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What are and where are the bioactive terpenoids metabolites from Dictyotaceae (Phaeophyceae)

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Abstract: Dictyotaceae are a rich source of secondary metabolites, especially terpenes. These natural products have been studied for their bioactivity for human and for their ecological role in nature. The present work highlights de diversity of the Dictyotaceae terpenes, emphasizing their bioactivities and the biogeography of their sources. The sesquiterpenes are found in *Padina, Dictyopteris* and *Taonia*. Although *Dictyopteris* and *Padina* can be found in all oceans, *Taonia* has a more restricted distribution. Diterpenes of mixed origin have been reported in *Lobophora, Taonia* and *Stypopodium*. *Stypopodium* is a typically tropical and warm temperate genus. Diterpenes with the spatane and seco-spatanes skeletons are known from *Spatoglossum, Stoechospermum* and *Rugulopteryx*. *Spatoglossum* is distributed over all the tropical marine world. Stoechospermum is known to occur in the Indian Ocean and *Rugulopteryx* is distributed mainly in Asia and on the Pacific Coast of Australia. The genus *Dictyota* contains diterpenes as the major metabolite and are present in all oceans, reaching even the cold temperate regions of northern and southern hemispheres. The terpenoids from Dictyotaceae exhibit bioactivities such as inhibition of herbivores and antifungal, cytotoxic, antibiotic, anti-inflammatory, insecticidal and antiviral activities.

Introduction

Many marine organisms are able to produce substances derived from secondary metabolism. These metabolites, also called natural products, are present from bacteria and algae to echinoderms, mollusks, tunicates and vertebrates, through the sponges and corals (Blunt et al., 2010).

The knowledge of metabolites has helped to characterize the algae at different hierarchical levels (divisions, classes etc.) down to species (De Paula et al., 2007), and has importance for phytochemical, phylogenetic and ecological studies (Teixeira et al., 1991). Moreover, these substances have a high biotechnological potential, as evidenced by their use in the food and pharmaceutical industris that generates billions of dollars (Smit, 2004).

Technological advances in disease diagnosis, combined with democratization of access to this technology, are reflected in the increase in the number of people diagnosed with diseases caused by biological agents. In response to this scenario, the search for substances that can counteract the presence and multiplication of infection by the biological pathogens has increased. In this context, studies of natural metabolites have been shown to be a good alternative, with a diversity of sources, chemical structures and applicability. The oceans, which cover 70% of the biosphere, are also the cradle of life on Earth. Due to the longer existence of life in the marine environment, it harbors the largest Phyletic diversity of the planet. The brown algae (Phaeophyceae) are a class of almost exclusively marine organisms that have been explored for the bioactivity potential of its metabolic products, especially those of the representative family Dictyotaceae. Although it is only the third in number of species within the class, this family is a rich and diverse source of natural products, which makes it the most studied with the greatest number of known metabolites. Dictytotaceae is represented by species with apical growth from a single cell or a row of cells making up the margin. The macromorphology of these species includes flabeliform to ribbonlike plants. Micromorphologically, all have reproductive elements with only one plumose flagellum, while the other Phaeophyceae possess a pair of flagella. The chemistry of Dictyotaceae natural products include a rich production of terpenoids molecules of different origins and are therefore important in studies of metabolites of marine origin.

Two biogenic pathways have been described for the terpenoid formation, the mevalonate pathway and the mevalonate-independent pathway via deoxyxylulose phosphate (Dewick, 2002). Terpenoids are composed of five carbon subunits (an isoprenoid) disposed in a configuration called head and tail and are classified according to the number of isoprenoid units incorporated. In Dictyotaceae and in particular in this paper, the most bioactive products have three or four isoprenoid units, corresponding to the sesquiterpenes and diterpenes, respectively. These two classes of terpenoids can have many different structures and variants, including the addition of halogen atoms (the most common being chlorine or bromine) or fragments from other biogenic pathways. In this latter case, they are called terpenes of mixed origin, an example being the incorporation of a phloroglucinol unit into a diterpene.

As a natural source, the terpenes are strongly influenced by population distributions. For example, Freitas et al., (2007) and Vallim et al. (2007) found differences in the diterpene expression by *Dictyota mertensii* in different distant beaches and Ali & Pervez (2003a, 2003b) and Ali et al. (2003; 2004) described highly oxidized diterpenes from a seco-dolastane and related dolastane producing *Canistrocarpus* population from the Karachi coast of the Arabian Sea.

The present work is a bried description of terpenoid diversity in Dictyotaceae and their bioactivity, algae source and distribution in the oceans. These results were presented at the II Workshop on New Bioactivies from Macroalgae.

Materials and Methods

The Dictyotaceae bioactivities were taken from the original papers and/or the annual review series Marine Natural Products, published by *Natural Product Reports* and covering the literature from 1977 (Faulkner, 1984) to 2009 (Blunt et al., 2011). Only bioactivities for which the active substance was described were selected. No information was used from studies limited to extracts or enriched fractions. The scientific names of the Dictyotaceae and their geographical distribution were based on information from the site algaebase (Guiry & Guiry, 2011).

Results

Halogenated sesquiterpenes (whose main sources are the red algae) are reported in *Padina antillarum* (Parameswaran et al., 1994, 1996) and *Dictyopteris divaricata* (Ji et al., 2009), and sesquiterpenes without halogens in *Dictyopteris divaricata* (Song et al., 2005, 2006; Qiao et al., 2009; Wen et al., 2009), *D. undulata* (Song et al., 2004a) and *Taonia atomaria* (De Rosa et al., 1994). For the latter two genera, 36 and six species are recognized, respectively, while for *Padina* 37 species are still valid. The sesquiterpenes in which a phloroglucinol unit is added were reported in *Dictyopteris undulata* (Ochi et al., 1979a; 1979b; Cortés et al., 2001; Dave et al., 1984) and *Dictyopteris divaricata* (Song et al., 2004b). Alhough *Dictyopteris* and *Padina* can be found in all oceans with predominant occurrence in tropical areas, *Taonia* is more restricted to the North Atlantic Ocean, Caribbean, Mediterranean, South Australia and Pakistan (Figure 1). The sesquiterpenes of these genera are known to exhibit activity as an inhibitor of herbivores and antifungal, cytotoxic, antibiotic and ichthyotoxic activities. Table 1 illustrates some of the products and their activities.

Meroditerpenes, *i.e.*, polycyclic diterpenes of mixed biogenesis characterized by a methyl hydroquinone nucleus linked to a diterpenic chain, have been reported in *Lobophora papenfussii* (Gerwick & Fenical, 1982), *Taonia atomaria* (Ishitsuka et al., 1990), *Stypopodium zonale* (Gerwick & Fenical, 1981), *S. flabelliforme* (Gerwick et al., 1979) and *S. schimperii* (Sampli et al., 2000). These metabolites can be linear, similar to those found in Fucales (Ishitsuka et al., 1979; Kusumi et al., 1979; Amico et al., 1982a,b;, Banaigs et al. 1982; 1983), or have polycyclic skeletons similar to each other, which may reveal a phylogenetic similarity between *Stypopodium* and *Taonia.* Meroditerpene compounds were reported in *Stypopodium flabelliforme* (Areche et al., 2009). This is a typically tropical and warm temperate genus (Figure 2) with six currently accepted species, including *S. flabelliforme, S. schimperii* and *S. zonale* that have been studied chemically. The meroditerpenes of these genera are known to exhibit cytotoxic, anti-inflammatory, insecticidal, and antivira activities. Table 2 illustrates some of the activities of meroditerpenes.

Besides the above mentioned skeletal types, Dictyotaceae are the second richest source of cyclic terpenes from marine algae, after the genus *Laurencia* (Rhodophyta). More than 300 diterpenoids have been reported, distributed in six genera. Diterpenes of the spatane and seco-spatane types are known from *Spatoglossum* (*S. schmittii* and *S. howleii*), Stoechospermum polypodioides and *Rugulopteryx*. While the first two genera exhibit growth via a small group of apical cells, *Rugulopteryx* grows by a single apical cell (De Clerck et al., 2006). *Spatoglossum* has twenty known species of which only the diterpenoid content of *S. howlleii* and *S. schmittii* have been reported (Gerwick & Fenical, 1983; Gerwick et al., 1983). This genus is distributed over the entire tropical marine world, also reaching some warm temperate regions. *Stoechospermum polypodioides* is the only species of the genus known in the Indian Ocean. *Rugulopteryx*, with its four species, is distributed mainly in Asia and the Pacific Coast of Australia and, in a few instances, in the Mexican Pacific, Indian, Atlantic and eastern Mediterranean (Figure 3). These diterpenes exhibit great structural similarity, even from different genera. and there are reports of antiherbivory, antibiotic, cytotoxic, cell division inhibition and HSV antiviral activities. Table 3 shows some spatanes and related products and their bioactivities.

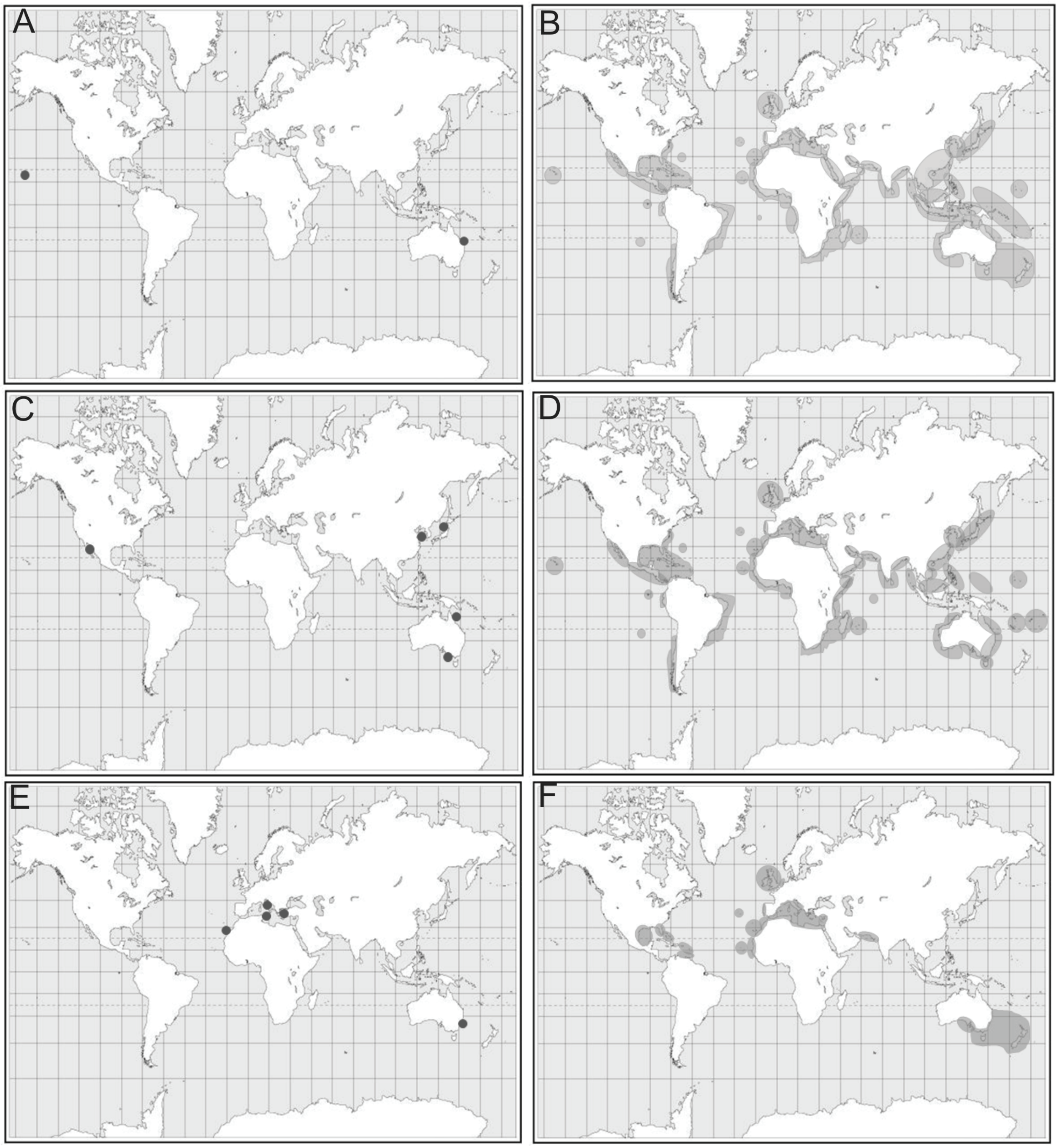
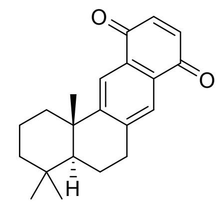
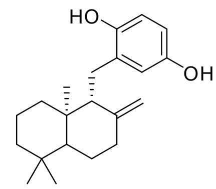
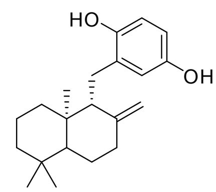
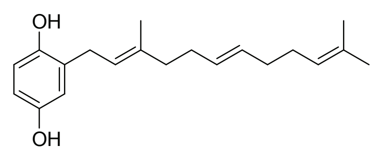
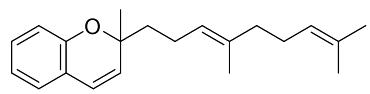


Figure 1. Places where the genera were studied chemically: *Padina* (A), *Dictyopteris* (C) e *Taonia* (E) and the known distribution of the genera *Padina* (B), *Dictyopteris* (D) e *Taonia* (F).

Table 1. Bioactive sesquiterpenes.

Source	Activity	Product	Reference
Dictyopteris undulata	antiherbivory		Kurata et al., 1996
Dictyopteris zonaroides	antifungal		Fenical et al., 1973
Dictyopteris zonaroides	citotoxic/antitumoral		Fenical et al., 1973
Dictyopteris undulata	antibiotic		Ochi et al., 1979a
Dictyopteris undulata	ichthyotoxic		Dave et al., 1984

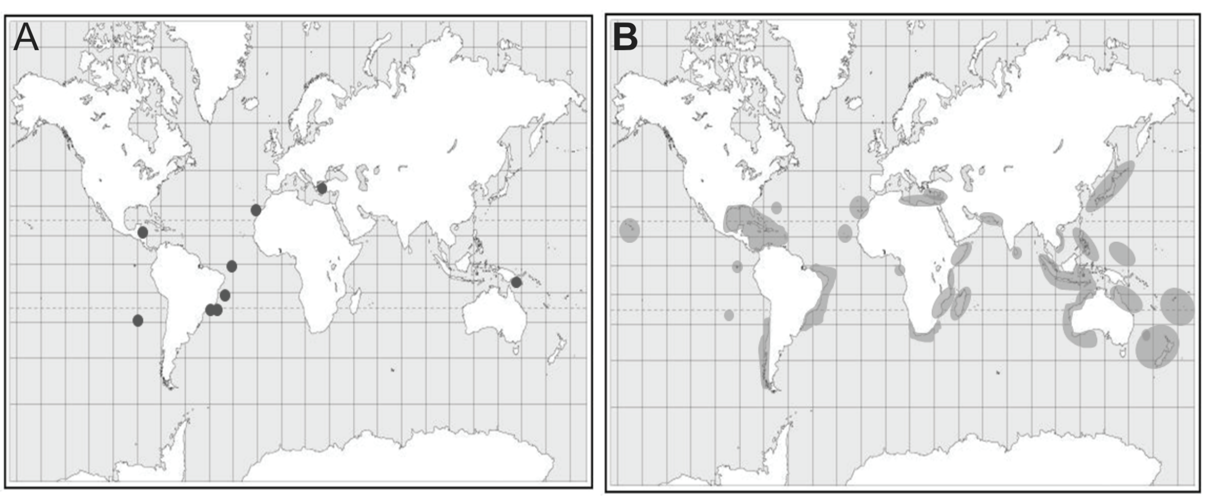
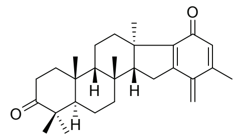
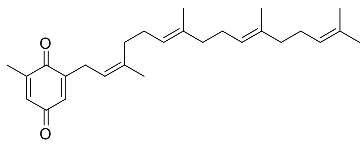
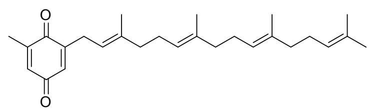
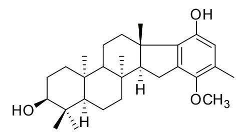
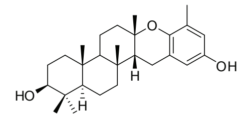
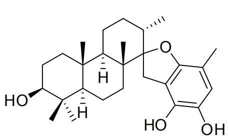
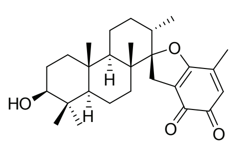
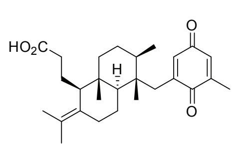
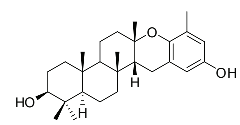


Figure 2. Places where *Stypopodium* was studied chemically (A) and the known distribution of the genus (B).

Table 2. Bioactive meroditerpenes.

Source	Activity	Product	Reference
Taonia atomaria	cytotoxic/antitumoral		Abatis et al., 2005
Taonia atomaria	anti-inflammatory		Tziveleka et al., 2005
Taonia atomaria	radical-scavenging activity		Nahas et al., 2007
Stypopodium flabelliforme	sodium channel blocking activity		Sabry et al., 2005
Stypopodium flabelliforme	insecticidal		Rovirosa et al., 1992
Stypopodium zonale	ichthyotoxic		Gerwick and Fenical, 1981
Stypopodium zonale	inhibition of polymerization of microtubules		Jacobs et al., 1985
Stypopodium zonale	tyrosine kinase inhibitor		Wessels et al., 1999
Stypopodium zonale	antiviral		Soares et al., 2007

The genus *Dictyota* has two distinct species groups: (1) one in which the major diterpenes have prenylated guaiane skeletons associated with xenianes, crenulidanes or dichotomanes, with other related skeletons present in lower abundance; and (2) another in which the major products are dolabellanes and related dolastanes with other related skeletons in lower abundance. There is no co-occurrence of these two different kinds of major products or of those with smaller abundance in the same species. When this co-occurrance is reported in the literature, it is attributed to the presence of a mixture of species. Awad et al. (2008) recorded the presence of xeniane in *Padina pavonica*. Prenylated guaiane species are distributed mainly in the tropics, but are present in all oceans, even reaching the cold temperate regions of the northern and southern hemispheres (Figure 4). Among the biological activities described are anti-retroviral, cytotoxic, antibiotic, and anti-herbivory activities. Table 4 illustrates prenylated guaiane and related products and their bioactivities.

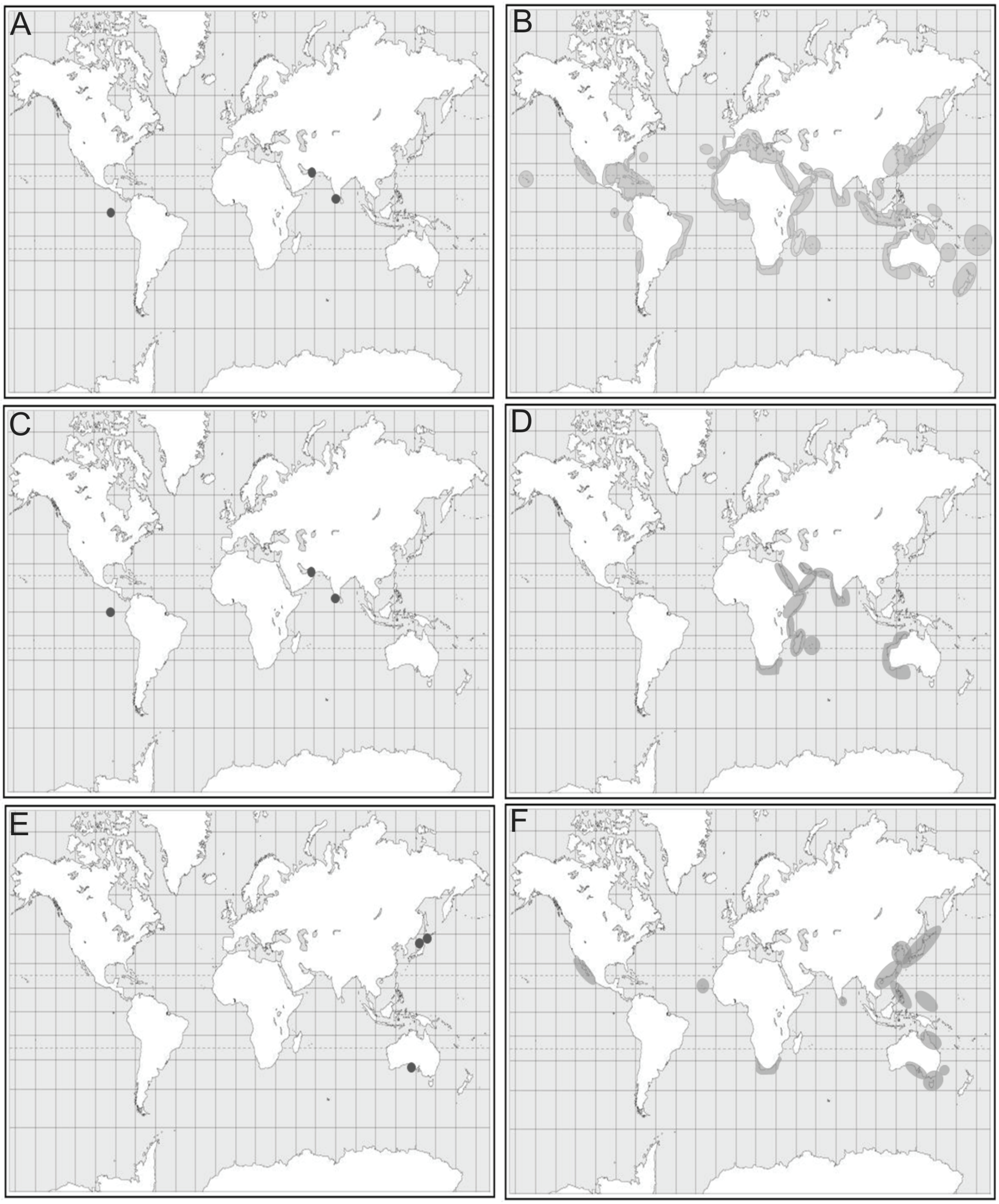
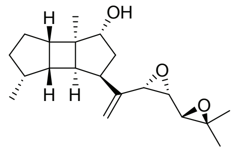
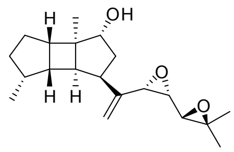
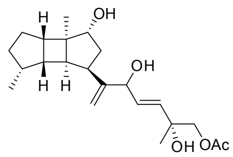
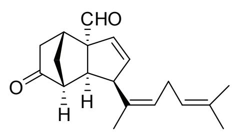


Figure 3. Places where the spatane producing genera were studied chemically: *Spatoglossum* (A), *Stoechospermum* (C) and *Rugulopteryx* (E) and the known distribution of the genera *Spatoglossum* (B), *Stoechospermum* (D) and *Rugulopteryx* (F).

Table 3. Bioactivity of spatane and related metabolites.

Source	Activity	Product	Reference
Spatoglossum schmittii	inhibitor of cell division		Gerwick & Fenical, 1983
Spatoglossum schmittii	cytotoxic/antitumoral		Gerwick & Fenical, 1983
Stoechospermum polypodioides	anti-bacterial activity		De Silva et al., 1982
Rugulopteryx okamurae	anti-herbivory		Suzuki et al., 2002

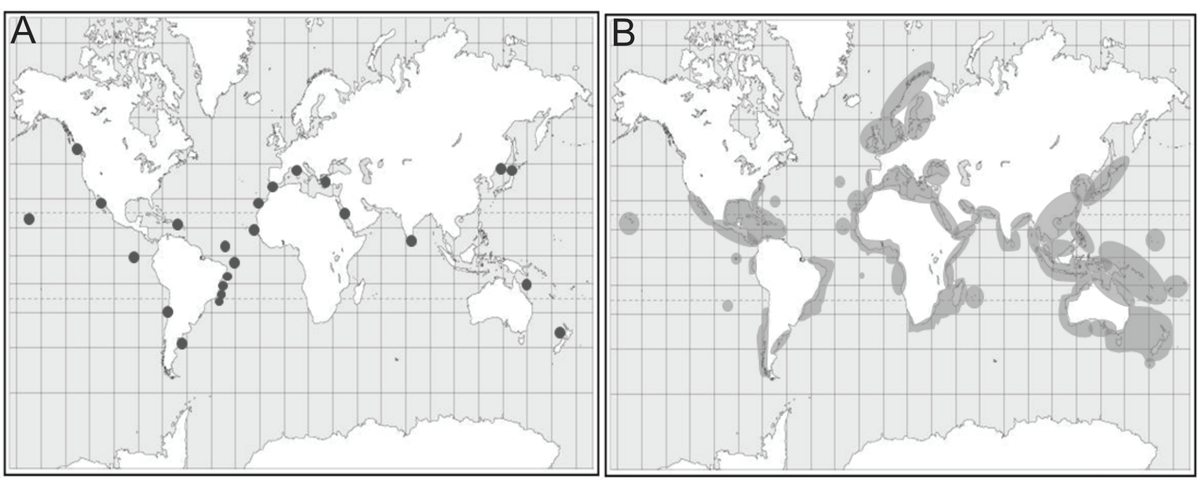
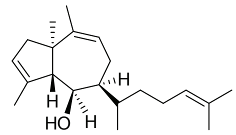
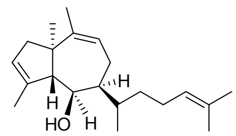
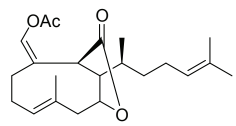
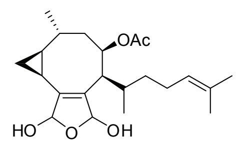
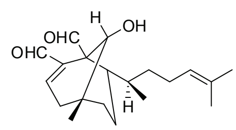


Figure 4. Places where prenylated guaiane species were studied chemically (A) and the known distribution of the genus *Dictyota* (B).

The *Dictyota* species that produce dolabellanes have a geographical distribution that is somewhat more restricted to tropical regions, extending to the subtropics compared to their prenylated guaiane counterparts (Figure 5). Natural products of these species are reported to have antiviral, chemical defense, bactericidal and ichthyotoxic activities. Table 5 illustrates dolabellanes and their bioactivities.

The *Dictyota* species that produce seco-dolastanes and dolastanes were transferred by De Clerck et al. (2006) to the genus *Canistrocarpus*. Although these species also produce dolastanes, these products have chemical characteristics that distinguish them from those of *Dictyota* origin. The bioactivities of this genus include antiviral, anti-herbivory and enzyme inhibitor activities. *Canistrocarpus* has three species, distributed mainly in the tropical regions of all oceans and extending to warm temperate regions (Figure 6). Table 6 illustrates seco-dolastanes and related dolastanes and their bioactivities. Discussion

Table 4: Bioactivity of prenylated guaianes and related metabolites.

Source	Activity	Product	Reference
Dictyota dichotoma	citotoxic/antitumoral		Durán et al., 1997
Dictyota coriacea	antibiotic activity		Hirschfeld et al., 1973
Dictyota ligulata	citotoxic/antitumoral		Bouaicha et al., 1993
Dictyota ligulata	antibacterial activity		Tringali et al., 1988
Dictyota menstrualis	antiviral		Pereira et al., 2004

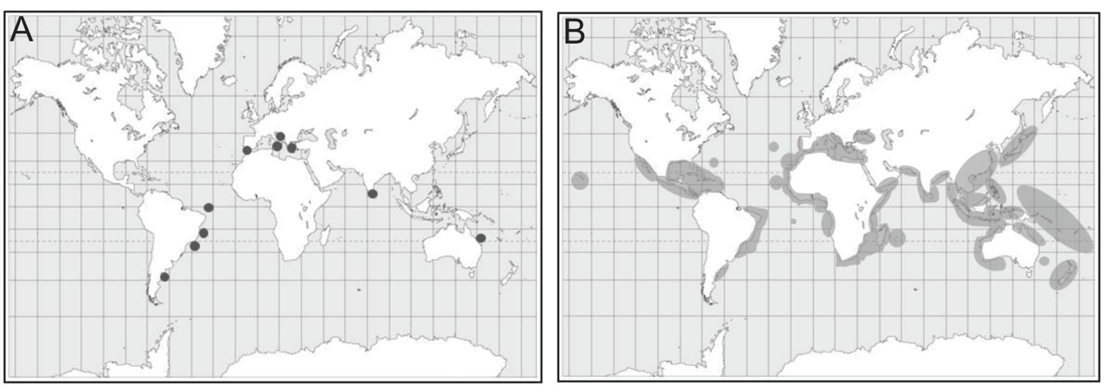


Figure 5. Places where dolabellane producing species were studied chemically (A) and the known distribution of the *Dictyota* dolabellanes producing species (B).

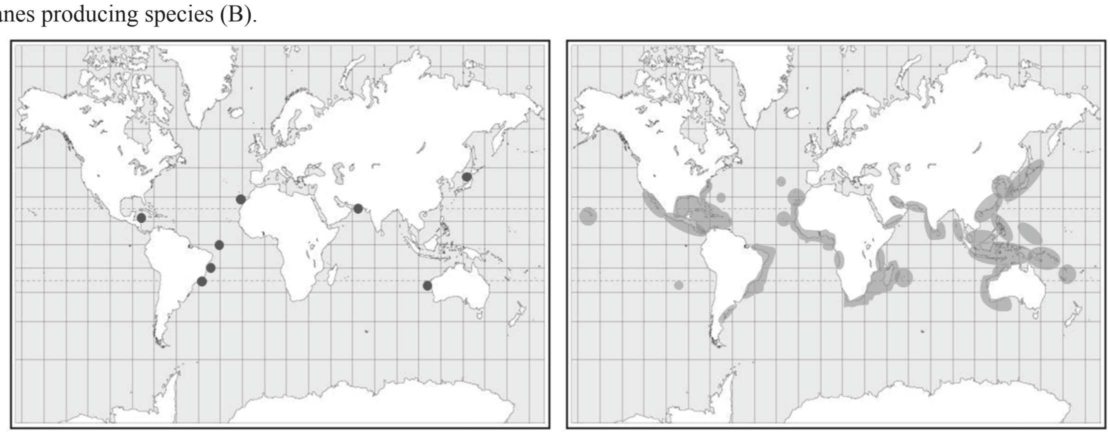


Figure 6. Places where seco-dolastanes were studied chemically (A) and the known distribution of the genus *Canistrocarpus* (B).

Table 5. Dolabellane bioactivity

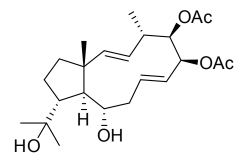
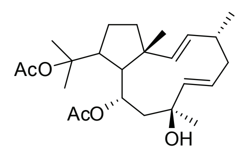
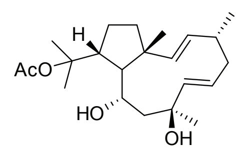
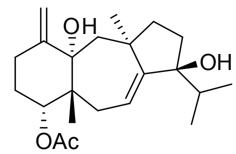
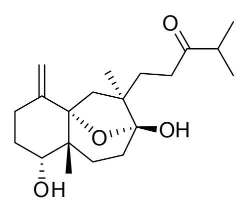
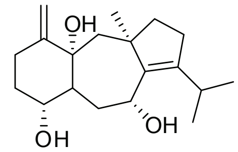
Source	Activity	Product	Reference
Dictyota fasciola	ichthyotoxic		De Rosa et al., 1984
Dictyota friabilis	antiherbivory activity		Barbosa et al., 2004b
Dictyota friabilis	antiviral		Barbosa et al., 2004a

Table 6. Bioactivity of seco-dolastanes and related dolastanes.

Source	Activity	Product	Reference
Canistrocarpus cervicornis	ATPase inhibitory		Garcia et al., 2009
Canistrocarpus cervicornis	anti-herbivory		De Paula et al., 2001
Canistrocarpus cervicornis	antiviral		Vallim et al., 2010

The Dictyotaceae are a rich source of bioactive terpenes (Vallim et al., 2010). Feeding-deterrence activity could be found for the sesquiterpenes in *Dictyopteris* (Kurata et al., 1996), for spatanes in *Rugulopteryx* (Kurata et al., 1988; 1989), for prenylated guaianes and dolabellanes in *Dictyota* (Hardt et al., 1996; Barbosa et al., 2004b) and for secodolastanes in *Canistrocarpus* (De Paula et al., 2001). Several of these compounds found in Dictyotaceae exhibit a broad spectrum of feeding deterrence against herbivores (Pereira et al., 2000a; 2000b), including mollusks, fishes, sea urchins, amphipods and crabs. The biogeographical distribution of secondary metabolites from Dictyotaceae could be the result of different evolutionary herbivore pressures (Pereira et al., 2000a; Vallim et al., 2005).

Cytotoxic activities were evaluated in several human tumor cell lines for sesquiterpenes from *Dictyopteris* (Fenical et al., 1973), for meroditerpenes from *Stypopodium* and *Taonia* (Dorta et al., 2002; Abatis et al., 2005) as well as for prenylated guaianes and dolabellane diterpenes from *Dictyota* (Durán et al., 1997; Tringali et al., 1984), and for spatanes from *Spatoglossum* (Gerwick & Fenical, 1983). *Taonia* and the diterpene producing species of Spatoglossum have restricted distributions. Hence, the places where they occur must be adequately protected in order to preserve them for future research.

Antifungal activity was found only for sesquiterpenes from *Dictyopteris*. The terpene from another Phaeophyceae, *Lobophora variegata*, did not exhibit this activity (Kubanek et al., 2003).

Compounds with anti-inflammatory activity were found in *Taonia* (Tziveleka et al., 2005) and inhibition of microtubules (Jacobs et al., 1985) and enzymes (Wessels et al., 1999) was exhibited by merodíterpenes from *Stypopodium*. This last activity was also shown by *Canistrocarpus* dolastanes (Garcia et al., 2009).

Antiviral activity, in particular that against HIV and HSV, was exhibited by several Meroditerpenes from *Stypopodium* (Soares et al., 2007), by dichotomane (Pereira et al., 2004), and by dolabellane (Barbosa et al., 2004a). Although not from a Dictyotaceae, a halogenated sesquiterpene from the red alga *Peyssonelia* also exhibit antiviral activity (Loya et al., 1995). Because *Padina* (Parameswaran et al., 1994; 1996) and *Dictyopteris* (Ji et al., 2009) also contain halogenated sesquiterpenes, these algae could become a source of antiviral molecules.

Comparing the places in the world where these algae have been chemically studied with those where the presence of terpenoids is known and with the species distribution, it is easy to recognize that bioactivies of metabolites from Dictyotaceae have a vast potential, given the changes that might occur in gene expression in local populations. In this context, greater attention to preservation of coastal areas is necessary in places where human pressures have increased and where seaweeds and their metabolites are found, given their importance for marine ecology and human health.

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