Abstract
Nature remains the major source of drugs with complex structures and novel biological activities. The search for bioactive molecules from nature remains the most important strategy to find new medicinal agents. Recent findings indicate that hypertension is a major health burden in economically developing countries. Thus a source of less expensive treatments needs to be identified. Current hypertension pharmacotherapy consists in administration of drugs capable of interacting with one or several molecular mediators. Within the group of drugs acting as inhibitors of receptors involved in blood pressure regulation, endothelin receptor antagonists have been the most prominent class containing drugs which were first found in nature. Thus the present review focuses on endothelin receptor as drug targets.

Key words: endothelin receptors, hypertension, marine natural products, plants, traditional medicine.

Introduction
Nature remains unrivaled in its ability to produce organic molecules with structural complexity and biological potency, which is why it has been a major source of drugs for centuries. Interest in natural product research within the new era of drug discovery includes issues like unmet medical needs, diversity of both chemical structures and biological activities (1). During the early decades of the last century, natural substances played a leading role as therapeutic agents. However, this role has declined in modern medicine; nowadays the search for bioactive molecules from nature (plants, animals, microflora) remains the most important strategy to find new medicinal agents (2). Hypertension is a public-health concern worldwide, because of its high frequency and its role as leading factor for mortality (3, 4). Approximately 8 million deaths each year worldwide are blood-pressure related (5). In the year 2000, nearly one billion of the world’s population had hypertension and the projections for 2025 estimate an increase to 1.56 billion people (6). Interestingly, recent findings indicate that hypertension is a major health burden in economically developing countries (7), where health-care resources are especially inadequate (6). For these countries, investment in primary prevention strategies such as weight loss, reduced intake of dietary sodium, moderate alcohol consumption, potassium supplementation, modification of eating habits, and increased physical activity would yield the greatest benefit (6) and should be the first line of prevention of chronic diseases such as...
hypothesis. A second alternative could be used taking in consideration the advice of the World Health Organization, which has been promoting a rational use of traditional medicine as a source of less expensive medical care (8).

Current pharmacotherapy of hypertension consists mainly on the use of two strategies. The first strategy is the application of a single drug capable of interacting with molecular mediators involved in the rennin-angiotensin system (9) and the endothelin system (10); with adrenergic (11) and urotensin II receptors (12); and with the atrial natriuretic peptide (13). The second strategy consists in the use of a “multi-target approach” (14) focused on the simultaneous treatment of more than one target involved in blood pressure regulation and the development of the disease. This second approach has been successfully tested combining drugs capable of inhibiting the activity of ACE and NEP; ECE and NEP; AT₁ and ET₁ receptors (14).

From the group of drugs acting as inhibitors of receptors involved in blood pressure regulation, endothelin receptor antagonists have been the most prominent group containing drugs which were first found in nature (e.g. microorganisms, plants); thus the present review focuses on endothelin receptor as drug targets.

Pathophysiology of hypertension: the endothelin system

Endothelins are a family of vasoconstrictive peptides synthesized from larger precursors and expressed in different tissues (15). They consist of three isoforms, namely, endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3), being ET-1 the most widely distributed, best studied, and most powerful (16). ET-1 is synthesized in endothelial cells by means of a specific endothelin-converting enzyme (ECE) (15, 17). ET-1 appears to be the predominant member of the family with direct vascular effects, inotropic and mitogenic properties; it influences homeostasis of salts and water, alters central and peripheral sympathetic activity and stimulates the renin-angiotensin-aldosterone system (10).

Generation of endotheins: The major site of generation of ET-1 is in endothelial cells and to a lesser extent in smooth muscle cells, the heart, kidneys, posterior pituitary and central nervous systems (10). The initial product of the human endothelin-1 gene is preproendothelin-1 (212 amino acid peptide), which is then transformed into proendothelin-1 by removal of a short secretory sequence. Proendothelin-1 is further cleaved by a furin-like enzyme generating big endothelin-1 (38 amino acid peptide) (18). The formation of mature ET-1 requires cleavage of big endothelin-1 by one of several unique ECE. Several forms of ECE have been identified to have distinct roles and tissue distribution (10). ECE-1 and ECE-2 are relatively selective for big endothelin-1, having much less activity in cleaving big endothelin-2 and big endothelin 3. A third type of ECE was purified from bovine iris and named ECE-3, which selectively cleaved big endothelin-3 (15).

Endothelin receptors: Endogenous ET-1 contributes to maintenance of basal vascular tone and blood pressure through activation of two G-protein coupled receptors (GPCR), namely, endothelin ET₁ (ET₁) and endothelin ET₂ (ET₂) (19), the only two receptor subtypes identified in mammalian species, as mediating the different actions of endotheins (20). As a member of the GPCR superfamily, the ET₁ receptor has seven hydrophobic membrane-spanning domains and a relatively long extracellular N terminal (10). A model for the ET₁/ET₁ receptor interaction showed that ET₁ docks principally at the extracellular ends of the transmembrane domain 1 (TM1), TM2 and TM7 of the receptor as well as the extracellular loop 1 (EXL1) and, to a lesser...
The binding of ET-1 to the ETA receptor activates phospholipase C (PLC), which hydrolyses phosphatidylinositol-4,5-biphosphate (PIP2) into two products, inositol-triphosphate (IP3) and diacylglycerol (DAG). IP3 leads to an initial increase of calcium concentration from the intracellular calcium stores. Afterwards a maintained increase in intracellular calcium levels is brought about by the binding of endothelin to its receptor or by the IP3 metabolite, IP4. The increase in intracellular calcium promotes contraction which could also be partially affected by the action of DAG which is an activator of protein kinase C (PKC) (17). The activation of the ETA receptor also induces cell proliferation in different tissues. In contrast, the activation of endothelial ETB receptor stimulates the release of nitric oxide (NO) and prostacyclin, prevents apoptosis, and inhibits ECE-1 expression in endothelial cells (22).

**Pathophysiology of endothelins:** Resistance vessels and veins are particularly sensitive to the effects of ET-1. On smooth muscle cells, the vasoconstrictor effect caused by ET-1 is mediated by activation of both ETA and ETB receptors present on these cells (10, 23). The opposite effect is mediated by stimulation of the ETB receptor on the endothelial cells by means of NO and prostacyclin (24). Due to this situation the net effect of ET-1 depends not only on the balance between ETA and ETB, but also on vessel type-size and the receptors localization (10, 23). This is the reason why available literature suggests that dual ETA/ETB receptor antagonism is more effective than selective ETA receptor antagonism in order to fully prevent the deleterious actions of ET-1 in cardiovascular disease (23). It has been demonstrated that ET-1 is involved as an etiologic or aggravating factor in a number of cardiovascular diseases, including essential hypertension, pulmonary hypertension, acute renal failure, cerebral vasospasm after subarachnoid hemorrhage, vascular remodeling, cardiac hypertrophy, and congestive heart failure (25). During the development of cardiovascular disease the expression and biological activities of ET-1 and its receptors are altered. For instance, patients with pulmonary hypertension, a devastating disease with a median life expectancy of less than 2.8 years postdiagnosis, have increased plasma levels of ET-1 due to either an increase in its synthesis or a reduction in its clearance (26). In patients with congestive heart failure, ETA receptors are upregulated, while ETB receptors are downregulated (27, 28); and in patients with systemic hypertension ET-1 plasma levels are normal, with a local increase of ET-1 levels in the vascular wall (28, 29).

**Endothelin receptor antagonists: Structural differences**

The development of endothelin receptor antagonists is a rapid evolving area (30). Many pharmaceutical companies have discovered a large number of endothelin receptor antagonists by random screening of their compound libraries. This section intends to review those of most common use in clinical and preclinical investigations (Table 1).

**Peptides and peptidomimetics:** The first endothelin receptor antagonists developed were of a peptide nature. It was discovered that the ETA receptor recognizes the tertiary structure of the N-terminal and C-terminal portion of the endothelin molecules. A major advance was made with the discovery of two cyclic pentapeptides BE-18257A and BE-18257B isolated from the bacteria *Streptomyces misakiensis* (Table 2) (31, 32). Chemical modifications on the structure of compound BE-
18257B originated the first selective endothelin ET_A receptor antagonist BQ-123, a cyclic pentapeptide possessing three diaminopropionic acids (Table 1) (33). Another endothelin ET_A receptor antagonist of a peptide nature is the compound BQ-610, which is used in cerebral vasoconstriction produced by subarachnoid haemorrhage (34). Three examples more are the cyclic hexapeptide TAK-044, a non-selective endothelin ET_A/ET_B receptor, and the linear peptides PD-145065 and FR-139317 (Table 1) (35).

**Myriceric acid derivatives:** Non-peptide endothelin antagonists have also been developed. The first was myriceric acid A (compound 50-235) (Table 2), an oleanane triterpene selective for the endothelin ET_A receptor, which was isolated from the bayberry *Myrica cerifera* (36). Its analog, S-0139, faced problems of oral bioavailability and it was developed in parenteral formulations as neuroprotector in cerebral ischemia (Table 1) (35, 37).

**Carboxylic acid derivatives:** In the search of highly potent endothelin receptor antagonists, pharmaceutical companies incorporated carboxylic acid moieties. Within this group, Abbott synthesized atrasentan, a pyrrolidine-3-carboxylic acid derivative selective for the endothelin ET_A receptor; SmithKline Beecham synthesized enrasentan and SB-209670, two indane-2-carboxylic acids derivatives (38), and compounds J-104132 and PD-156707, which were further derived (Table 1) (35).

**Phenyl acetic acid derivatives:** The most prominent compounds of this group are the highly potent non-selective endothelin ET_A/ET_B receptor antagonists L-754142 developed by Merck and PABSA developed by Shionogi (Table 1) (35).

**Heteroaryl sulphonamide derivatives:** This group contains the well-known oral and parenteral endothelin ET_A selective antagonist TBC-11251 (situxetan) and the orally active endothelin ET_A selective antagonists BMS-181874 and BMS-193884. Also from this group is ZD-1611, a selective endothelin ET_A antagonist which has been discontinued from further development (Table 1) (35).

**3,3-Diphenylpropionic acid derivatives:** Darusentan is the best-known compound of this group, which shows endothelin ET_A selective antagonism and is used in clinical studies for congestive heart failure and hypertension (35).

**Tetra-substituted pyrimidines:** From this group, the most important non-peptide endothelin antagonist is the compound Ro-47-0203 (bosentan) (39), a more potent analog of Ro-46-2005 (40, 41) which was discovered by high-throughput screening. Both compounds Ro-46-2005 and Ro-47-0203 are non-selective endothelin ET_A/ET_B receptor antagonists (39, 42). Other examples are tezosentan (Ro-61-0612) a non-selective ET_A/ET_B receptor antagonist for parenteral use, TA-0201 an orally active ET_A selective antagonist and the non-selective ET_A/ET_B receptor antagonist YM-598 for oral and parenteral administration (Table 1) (35).

**Non-sulphonamide derivative:** Ambrisentan is the first non-sulphonamide ET_A receptor antagonist with proven efficacy for the treatment of pulmonary arterial hypertension. Its chemical structure (propanoic-acid class), may confer benefits over other endothelin antagonists in terms of a lower risk of drug interactions (Table 1) (43).

**Rational design of selective receptor antagonists:** Requires a good understanding of the binding properties and binding sites of the endogenous agonist. Early attempts to determine specific conformational features necessary for receptor binding and vasoconstricting activity of
Table 1. Applications, structural requirements and origin of most common endothelin ET<sub>A</sub> receptor antagonists.

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Base</th>
<th>Origin</th>
<th>Selectivity</th>
<th>Structural requirements for the activity</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>BQ-123</td>
<td></td>
<td>Cyclic pentapeptide</td>
<td>Semi-synthetic</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;</td>
<td>β, γ-backbone conformation and common features with C-terminus of ET-1 (58)</td>
<td>Arrhythmias, cerebral ischemia, diabetic complications, hypertension (33, 35)</td>
</tr>
<tr>
<td>BQ-610</td>
<td></td>
<td>Linear peptide</td>
<td>Synthetic</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;</td>
<td>common features with C-terminus of ET-1 (58)</td>
<td>Subarachnoid haemorrhage (34, 44)</td>
</tr>
<tr>
<td>TAK-044</td>
<td></td>
<td>Cyclic hexapeptide</td>
<td>Synthetic</td>
<td>ET&lt;sub&gt;A/ET&lt;sub&gt;B&lt;/sub&gt;</td>
<td>common features with C-terminus of ET-1 (58)</td>
<td>Renal failure, acute myocardial infarction (35, 45)</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Type</td>
<td>Origin</td>
<td>Pharmacological Activity</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>---------------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>PD-145065</td>
<td><img src="image1" alt="Molecular Structure" /></td>
<td>Linear hexapeptide</td>
<td>Synthetic</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;/ET&lt;sub&gt;B&lt;/sub&gt;</td>
<td>common features with C-terminus of ET-1 (58)</td>
<td>Hypertension (35, 46, 47)</td>
</tr>
<tr>
<td>FR-139317</td>
<td><img src="image2" alt="Molecular Structure" /></td>
<td>Linear tripeptide</td>
<td>Natural (Streptomyces sp.)</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;</td>
<td>common features with C-terminus of ET-1 (58)</td>
<td>Hypertension (35, 48)</td>
</tr>
<tr>
<td>S-0139 (SB-737004)</td>
<td><img src="image3" alt="Molecular Structure" /></td>
<td>Non-peptide, triterpene derivative</td>
<td>Semi-synthetic</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;</td>
<td>Carbonyl group at C-3; carboxylic acid group at C-17, trans-caffeoyloxy group at C-27, dimethyl group at C-27, dimethyl group at C-20 (64)</td>
<td>Cerebral ischemia (37), hemorrhagic and ischemic stroke (35, 49)</td>
</tr>
</tbody>
</table>

**Carboxylic acid derivatives**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical Structure</th>
<th>Type</th>
<th>Action</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrasentan</td>
<td><img src="image" alt="Atrasentan" /></td>
<td>Synthetic</td>
<td>ET(A)</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>Enrasentan</td>
<td><img src="image" alt="Enrasentan" /></td>
<td>Synthetic</td>
<td>ET(A)/ET(B)</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>SB-209670</td>
<td><img src="image" alt="SB-209670" /></td>
<td>Synthetic</td>
<td>ET(A)/ET(B)</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
</tbody>
</table>

Does nature have the cure for hypertension?

- Prostate cancer, heart failure, diabetic nephropathy (38, 50)
- Pulmonary hypertension, congestive heart failure (38)
- Acute renal failure (38)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Pharmacological Activity</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-104132</td>
<td>Congestive heart failure, hypertension (35, 45)</td>
<td><img src="image1" alt="J-104132" /></td>
</tr>
<tr>
<td>PD-157607</td>
<td>Hypertension (35, 45)</td>
<td><img src="image2" alt="PD-157607" /></td>
</tr>
<tr>
<td>Phenyl acetic acid</td>
<td>Renal protection in the experimental model (35, 51)</td>
<td><img src="image3" alt="Phenyl acetic acid" /></td>
</tr>
<tr>
<td>L-754442</td>
<td>Hypertension, renal failure (35)</td>
<td><img src="image4" alt="L-754442" /></td>
</tr>
<tr>
<td>PABSA</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
<td><img src="image5" alt="PABSA" /></td>
</tr>
</tbody>
</table>

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Does nature have the cure for hypertension?
<table>
<thead>
<tr>
<th>3,3'-Diphenyl propionic acid derivatives</th>
<th>Acetic group between two aromatic rings (35, 64)</th>
<th>Congestive heart failure (45), resistant hypertension (35, 52)</th>
<th>Acetic group between two aromatic rings (35, 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LU-135357 (darastatran)</td>
<td>ETRA</td>
<td>Synthetic</td>
<td>Acetic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>Non-peptide, substituted pyrimidines</td>
<td>Non-peptide, tetra-substituted pyrimidines</td>
<td>Synthetic</td>
<td>Acetic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>R0-47-0203 (bosantan)</td>
<td>ETRA/ETB</td>
<td>Non-peptide, tetra-substituted pyrimidines</td>
<td>Hypertension (40, 41)</td>
</tr>
<tr>
<td>R0-86-0005</td>
<td>ETRA/ETB</td>
<td>Non-peptide, tetra-substituted pyrimidines</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
<th>Type</th>
<th>Description</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ro-61-0612 (tezosentan)</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Non-peptide, tetra-substituted pyrimidines</td>
<td>Synthetic</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>TA-0201</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Non-peptide, tri-substituted pyrimidines</td>
<td>Synthetic</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>YM-598</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Non-peptide, tetra-substituted pyrimidines</td>
<td>Synthetic</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
<tr>
<td>Macitentan (Actelion-I, ACT-064992)</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Non-peptide, tri-substituted pyrimidines</td>
<td>Synthetic</td>
<td>Acidic group between two aromatic rings (35, 64)</td>
</tr>
</tbody>
</table>

**Non-sulphonamide, propanoic acid**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
<th>Type</th>
<th>Description</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Propanoic acid</td>
<td>Synthetic</td>
<td>Possible same mechanism as diphenylproprionic acid derivatives</td>
</tr>
</tbody>
</table>
ET-1 utilized the help of circular dichroism (CD) studies, nuclear magnetic resonance (NMR) and molecular dynamics simulation (59). ET-1 was identified to be 30-35% helical between residues Lys9 and Cys15, being the disulfide the responsible for this helicity (60). Additionally, the cyclic structure of the peptides would seem to be essential for binding and functional activity, where the outer disulfide bond Cys1-Cys15 would appear to be indispensable (61). L-Stereochemistry of the C-terminal of ET-1 is also crucial for binding and functionality, thus antagonists have been designed to have D-stereochemistry at position 16 (59).

Findings from structure-activity relationship studies of cyclic pentapeptide antagonists showed that these antagonists required a type II $\beta,\gamma$ backbone conformation with DDL IDL chirality to show affinity for the ETA receptor (62). However, the amino acid residue at position 3 can be deleted to generate linear peptides while retaining the $\beta$-turn structure (63). Moreover, addition of functional groups on the side chain of the amino acid at position 3 residue can generate an antagonist with a more preferable pharmacokinetics. The D-Val$^4$ position is critical for activity, and a lipophilic D-amino acid with a $\beta$-position branched alkyl side chain such as D-Val or D-Cpg or a lipophilic D-heteroarylglycine such as D-Thg is preferable (62).

Plenty of studies have shown that diverse structural classes of molecules can function as endothelin receptor antagonists (35). These studies showed common features for the different chemical groups. For instance, most of non-peptidic endothelin receptor antagonists like carboxylic acids, tetra-substituted pyrimidines and sulfonamides have at least two aromatic groups placed around one acidic functional group (35, 64). Chemical improvements have been made on carboxylic acid derivatives by replacement of the indan ring for a pyrrolidine ring, like compound SB-209670. Moreover, the type of N substituent has been shown crucial for endothelin receptor antagonism, like featured by atrasentan (A-127722) (64).

For the case of triterpene derivatives like myriceric acid A four functional groups have been identified as essential for their activity and affinity to the ET$_\alpha$ receptor; namely, the carbonyl group at C-3, carboxylic acid group at C-17, dimethyl group at C-20 and trans-caffeoyloxy group at C-27. Moreover, the study revealed that when the hydroxyl groups on the trans-caffeoyl moiety where sulfated, the binding affinity increased up to 20-fold (65).

Diverse origins for endothelin receptor antagonists

The need to find selective, potent and safe endothelin ET$_\alpha$ receptor antagonists has moved forward the development of drug discovery programs within natural product research. Since random screening of natural products followed by rational chemical design have played a major role in the discovery of successful antihypertensive drugs acting on the rennin-angiotensin system (angiotensin converting enzyme inhibitors and angiotensin II AT$_1$ blockers) (66) and the endothelin system (35), it is important to keep screening natural resources for new molecules with new properties.

Microorganisms : The first cyclic pentapeptide ET$_\alpha$ receptor antagonists were discovered within a screening program for endothelin-binding inhibitors from the culture broths of microorganisms. Compounds BE-18257A and BE-18257B were isolated from the bacteria Streptomyces misakiensis obtained from soil samples (Table 2) (67). These novel cyclic pentapeptides gave origin to the most commonly used selective ET$_\alpha$ receptor antagonist, the
analogue BQ-123 (Table 1) (68). The observed potency and selectivity of these cyclic pentapeptides has promoted the development of several tripeptide analogues having N-terminal amide, urethane and urea moieties or derivatives of the tryptophan indole ring, such as BQ-788 and BQ-017 (selective ET<sub>a</sub> receptor antagonists), and BQ-928 a non-selective ET<sub>a</sub>/ET<sub>a</sub> antagonist (69). More recently, within a screening program for compounds which inhibit binding of endothelin to its receptor, three novel pentapeptolides named aselacin A, aselacin B and aselacin C were isolated from the fungus Acremonium <i>spp</i>. grown in stationary culture. Aselacin A (Table 2) was found to be a selective inhibitor of the ETA receptor. These compounds have a ring formed by cyclo[Gly-<i>D</i>-Ser-<i>D</i>-Trp-\(\beta\)<i>-Ala-L-Thr</i>] and an additional exocyclic D-Gln to which is attached to a functionalized long chain fatty acid (70, 71).

**Plants** : Myriceric acid A was isolated from the twigs of the southern bayberry (<i>Myrica cerifera</i>) during a screening program of approximately 400 different plants (36, 72, 73).

Since random screening of natural products has led to the discovery of several bioactive compounds (41), diverse screening programs have been designed to search for potent endothelin antagonists. Example of this is a study carried out using crude drugs from Chinese medicines, in which phoephorbide a was found (Table 2) (74). In the same line, 149 extracts from nineteen plants described by traditional Panamanian medicine has also led to identification of potential sources of new active molecules. The results suggest further investigation of the chemical constituents in the ethanolic extracts of the leaves of <i>Cecropia cf.obtusifolia</i> Bertol., the leaves of <i>Hedyosmum bonplandianum</i> H.B.K., the roots of <i>Bocconia frutescens</i> L., the stem of <i>Cecropia cf.obtusifolia</i> Bertol. and the branches of <i>Psychotria elata</i> (Sw.) Hammel (75).

Additionally, a random screening of triterpenoid saponins and the corresponding aglycons was carried out on the human ET<sub>a</sub> receptor. The results showed that selectivity for the ET<sub>a</sub> receptor was exhibited by asiatic acid and its saponins; and to a lesser extent by betulinic acid, \(\beta\)-amyrin and friedelin (Table 2) (76).

**Animals** : Attempts at finding more selective and potent ET<sub>a</sub> receptor antagonists have led researchers to study natural sources of diverse habitats. Sponges of the genus <i>Iantbella</i> have been reported to contain bromotyrosine derivatives, called bastadins, showing variable numbers of tyrosine units as well as different substitution patterns on the tyrosine units. These bastadins possesses a different ring pattern with an alternative oxidative cyclization of the general bastadin backbone. The first isolated sulfated compound of the bastadin series was 34-sulfobastadin 13, which showed some inhibition of endothelin binding to its receptor (Table 2) (77). In the same line, further screening of marine natural products showed that plakortide N isolated from the sponge <i>Plakortis halichondrioides</i> caused a moderate inhibition of \([^{3}H]\) BQ-123 binding to the ET<sub>a</sub> receptor (Table 2) (78).

**Other mechanisms by which natural products inhibit the endothelin system**

Polyphenols from red wine (Cabernet Sauvignon grapes) decreased ET-1 synthesis in cultured bovine aortic endothelial cells by suppressing transcription of the ET-1 gene. Red-grape juice also inhibits ET-1 synthesis, but it is markedly less potent than red wine. On the other hand, the white and rosé wines had no effect (79).

Freeze-dried garlic powder caplets were tested on rat’s isolated pulmonary arteries and...
Table 2. Natural occurring compounds found to inhibit binding of specific ligands to the ET₄ receptor.

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Base</th>
<th>Origin</th>
<th>Inhibition of binding to ET₄ receptor (IC₅₀ values or % of binding inhibition)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF-18257A</td>
<td></td>
<td>Cyclic pentapeptide</td>
<td>Bacteria (Streptomyces musatokensis)</td>
<td>3.00 µM (IC₅₀)</td>
<td>(31)</td>
</tr>
<tr>
<td>BF-18257B</td>
<td></td>
<td>Cyclic pentapeptide</td>
<td>Bacteria (Streptomyces musatokensis)</td>
<td>1.40 µM (IC₅₀)</td>
<td>(31, 32)</td>
</tr>
<tr>
<td>Aselacin A</td>
<td></td>
<td>cyclopropanedipeptide</td>
<td>Natural (Acromonum spp.)</td>
<td>24.20 µM (IC₅₀)</td>
<td>(70, 71)</td>
</tr>
<tr>
<td>Myristic acid A (50-235)</td>
<td></td>
<td>Non-peptide, triterpene</td>
<td>Natural (Myrica cerifera)</td>
<td>0.06 µM (IC₅₀)</td>
<td>(65, 72, 73)</td>
</tr>
<tr>
<td>Phosphorhine a</td>
<td></td>
<td></td>
<td>Plant (Artemisia capillaris Thunb.)</td>
<td>0.08 µM (IC₅₀)</td>
<td>(74)</td>
</tr>
<tr>
<td>Asiatic acid</td>
<td></td>
<td>Triterpene</td>
<td>Plant</td>
<td>74% (10µg/mL)</td>
<td>(76)</td>
</tr>
<tr>
<td>Asiaticoside</td>
<td></td>
<td>Triterpervoidal saponin</td>
<td>Plant</td>
<td>44% (10µg/mL)</td>
<td>(76)</td>
</tr>
</tbody>
</table>
showed both an endothelium (NO)-dependent and –independent relaxation with inhibition of ET-1 contraction (80). These preliminary findings cannot differentiate whether this inhibition was at the receptor level or by direct relaxation on vascular smooth muscle cells. Thus further studies are required to determine the molecular interactions responsible for this effect.

Compound CPU 86017 (p-chloro benzyl tetra hydroberberine), obtained as a derivative of berberine, is capable of indirectly inhibiting the endothelin system by blocking voltage-dependent calcium channels coupled to ET<sub>A</sub> receptors by G proteins. Additionally, CPU 86017 suppresses the the endothelin-reactive oxygen species pathway responsible for the increase in mRNA of prepro-ET-1, eNOS, and iNOS due to increments of ROS (81).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Source</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPU 86017</td>
<td>Tetrapone</td>
<td>Plant</td>
<td>39.09 (IC&lt;sub&gt;50&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Plakortide N</td>
<td>Polyketide</td>
<td>Marine sponge</td>
<td>44% (100 μg/mL)</td>
</tr>
</tbody>
</table>

**Conclusions**

Pharmaceutical companies have invested huge resources screening thousands of compounds from their chemical libraries in search for novel and more active molecules. Nevertheless, plenty of evidence supports the fact that nature remains the first class source of diverse, complex and active new chemical structures (2). The case of endothelin receptor antagonists is a good example of the uniqueness of nature’s ability to create chemical diversity, and how the researchers’ work has been focused to only perform small modifications of these natural occurring substances in order to improve their activities.

Remarkable chemical diversity has been found when analyzing endothelin receptor antagonists from different sources. For instance,
microorganisms and marine sponges showed to produce related peptide-like structures, capable of mimicking the binding of endogenous peptides without displaying their functionality. Interestingly, it has been proven that many bioactive compounds isolated from marine sponges are produced by its associated microorganisms (82), suggesting that more research should be done in isolating the chemical entities amongst the microbiota of marine sponges.

Additionally, selectivity for one receptor was found in plant-derived compounds, suggesting that they are a good source of potential lead compounds and that compounds identified during screening programs could end up as novel, more active and safer structures and should be then promoted for further evaluation.

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