More than three decades of research on marine natural products have exposed their potential as antimicrobial, antiviral, antiparasitic, anticancer, anti-inflammatory, neuroprotective, and immunomodulatory agents [1–6]. However, very little is known about their cardioprotective potential [5,6]. Cardiovascular disorders remain the main cause of mortality, morbidity, and health care burden worldwide [7]. The endothelin system is a key player in many conditions associated with cardiovascular disorders including hypertension, heart failure [7–9], and atherosclerosis [10]. The current literature regarding the screening of marine natural products for cardioprotection focuses on well validated targets such as the angiotensin converting enzyme of renin-angiotensin [11] and the endothelin receptors [12–15]. The emerging data suggest the underestimated potential of marine microorganisms for producing leads with cardioprotective potential. The present work reviews natural products identified as inhibitors of the endothelin system, their origin, their mechanism of action, and their ecological significance.

Abstract
Inhibition of the endothelin system is a recognized therapeutic approach for treating complex cardiovascular diseases. The search for natural inhibitors of the endothelin system has focused mainly on land, with recent, emerging data suggesting the underestimated potential of marine microorganisms for producing leads with cardioprotective potential. The present work reviews natural products identified as inhibitors of the endothelin system, their origin, their mechanism of action, and their ecological significance.

Introduction
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The Endothelin System and Its Drug Targets
Endothelin-1 (ET-1) is a potent vasoconstrictor and the predominant compound of the endothelin family with the highest clinical relevance [16]. The biosynthesis of ET-1 starts with the large precursor protein of 212 amino acids (AA) called preproendothelin-1 (PPET1), which is encoded by the ET-1 gene (EDN1) in the human chromosome 6 (Fig. 1). Removal of a short secretory sequence generates proendothelin-1 (proET-1, 195 AA) [16]. In the cytosol, proET-1 is then cleaved by a furin-like endopeptidase producing the 38 AA-peptide precursor big ET-1 [17]. Big ET-1 can also be cleaved by human chymase and neutral endopeptidase (NEP) to produce ET-1 [19]. The activation of EDN1 expression may be mediated by angiotensin II (Ang II), catecholamines, cardiothropin-1, thrombin, growth factors, cytokines, free radicals, insulin, hypoxia, shear stress, lipoproteins, cyclosorine, as well as by the same ET-1 (Fig. 1) [20,21]. ET-1 mediates its effects by means of two G-protein coupled receptors (GPCRs), namely ETA, responsible for vasoconstriction and cell proliferation, and ETB, mainly responsible for vasodilatation, inhibition of cell growth and fluid retention, and ET-1 clearance [21]. ET-1 acts as an autocrine/paracrine mediator, with similar affinity for both
receptors [20]. When ET-1 interacts with the ET$_A$ receptor, a G protein hydrolyzes phospholipase C to form diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP$_3$). IP$_3$ increases cytoplasmic calcium ($Ca^{2+}$) through activation of its receptors and transmembrane $Ca^{2+}$ channels located on the endoplasmic reticulum resulting in vasoconstriction (**Fig. 1**) [22]. DAG can also lead to activation of proto-oncogenes including those involved in the MAPK cascade [22].

Stimulation of ET$_B$ receptors leads to activation of phosphoinositide 3-kinase (PI3K) and downstream activation of protein B kinase/Akt. The PI3K/Akt pathway is responsible for activation of endothelial nitric oxide synthase (eNOS), where nitric oxide (NO) antagonizes ET-1 synthesis via inhibition of PPET1 transcription. ET$_B$ receptors mediate the release of other vasodilators like prostaglandins and the endothelium-derived hyperpolarizing factor [23]. The deleterious effects of ET-1 can be prevented by different mechanisms. They include suppression of the expression of EDN1, translation of proET-1, and activation of ECE and endothelin receptors [24, 25].

**Endothelin-1 gene inhibitors**

There is a specific gene that encodes for each precursor of the mature isoforms of the endothelin family [21]. These genes are susceptible to inhibition by diverse factors. For instance, EDN1 expression may be inhibited by endothelium-derived NO, nitravasodilators, natriuretic peptides, heparin, and prostaglandins (**Fig. 1**) [20, 21], as well as high shear stress [26].

**Endothelin converting enzyme, neutral endopeptidase and chymase inhibitors**

Among the metalloproteases that may cleave big ET-1 to produce ET-1 are pepsin, cathepsin D, and thiol proteases [26], which are sensitive to inhibition by phosphoramidon [27]. Another ECE inhibitor is RS68 [28], a calcimimetic substance that induces changes in the synthesis of endothelial vasoactive factors. In addi-
tion, NEP is an important enzymatic target which may be inhibited by both phosphoramidon and thiorphon. The combination of NEP/ECE inhibition, as in SLV 306 (daglutril), is a recent approach to reduce adverse effects produced by NEP inhibition [29].

Endothelin receptor antagonists

Effective antagonism of endothelin receptors has been achieved by compounds like bosentan (non-selective ETα/ETβ), BQ-123 (selective ETα), BQ-788 (selective ETβ) [24,30], sitaxentan (selective ETβ, atrasentan (selective ETβ), ambrisentan (selective ETα), and darusentan (selective ETα) [24]. Selective antagonism of the ETβ receptor has been effective for treating pulmonary arterial hypertension [24]. Potential underlying mechanisms include reducing pulmonary artery pressure, inhibiting vascular remodeling, improving exercise capacity and pulmonary haemodynamics, and reducing the Borg dyspnea index [21]. Although non-selective ETα/ETβ receptor antagonism effectively decreases blood pressure, it causes vasoconstriction by blockade of tonic endothelial ETα-receptor-mediated stimulation of NO and prostacyclin generation and affects the clearance of circulating ET-1 (Fig. 1) [24]. Thus, the selection between selective and non-selective antagonism of endothelin receptors depends on the individual patient response.

Marine Natural Products as Inhibitors of the Endothelin System

A number of marine natural products of diverse chemical structures have been found to possess cardiovascular activities. These include small peptides produced by enzymatic hydrolisis of marine proteins, chitosan derivatives, and phlorotannins which inhibit the angiotensins converting enzyme [11]; xestoxamine (Fig. 2, 1), a pentacyclic quinone with inotropic activity and capacity to inhibit Na+/K-ATPase [31] obtained from Xestospongia sparsa; D-polyamunnuronic sulfate (Fig. 2, 2) obtained from brown algae that increase NO and decrease plasma levels of Ang II and ET-1 [32]; and xestospongin C (Fig. 2, 3) an alkaloid from Xestospongia exigua, spongosine (Fig. 2, 4) a nucleoside from Cryptothecia crypta [34], 12-epi-scalaradial (Fig. 2, 5) a sesterpenne from Hyrtios erecta [33], and eldeoisin (Fig. 2, 6), a peptide from Eleodes sp. [35] with hypertensive activity. The majority of natural products capable of inhibiting the endothelin system have been obtained from microorganisms and plants of terrestrial origin. Since the discovery of the cyclic pentapeptide BE-18257B (Fig. 2, 7) in the bacteria Streptomyces misakiensis [36], which originated the first selective endothelin ETα receptor antagonist BQ-123 [37], more attention has been given to finding endothelin antagonists within microorganisms.

Bacteria

Following the discovery of BE-18257B, two more binding inhibitors of endothelin receptors were identified in soil-born Streptomyces, i.e., the benzoguanthraquinones WS009 A and B (Fig. 2, 8–9) (Table 1) [38]. Blastorbact sp. has been the one bacteria obtained from sea water, from which the non-peptide metalloprotease inhibitor B90063 (Fig. 2, 10) has been obtained [39]. B90063 inhibits both ECE and NEP, preventing the generation of ET-1 (Table 1). Other inhibitors of ECE were the benzoguanthacene quinones WS79089 A, B, and C (Fig. 2, 11–13) (Table 1) obtained from the soil-born Streptosporangium roseum 79089 (Fig. 2) [40].

Fungi

An interesting fact is that compounds obtained from soil-born fungi, which exhibited endothelin receptor binding capacity, were also found in fungi from marine habitats. This is the case of the spirocyclic drimanes stachybotacin A and B (Fig. 2, 14–15) isolated from Stachybotrys sp. MF347 found in driftwood [42]. Drimane sesquiterpenoids have been commonly isolated from marine-derived fungi specially those associated with mangrove [43] and sponges [44]. Dimeric spirodihydrobenzofuranlactam compounds [41, 45] and those with the sesquiterpene drimane skeleton [46,47] (Fig. 2, 17–23) inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETβ receptor (Table 1).

Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in Penicillium sclerotiorum X1853 inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETα receptor (Fig. 2, 24–29) (Table 1) [13]. Other compounds like diphenyl ether RES-1214-1 and -2 (Fig. 2, 30–31) obtained from soil-born Pestalotiopsis sp. also inhibited the binding of [125I]ET-1 to the ETβ receptor [51].

Porifera

Although marine invertebrates, especially sponges, have been claimed as the largest source of chemically diverse marine natural products [52], it is intriguing why information on cardiovascular activity of compounds obtained from sponges is scarce. The literature shows that two compounds obtained from sponges have been identified as inhibitors of the endothelin systems. The first is 34-sulfatobastadin 13 (Fig. 2, 32), a bromotyrosine derivative which inhibited the binding of [125I]ET-1 to the ETα receptor [12], and the second is the novel sterol sulfate halistanol disulfate B (Fig. 2, 33) that inhibited ECE (Table 1) [53].

Ecological Significance of Natural Inhibitors of the Endothelin System

The majority of the active natural products found within this group are drimane sesquiterpenes. Terpenes have been thought to play a critical role in antagonistic or mutualistic interactions among organisms. They are associated with defense mechanisms in terrestrial as well as in marine environments. In both habitats, molecules with deterrent and antimicrobial activity are the typical chemical defenses of sedentary, slow-moving, or otherwise poorly defended organisms [54]. Drimane sesquiterpenes are potent antimicrobials and believed to deter feeding on plants and sponges by acting directly on taste receptors [54]. Interestingly, taste receptors belong to the GPCR family as so the endothelin receptors [55,56]. Thus, it is possible that drimanes are non-selective GPCR ligands, which might explain their ability to bind ETα and ETβ. The microorganisms reviewed in this work, which produce these sesquiterpenes, are frequently present in association with sponges, corals, and algae, thus validating their ecological significance in the marine ecosystem.

The significance of sulfated polysaccharides as the vasoactive glycoproteins has been the one bacteria Stichorbis sp. obtained from fresh seawater (Table 1) [39]. Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in Penicillium sclerotiorum X1853 inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETβ receptor (Table 1). Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in Penicillium sclerotiorum X1853 inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETβ receptor (Table 1). Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in Penicillium sclerotiorum X1853 inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETβ receptor (Table 1). Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in Penicillium sclerotiorum X1853 inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETβ receptor (Table 1). Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in Penicillium sclerotiorum X1853 inhibited the binding of [125I]ET-1 to both endothelin receptors, with a consistent preference for the ETβ receptor (Table 1).
interactions, cell signaling and development [57]. They represent an enormous source of different chemical structures with the advantage of a lower risk to patients [57].

Additional, peptides are another group of compounds from microbes and sponges that act on the endothelin system. These sub-

Fig. 2  Marine and soil derived natural products with cardiovascular actions. (Color figure available online only.)
Table 1  Natural products from microorganisms and marine sponges acting as inhibitors of the endothelin system.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Number of structure</th>
<th>Chemistry</th>
<th>ORG(^a)</th>
<th>Species</th>
<th>Origin</th>
<th>MMOA(^b)</th>
<th>IC(_{50}) (µM)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE-18257B</td>
<td>7</td>
<td>cyclic pentapeptide</td>
<td>BA</td>
<td>Streptomyces misa-</td>
<td>Soil</td>
<td>ET(_A)</td>
<td>3.0</td>
<td>[36]</td>
</tr>
<tr>
<td>W5009 A</td>
<td>8</td>
<td>benz[α]anthra-quinone</td>
<td>BA</td>
<td>Streptomyces sp.</td>
<td>Soil</td>
<td>ETs</td>
<td>5.8</td>
<td>[38]</td>
</tr>
<tr>
<td>W5009 B</td>
<td>9</td>
<td>benz[α]anthra-quinone</td>
<td>BA</td>
<td>Streptomyces sp.</td>
<td>Soil</td>
<td>ETs</td>
<td>67.0</td>
<td>[41]</td>
</tr>
<tr>
<td>B-90063</td>
<td>10</td>
<td>pyridone</td>
<td>BA</td>
<td>Blastobacter sp. SANK</td>
<td>Sea water</td>
<td>ECE</td>
<td>NEP.</td>
<td>1.0/66.0</td>
</tr>
<tr>
<td>WS79089 A</td>
<td>11</td>
<td>benzo[α]naph-tac quinone</td>
<td>EU</td>
<td>Streptosporangium roseum</td>
<td>Soil</td>
<td>ECE</td>
<td>0.7</td>
<td>[40]</td>
</tr>
<tr>
<td>WS79089 B</td>
<td>12</td>
<td>benzo[α]naph-tac quinone</td>
<td>EU</td>
<td>Streptosporangium roseum</td>
<td>Soil</td>
<td>ECE</td>
<td>0.1</td>
<td>[40]</td>
</tr>
<tr>
<td>WS79089 C</td>
<td>13</td>
<td>benzo[α]naph-tac quinone</td>
<td>EU</td>
<td>Streptosporangium roseum</td>
<td>Soil</td>
<td>ECE</td>
<td>3.4</td>
<td>[40]</td>
</tr>
<tr>
<td>Stachybocin A</td>
<td>14</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Stachybotrys sp. M 6222</td>
<td>Soil</td>
<td>ET(_A)/ET(_B)</td>
<td>13.0/7.9</td>
<td>[41]</td>
</tr>
<tr>
<td>Stachybocin B</td>
<td>15</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Stachybotrys sp. M 6222</td>
<td>Soil</td>
<td>ET(_A)/ET(_B)</td>
<td>12.0/9.5</td>
<td>[41]</td>
</tr>
<tr>
<td>Stachybocin C</td>
<td>16</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Stachybotrys sp. M 6222</td>
<td>Soil</td>
<td>ET(_A)/ET(_B)</td>
<td>15.0/9.4</td>
<td>[41]</td>
</tr>
<tr>
<td>Spirodiydro-benzofuranlactam VI</td>
<td>17</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Stachybotrys chartar-um</td>
<td>Soil</td>
<td>ET(_A)</td>
<td>1.5</td>
<td>[45]</td>
</tr>
<tr>
<td>RES-1149-1</td>
<td>18</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Aspergillus sp. RE- 1149</td>
<td>UN(^4)</td>
<td>ET(_A)/ET(_B)</td>
<td>25.8/1.6</td>
<td>[46]</td>
</tr>
<tr>
<td>RES-1149-2</td>
<td>19</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Aspergillus sp. RE- 1149</td>
<td>Soil</td>
<td>ET(_B)</td>
<td>20.0</td>
<td>[46]</td>
</tr>
<tr>
<td>Drimane 1</td>
<td>20</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Aspergillus ust var. pseudodeflectus X3811</td>
<td>Desert soil</td>
<td>ET(_A)/ET(_B)</td>
<td>155.0/50/50</td>
<td>[47]</td>
</tr>
<tr>
<td>Drimane 2</td>
<td>21</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Aspergillus ust var. pseudodeflectus X3811</td>
<td>Desert soil</td>
<td>ET(_A)/ET(_B)</td>
<td>80.0/55.0</td>
<td>[47]</td>
</tr>
<tr>
<td>Drimane 3</td>
<td>22</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Aspergillus ust var. pseudodeflectus X3811</td>
<td>Desert soil</td>
<td>ET(_A)/ET(_B)</td>
<td>65.0/21.0</td>
<td>[47]</td>
</tr>
<tr>
<td>Drimane 5</td>
<td>23</td>
<td>drimane ses-quiterpene</td>
<td>FU</td>
<td>Aspergillus ust var. pseudodeflectus X3811</td>
<td>Desert soil</td>
<td>ET(_A)/ET(_B)</td>
<td>50.0/70.0</td>
<td>[47]</td>
</tr>
<tr>
<td>Isochromophilone III</td>
<td>24</td>
<td>azaphilones</td>
<td>FU</td>
<td>Penicillium sclerotio-rum X11853</td>
<td>Tropical forest stream</td>
<td>ET(_A)/ET(_B)</td>
<td>9.0/77.0</td>
<td>[13]</td>
</tr>
<tr>
<td>Isochromophilone III dechloro analogue</td>
<td>25</td>
<td>azaphilones</td>
<td>FU</td>
<td>Penicillium sclerotio-rum X11853</td>
<td>Tropical forest stream</td>
<td>ET(_A)/ET(_B)</td>
<td>28.0/172.0</td>
<td>[13]</td>
</tr>
<tr>
<td>(8R)-7-deacetyl-O,8-dihydro-7-epi-sclerotiorin</td>
<td>26</td>
<td>azaphilones</td>
<td>FU</td>
<td>Penicillium sclerotio-rum X11853</td>
<td>Tropical forest stream</td>
<td>ET(_A)/ET(_B); ARA</td>
<td>5.0/50.0; 33.0</td>
<td>[13]</td>
</tr>
<tr>
<td>(+)-sclerotiorin</td>
<td>27</td>
<td>azaphilones</td>
<td>FU</td>
<td>Penicillium sclerotio-rum X11853</td>
<td>Tropical forest stream</td>
<td>ET(_A)/ET(_B)</td>
<td>75.0/12.0</td>
<td>[13]</td>
</tr>
<tr>
<td>5-chlorosorotiorin</td>
<td>28</td>
<td>azaphilones</td>
<td>FU</td>
<td>Penicillium sclerotio-rum X11853</td>
<td>Tropical forest stream</td>
<td>ET(_A)/ET(_B)</td>
<td>35.0/8.0</td>
<td>[13]</td>
</tr>
<tr>
<td>Ochrephilone</td>
<td>29</td>
<td>azaphilones</td>
<td>FU</td>
<td>Penicillium sclerotio-rum X11853</td>
<td>Tropical forest stream</td>
<td>ET(_A)/ET(_B)</td>
<td>26.0/85.0</td>
<td>[13]</td>
</tr>
<tr>
<td>RES-1214-1</td>
<td>30</td>
<td>diphenyl ether</td>
<td>FU</td>
<td>Pestalotiopsis sp.</td>
<td>Soil</td>
<td>ET(_A)</td>
<td>14.9</td>
<td>[51]</td>
</tr>
<tr>
<td>RES-1214-2</td>
<td>31</td>
<td>diphenyl ether</td>
<td>FU</td>
<td>Pestalotiopsis sp.</td>
<td>Soil</td>
<td>ET(_A)</td>
<td>49.7</td>
<td>[51]</td>
</tr>
<tr>
<td>34-Sulfatobastadin</td>
<td>32</td>
<td>bromotyrosine</td>
<td>PO</td>
<td>Ionthello sp.</td>
<td>Sandy-rublle reef</td>
<td>ET(_A)</td>
<td>39.0</td>
<td>[12]</td>
</tr>
<tr>
<td>Halistanol disulfate B</td>
<td>33</td>
<td>sulfated sterol</td>
<td>PO</td>
<td>Pocastrella sp.</td>
<td>Marine rocky substrate</td>
<td>ECE</td>
<td>2.1</td>
<td>[53]</td>
</tr>
</tbody>
</table>

\(^a\) ORG: type of organism. BA: Bacteria; EU: Eubacteria; FU: Fungi; PO: Porifera.

\(^b\) MMOA: molecular mechanism of action. ET\(_A\)/ET\(_B\): receptor binding inhibition of \([^{125}\text{I}]\)ET-1; ETs: undetermined endothelin receptors; ECE: inhibition of endothelin converting enzyme; NEP: inhibition of neutral endopeptidase; ARA: receptor mediated arachidonic acid release.

\(^4\) UN: undetermined
stances are believed to belong to their classical chemical defense machinery [58, 59].

**Discussion**

Microorganisms are a major source for new drugs with more than 50,000 microbial natural products playing an important role in drug discovery [60]. The majority of these have been isolated from terrestrial-borne microbes [60], possibly because they were more readily available when compared to marine microbes. The available literature shows that the search for natural inhibitors of the endothelin system has been done mainly in land, yielding a wide variety of chemical compounds. Even though this search produces a biased sampling, it is exciting to note that the results accentuate the underestimated potential of microorganisms for producing leads with cardioprotective potential. While the question may arise whether the inhibitory activities found for the compounds described in this review are of therapeutic relevance or not, it is worth mentioning that lead compounds may have considerably low activities (IC_{50} values in the micromolar range) and still hold the potential to become very potent drugs after few modifications. For example, the selective ET_{A} receptor antagonist BQ123 (IC_{50} = 7.3 nM) [37], is a semisynthetic product obtained from the natural product BE-18257B (IC_{50} = 3.0 μM) (Table 1).

Oceans encompass a stressful and competitive habitat with unique conditions of pH, temperature, pressure, oxygen, light, nutrients, and salinity, all of which force organisms to adapt both chemically and physiologically to survive in it [1, 40]. The corresponding modifications in gene regulation and metabolic pathways increase the chances of finding unique and complex natural products that differ from organisms living in terrestrial habitats [1, 40]. The large display of novel and complex chemical structures found in marine natural products as well as the extension of their therapeutic applications, support the marine environment as a promising source of new drugs. The increasing number of bioactive natural products from marine-derived fungi presents a great challenge and sets high expectations in finding, in these groups of organisms, new leads for the protection of the cardiovascular system.

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**Conflict of Interest**

The authors declare no conflict of interest.

**References**

Habib GB, Basra SS. Pharmacol Res 2013; 76: 106


Anastasi A, Erspamer V. The isolation and amino acid sequence of doisin, the active endecapeptide of the posterior salivary glands of M. domestica. Biochem Biophys Res Commun 1991; 178: 132–137


