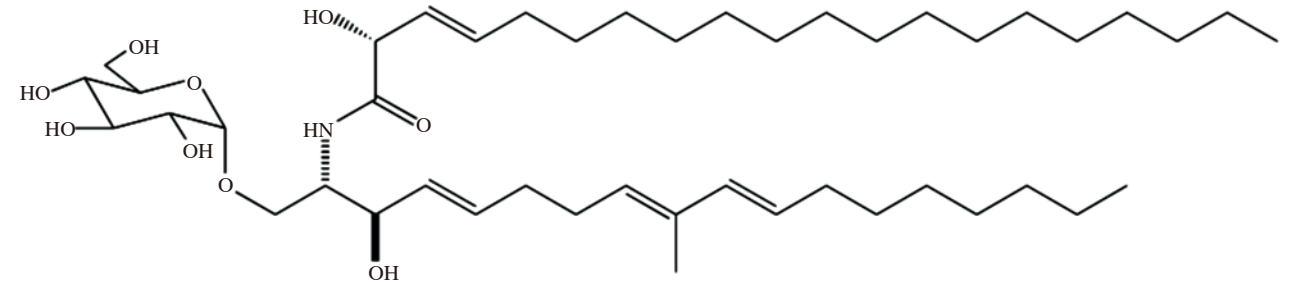


Gyrosanolide B (18)

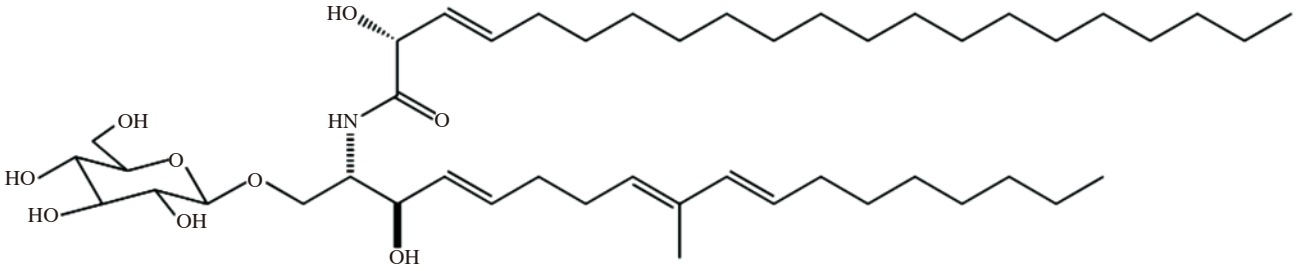


Gyrosanolide C (19)

Figure 2. Diterpenoid from soft corals.



Sarcoehrenoside A (23)



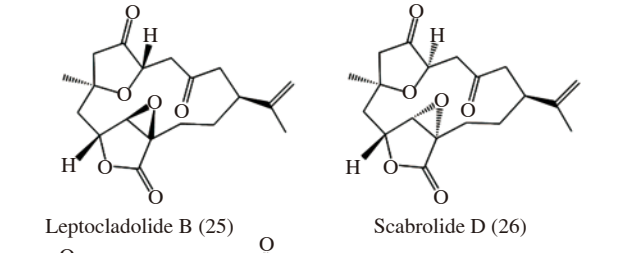
Sarcoehrenoside B (24)

Figure 4. Glycolipid from soft corals.

3. Anti-inflammatory activity from Indonesian soft corals

3.1. Diterpenoid

Chemical analysis of the less polar fractions of the organic extract obtained from *Sinularia* sp. (order Alcyonacea, family Alcyoniidae) resulted in two known C-4 norcembranoids, named leptocladolide B (25) and scabrolide D (26), and three new ones, named chloroscabrolides A (27) and B (28) and prescabrolide (29) (Figure 5). All the norcembranoids were evaluated for their anti-inflammatory activities. A 15% inhibition of NO_2-production was observed in scabrolide D (26) at a concentration of 10 μmol/L (Figure 5)[13].



Leptocladolide B (25) Scabrolide D (26)

Chloroscabrolide A (27) Chloroscabrolide B (28) Prescabrolide (29)

Figure 5. Norcembranoids from soft coral Sinularia sp.

3.2. Glycolipids

A new glycolipid, named sinularioside (30) isolated from *Sinularia* sp. At different concentrations (10, 30, 100 μmol/L) of sinularioside (30), a significant dose-dependent ($P < 0.001$) inhibition of NO_2-production was observed with 58% inhibition at 30 μmol/L (Figure 6)[14].

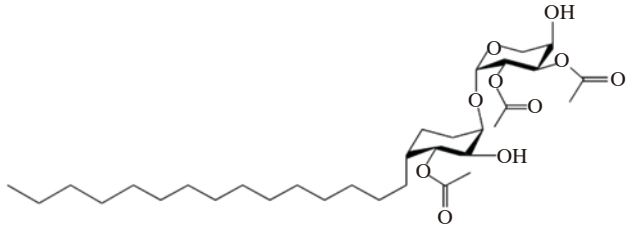
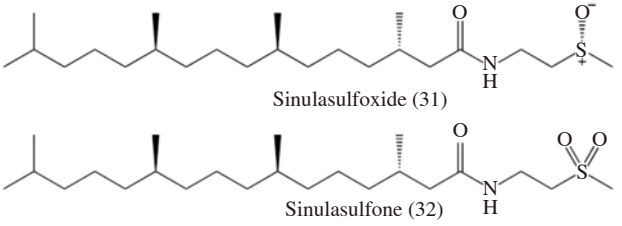


Figure 6. Marine glycolipids from *Sinularia* sp.

3.3. Alkaloids

Another polar fraction from *Sinularia* sp yielded two new alkaloids, named sinulasulfoxide (31) and sinulasulfone (32). Sinulasulfoxide (31) (Figure 7) was also evaluated for a inhibition of NO production on LPS-stimulated macrophages. The compound was moderately active with about 25% inhibition at 30 μmol/L[15].



Sinulasulfoxide (31)

Sinulasulfone (32)

Figure 7. Sulfur-containing alkaloids from soft coral *Sinularia* sp.

4. Conclusion

Since seven marine natural products or derivatives in different phases of the clinical pipeline have been approved by the Food and Drug Administration or the European Medicines Agency, twelve compounds are in Phase I, II and III of clinical development, and the global marine preclinical pharmaceutical pipeline remains very active. Marine soft corals have been recognized as prolific producers of a wide array of secondary metabolites. Most of secondary

metabolites from soft corals have been studied for their anti-inflammatory activities and have been focused on "screening-like" assays by using COX-2 and iNOS as target markers.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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