35. Marine Bioactive Compounds from Cnidarians

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Cnidaria is a large, diverse and ecologically important phylum of marine invertebrates, which includes corals, sea fans, anemones, and jellyfishes. It contains over 11 000 species, 7500 of them belonging to the class Anthozoa. Over 3000 marine natural products have been described from this phylum alone, most of them in the twenty-first century. The present work provides an overview of some of the most promising marine bioactive compounds, from a therapeutic point of view, isolated from cnidarians since the year 2000. The order Alcyonacea (class Anthozoa) exhibits the highest number of species yielding promising compounds. Antitumor activity has been the major area of interest in the screening of cnidarian compounds, the most promising ones being terpenoids (monoterpenoids, diterpenoids, and sesquiterpenoids). Future trends and challenges for the bioprospecting of new marine bioactive compounds produced by cnidarians are also discussed, with emphasis on the sustainable production of target cnidarians biomass and the role played by symbiotic microorganisms in the synthesis of important biomolecules.

35.1 Cnidarians

The phylum Cnidaria is a large, diverse and ecologically important group of marine invertebrates that contains over 11 000 extant species (Table 35.1) [35.1], including hydroids, jellyfish, anemones, and corals, among others (Fig. 35.1). This group of invertebrate animals is found exclusively in aquatic environments, mostly in marine ecosystems. Cnidarians have simple body forms, usually of a polyp or medusa (Fig. 35.2) [35.2]. For instance, an anemone is a single polyp, whereas corals are, in general, a colony of individual polyps, which are typically tubular and attached to a surface at their base. Both forms may occur during the life cycle of some cnidarians. All species within the phylum Cnidaria have tentacles surrounding the opening (mouth), with stinging cells in their tips that are used to capture and subdue prey. The stinging cells are coiled structures that shoot out and inject toxins via a dart-like tip [35.2].

Cnidarians are usually found in a wide geographic range: from deep waters near hydrothermal vents to polar seabeds and tropical reefs. Some cnidarian species, mostly from the class Scyphozoa (jellyfish), are pelagic and live in the water column. Cnidarians lack mechanical means to prey and have optimized their mechanisms to feed throughout evolutionary history, such as stinging cells with powerful toxins that help to disable their prey and drive off predators [35.3]. In addition to these chemical weapons present in the stinging cells, cnidarians also display other potent compounds that are useful for deterring predators and keeping competitors away [35.4–6]. For instance, tropical reefs are ecosystems with a vast biodiversity, where the substrate available for benthic cnidarian species to settle and develop is scarce [35.7]. Chemical interactions between different species are thus an important mechanism for inter-

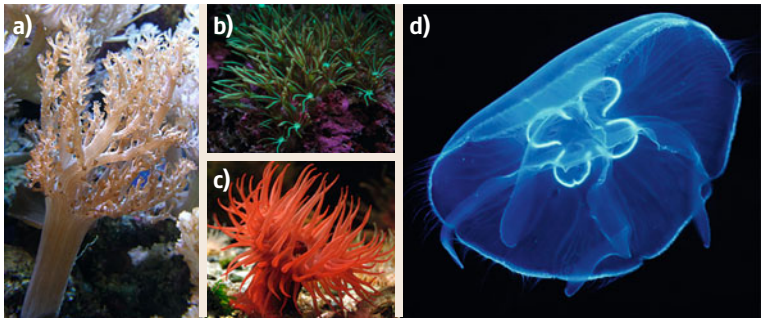

Fig. 35.1a–d Marine invertebrates from the phylum Cnidaria (all images by Ricardo Calado). **(a)** Soft coral (*Sinularia* sp.), **(b)** soft coral (*Briareum* sp.), **(c)** sea anemone (*Actinia equina* sp), **(d)** jellyfish (*Aurelia aurita*)

specific competition, which may have dramatic consequences for the organism being outcompeted in this *chemical war*. Therefore, organisms inhabiting highly biodiverse tropical areas, particularly coral reefs, have developed a large array of chemical compounds that have been the focus of recent bioprospecting efforts [35.8].

Corals form the structure and foundation of tropical coral reefs and are also important structural elements of some highly diverse deep-sea habitats. Other cnidarian species, such as anemones, are also very diverse and abundant in these tropical ecosystems [35.9]. These benthic cnidarians display a great variety of molecules that have different biological functions. The harsh chemical and physical environmental conditions of the areas inhabited by these organisms may have been important drivers for the production of a variety of molecules with unique structural features. For instance, the incidence of predation in the majority of these organisms is low due to the toxic compounds they produce to deter predators [35.10]. Other examples of biological functions of these compounds are defensive functions against pathogens, as well as against fouling organisms, herbivores, and microorganisms [35.11]. Such chemical compounds have been targeted by scientists searching for new chemical entities from the sea, usually known as marine natural products (MNP). Although more than 20 000 compounds have been discovered since the field of MNP began in the mid 1960s, only a very limited number have reached the end of the drug discovery pipeline [35.12].

Table 35.1 Classes and orders in the phylum Cnidaria (according to the classification proposed in the World Register of Marine Species (WoRMS)) [35.1]

Phylum	Class	Order
Cnidaria (≈ 11 287 species)	Anthozoa (≈ 7500 species)	Actiniaria; Zoanthidea Antipatharia; Alcyonacea Ceriantharia; Gorgonacea Corallimorpharia; Helioporacea Scleractinia; Pennatulacea
	Cubozoa (≈ 36 species)	Carybdeida; Chirodropida
	Hydrozoa (≈ 3500 species)	Anthoathecata Leptothecata; Limnomedusae Siphonophorae; Narcomedusae Actinulida; Trachymedusae
	Polypodiozoa (1 species)	Polypodiidea
	Scyphozoa (≈ 200 species)	Coronatae Rhizostomeae; Semaeostomeae
	Staurozoa (≈ 50 species)	Stauromedusae

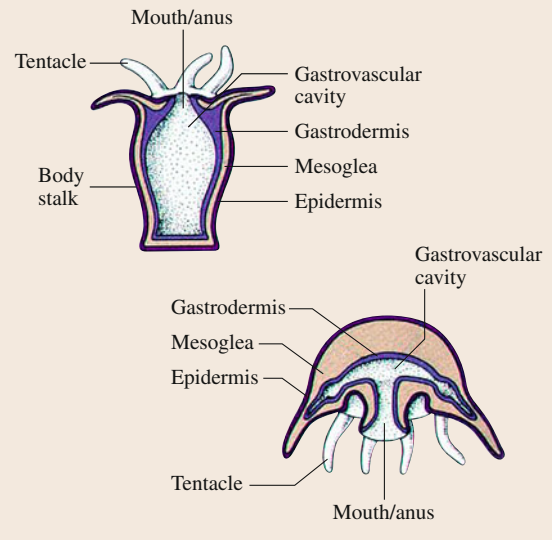

Fig. 35.2 Diagram of polyp and medusa forms of cnidarians

This chapter focuses the compounds that have been discovered from marine cnidarian species, providing a brief overview of this topic and discussing the role of biodiversity and biogeography in the chemical diversity of cnidarians. Cnidarian molecules discovered since the year 2000 that display important bioactivities and promising biotechnological applications are discussed in detail. The rationale for this approach is that the drug discovery pipeline, i. e., the time between discovering a new natural product and the commercialization of that marine drug, is a relatively long process that usually takes between 10–15 years. In this view, natural products discovered before 2000 had already had time to go through this pipeline, which means that their biotechnological potential is already fully exploited if the compound did not fail any step of the drug discovery process. Finally, we will discuss the challenges that we foresee for future research on bioactive compounds from cnidarians, as well as their biotechnological application to the industry.

35.1.1 Overview of Natural Product Discovery from Cnidarians

Research on marine natural products began in the 1950s [35.13], at a time when important breakthroughs in the taxonomy of marine animals took place [35.14]. This research field expanded during the 1970s and 1980s. It was only at the end of the 1980s and the beginning of the 1990s that an economically appealing activity started to take shape [35.6, 15]. Since the beginning of MNP, sponges (phylum Porifera) have been recognized as the most interesting group of marine invertebrates [35.16]. However, with growing bioprospecting efforts, and the screening of previously unexplored marine habitats and organisms, the biotechnological potential of other groups of marine invertebrates has also started to become appealing for researchers. The phylum Cnidaria is a large, diverse and ecologically important group of marine invertebrates, which is renowned for the ability to produce powerful toxins and venoms [35.17]. A total of 3244 marine natural products have been described from this phylum alone since 1990 (and until 2011), which shows the importance of cnidarians for marine natural product research. Since the early 1990s, the number of new compounds from marine cnidarians has been higher than the discovery of compounds from sponges [35.8], and the trend that we currently observe is still a continuous increase of natural product discovery (Fig. 35.3). This shows that bioprospecting efforts on these organisms have been continuously increasing.

Fig. 35.3 Number of new marine natural products from cnidarians discovered between 1990 and 2011

The quest for new MNP from cnidarians has benefited from a renaissance since 2005, namely due to the development of new methods in analytical technology, spectroscopy, and high-throughput screening [35.18]. It has also benefited from the failure to deliver new drug leads in significant numbers by competing technologies, such as chemical synthesis. These two different reasons may support the continuous growth of natural product discovery from cnidarians in the last decade.

Bioprospecting efforts have not been evenly distributed among cnidarian taxa. From the 3244 new compounds yielded by marine cnidarian species since 1990, 99% were discovered in within class Anthozoa. The remaining 1% is associated with species from class Hydrozoa. Anthozoans display a higher biodiversity, with a higher number of orders (Table 35.1). Nonetheless, 94% of the 3244 compounds were discovered in organisms from a single anthozoan order: the Alcyonacea. Only through the analysis of the taxonomic level below order, e.g., the family level, is it possible to observe a more even distribution of new compounds among taxa. Figure 35.4 shows the cumulative number of natural products discovered from alcyonaceans according to family level. It is important to emphasize the Alcyoniidae family due to the continuous increase of new compounds relative to other Aclyonacea families.

The overall increase of new compounds associated with different Cnidaria taxa is displayed in Table 35.2. Of the most representative families from the order Alcyonacea, only the family Briareidae showed a small decrease in the number of new compounds discovered in the last two decades. All other families represented in

Table 35.2 Number of new compounds discovered in the most representative taxa of the phylum Cnidaria in the 1990s and 2000s (after [35.8])

Taxon	New compounds in the 1990s	New compounds in the 2000s	Variation of new compounds per decade (%)
Phylum Cnidaria	1031	1773	+72%
Class Anthozoa	1017	1758	+73%
Sub-class Octocorallia	963	1715	+78%
Order Alcyonacea	934	1694	+84%
Family Alcyoniidae	293	489	+67%
Family Briareidae	158	156	−1%
Family Clavulariidae	41	150	+266%
Family Gorgoniidae	109	165	+51%
Family Nephtheidae	58	227	+291%
Family Plexauridae	97	99	+2%
Family Xeniidae	72	147	+107%

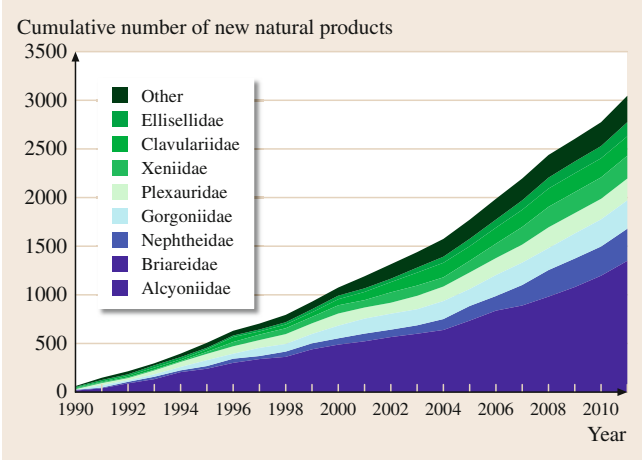

Fig. 35.4 Cumulative number of new marine natural products from cnidarians according to the taxonomical level *family*. The group *other* refers to the families Acanthogorgiidae, Anthothelidae, Coelogorgiidae, Isididae, Melithaeidae, Nidaliidae, Paragorgiidae, Paralcyoniidae, Primnoidae, Subergorgiidae, and Tubiporidae

Table 35.2 showed an increase, which in some particular cases was relatively high (e.g., families Clavulariidae and Neptheidae). These results recorded by *Leal* et al. [35.8] show that the popularity of cnidarians in bioprospecting efforts continues to increase, with large numbers of new compounds being discovered every year.

The high chemical diversity associated with cnidarians may be related to the high biodiversity displayed by this group. While about 11 000 cnidarian species are currently known [35.1], new compounds have only been recorded from 337 species (distributed over 117 genera). This means that only ≈ 3.1% of cnidarian biodiversity has yielded new chemical compounds. This does not necessarily mean that the remaining ≈ 97% of cnidarian species do not display any different compounds. Most likely, this is a result of the preference of scientists to search for new chemical entities in a relatively low number of species. For instance, the most popular species among the Alcyoniidae are *Clavularia viridis*, *Briareum excavatum*, and *Antillogorgia elisabethae* (Fig. 35.5), which have been important cnidarians in the history of MNP research [35.8]. Diversification of bioprospected species has been relatively low, as can be observed in Fig. 35.5. In this figure, we plot the number of new compounds discovered in cnidarian species since 1990 and sort that information according to the number of new compounds discovered in each species. The uneven result among bioprospected species is clearly observed. As most cnidarian species displaying a high number of new compounds inhabit tropical areas, this may suggest that bioprospecting efforts have been biased toward these particular species, probably driven by previous studies showing the high chemical diversity displayed by such taxa [35.8]. Although the assumption the all cnidarian species display similar chemical diversity is incorrect, Fig. 35.5 shows that a large number of new molecules associated to other cnidarians are yet to be unveiled. This is particularly evident if we consider that the compounds that are currently known were discovered from only ≈ 3% of total cnidarian biodiversity.

Another issue that should be noted is biodiscovery hotspots of new cnidarian compounds. Although

biogeography itself is a well-studied topic, its investigation in MNP research is still scarce. This is probably justified by the lack of precise geographical information on collection sites. However, recent studies already started to address this topic and clearly reveal bioprospecting efforts to be biased towards tropical areas [35.8, 19]. New molecules discovered from cnidarian species over the past decades have mostly resulted from bioprospecting on Asian territories close to tropical areas, particularly in Taiwan, Japan, and China. Remarkably, 50% of such new molecules discovered in cnidarians since 1990 resulted from organisms collected in the marine environment surrounding these two territories.

The compounds discovered in cnidarian species belong to various chemical groups, although the majority are terpenoids. *Leal* et al. [35.19] showed that in the last decade, 66% of the compounds discovered in cnidarians were terpenoids, which contrasts with the relatively low percentage of discovered alkaloids (10%), steroids (9%), aliphatic compounds (8%), and carbohydrates (6%). This data shows that particular chemical groups, such as terpenoids in the case of cnidarians, have been unquestionably more popular among researchers searching for new compounds. Terpenoids are secondary metabolites that are not directly involved in critical physiological processes. These compounds often play a role in interspecific and other ecological interactions. In terrestrial ecosystems, particularly in plants, terpenoids are known to be very abundant and structurally diverse [35.20]. Terpenoids are the chemical group that includes most natural products isolated so far from marine environments [35.21, 22]. This may be related to the large range of structural types that can be included in this group, which is, in part, associated with the fact that their biosynthetic unit can be rearranged and highly oxidized [35.14, 23]. Terpenoids also display a wide array of known bioactivities and biological functions [35.24–26]. Indeed, it was probably because previous studies showed that terpenoids usually display remarkable bioactivities that researchers would increase the chances for successful drug discovery and consequent patenting and commercialization by preferentially targeting molecules of this chemical group [35.27]. Several examples are already described

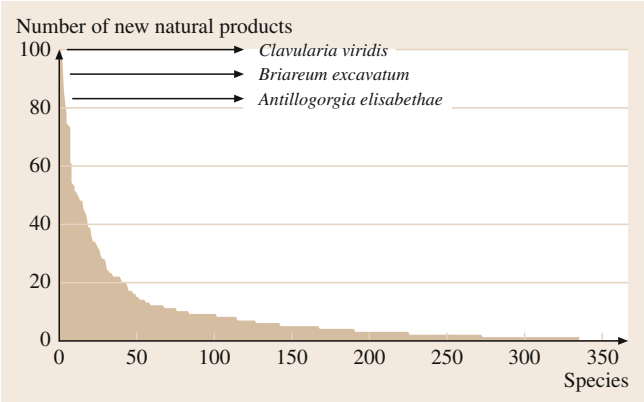

Fig. 35.5 Number of new natural products discovered per cnidarian species. Each bar corresponds to a single species (total of 337 species). The three species yielding the highest number of natural products are indicated

for the application of terpenoids in the pharmaceutical and food industry due to their potential and effectiveness as medicines and flavor enhancers [35.20, 27].

Besides bioprospecting efforts directed towards particular groups of organisms and chemical structures, researchers have also been narrowing their searches to particular molecules, with emphasis on the type and relevance of bioactivity displayed, in order to identify the most promising targets for their drug discovery pipelines [35.28]. These marine molecules display various types of biological activities, such as anticancer, anti-inflammatory, antitumor, antimalarial ones, etc. It is not surprising that over the past 40 years major advances in the discovery of marine drugs have been recorded in clinical trials for cancer [35.29]. Although there are several marine bioactive compounds in preclinical and clinical trials, only a relatively small number of molecules have reached this stage of the drug discovery pipeline. This process is very complex and encompasses several steps: target identification and validation, assay development, lead identification and optimization, predevelopment, preclinical development, clinical research phase I to phase III, regulatory approval, and phase IV (post-approval studies) [35.12, 18, 30]. The drug discovery pipeline usually takes 10–15 years from the first to the last step.

35.2 The Most Promising Marine Natural Products from Cnidaria

In this section, we overview the most promising marine bioactive compounds isolated from cnidarians in the twenty-first century. This information was assembled through the survey of the most relevant peer reviewed literature published during this period covering marine natural products [35.31–52]. Over 2000 molecules from cnidarians have been described in the twenty-first century. In order to address only those compounds displaying a high potential for industrial applications, it was decided to use the values of IC_{50} (half maximal inhibitory concentration) as guidelines. IC_{50} is a quantitative measure that indicates how much of a particular substance (inhibitor) is needed to inhibit a given biological process or component of a process by half. It is important to highlight that the NCI has renamed the IC_{50} to GI_{50} [35.53] in order to emphasize the correction for cell count at time zero in cancer cells; in this way, some results of this quantitative measure are now also presented under these directives. Additionally, ED_{50} (the median dose that produces the desired effect of a drug in half the test population) was also used to identify promising marine bioactive compounds produced by cnidarians. Only the compounds displaying an $IC_{50} \leq 10.0\,\mu g\,mL^{-1}$, or μM (except where stated otherwise), and $ED_{50} \leq 4.0\,\mu g\,mL^{-1}$ were considered in the present review, as these values are commonly used in the surveyed literature to ascertain relevant bioactivity (e.g., [35.54, 55]). In the few cases where neither IC_{50} nor ED_{50} values were described for an MNP in a study, that compound was selected to be part of the present survey only if either the authors of that study, or those citing it, clearly stated that the results recorded were highly promising for industrial applications. All species producing the compounds selected for the present topic were grouped into classes and orders of the phylum Cnidaria (Table 35.1) (according to the latest classification proposed in WoRMS) [35.1].

This approach allowed us to identify which taxonomic groups of cnidarians screened so far display the highest potential to yield new drugs or pharmacological products derived from marine bioactive compounds. Nonetheless, it is important to highlight that the identification of cnidarian species is a challenging task, and it is possible that some of the species (or even genera) referred to in the scientific literature may have been misidentified. In this way, it is of paramount importance that in future work, the authors addressing marine bioactive compounds produced by cnidarians provide a detailed description on how the target species was identified [35.28].

35.2.1 Class Anthozoa

The class Anthozoa currently includes 10 orders and over 7500 valid species (about $\frac{2}{3}$ of all known cnidarian species; Table 35.1). Within the Anthozoa class, the order Alcyonacea (soft corals and sea fans) is the one that has contributed with the highest number of promising bioactive marine compounds, although other orders, such as Actiniaria (sea anemones) and Scleractinia (hard corals), have also yielded relevant compounds [35.56–59].

The Order Alcyonacea (Soft Corals and Sea Fans)

Soft corals are generally brightly colored and rich in nutritionally important substances. However, the incidence of predation in the majority of these organisms is low due to the toxic compounds they produce to deter predators [35.60]. Several biosynthetic studies have been carried out on the metabolites of soft corals [35.61] and some of those compounds have already shown great potential for the development of new pharmaceuticals and antifoulants. Sea fans are also well-known sources of compounds exhibiting significant biological activity [35.62]. Table 35.3 summarizes the most promising compounds from the order Alcyonacea (class Anthozoa).

Soft corals are rich sources of secondary metabolites such as diterpenes, sesquiterpenes, furanoditerpenes, terpenoids, capnellene, and steroids (e.g., *Lobophytum*, *Sinularia*, *Sarcophyton* [35.141], *Capnella* [35.142], and *Dendronephthya* [35.143]), that have been shown to display HIV-inhibitory [35.73], cytotoxic [35.144, 145], anti-inflammatory [35.146, 147], anticancer [35.148, 149], and antimicrobial activity [35.150], as well as cardiac and vascular responses [35.151].

Chemical investigations on octocorals belonging to the genus *Cladiella* have resulted in a series of interesting diterpenoids. Terpenoids have been found to display complex structures and various bioactivities [35.63], especially anti-inflammatory properties. *Cladiella australis* produces an anti-inflammatory natural product, austrasulfone, which was found to

Table 35.3 The most promising compounds studied in the twenty-first century from cnidarian species in the order Alcyonacea (soft corals), class Anthozoa

Family and species	Drug class	Compound	Chemistry	Country	Reference
Alcyoniidae					
Cladiella sp.	Anti-inflammatory	Cladielloide B	Diterpenoid	TAIW	[35.63]
Cladiella sp.	Antitumor	Cladieunicellin B and E	Diterpenoid	ID	[35.64]
Cladiella sp.	Anti-inflammatory	Cladieunicellin C	Diterpenoid	ID	[35.64]
Cladiella australis	Anti-inflammatory	Austrasulfone	Sulfone	TAIW	[35.65]
Cladiella hirsuta	Anti-inflammatory	Hirsutalins B–D and H	Diterpenoid	TAIW	[35.66]
Klyxum simplex	Anti-inflammatory	Simplexin E	Diterpenoid	TAIW	[35.67]
Klyxum simplex	Antitumor	Klysimplexin B and H	Diterpenoid	TAIW	[35.68]
Klyxum simplex	Anti-inflammatory	Klysimplexin sulfoxide A–C	Diterpenoid	TAIW	[35.69]
Klyxum simplex	Anti-inflammatory	Klysimplexin J–N, R and S	Diterpenoid	TAIW	[35.70]
Klyxum molle	Anti-inflammatory	Klymollin F and G	Diterpenoid	TAIW	[35.71]
Lobophytum sp.	Antitumor	Lobophytene	Diterpenoid	VN	[35.72]
Lobophytum sp.	Anti-HIV	Lobohedleolide	Diterpenoid	PHL	[35.73]
Lobophytum sp.	Anti-HIV	(7Z)-lobohedleolide,	Diterpenoid	PHL	[35.73]
Lobophytum sp.	Anti-HIV	17-dimethylamino lobohedleolide	Diterpenoid	PHL	[35.73]
Lobophytum crassum	Anti-inflammatory	Crassumolides A and C	Terpenoid	TAIW	[35.74]
Lobophytum crassum	Antitumor	13-acetoxysarcophytoxide	Cembranoid	TAIW	[35.75]
Lobophytum crassum	Anti-inflammatory	Lobocrassin B	Cembranoid	TAIW	[35.76]
Lobophytum crassum	Antitumor	Lobocrassin B	Cembranoid	TAIW	[35.76]
Lobophytum crassum	Antitumor	Culobophylin A and B	Cembranoid	TAIW	[35.77]
Lobophytum cristagalli	Antitumor	Cembranolide diterpene	Diterpenoid	RSC	[35.78]
Lobophytum durum	Anti-inflammatory	Durumolides A–C	Terpenoid	TAIW	[35.79]
Lobophytum durum	Anti-inflammatory	Durumhemiketalolide A–C	Cembranoid	TAIW	[35.80]
Lobophytum durum	Antitumor	Durumolide P	Cembranoid	TAIW	[35.81]
Lobophytum durum	Antiviral	Durumolide Q	Cembranoid	TAIW	[35.81]
Lobophytum laevigatum	Antitumor	Lobophytosterol	Steroid	TAIW	[35.82]
Lobophytum pauciflorum	Anti-inflammatory	Lobophytone Z	Cembranoid	TAIW	[35.83]
Sarcophyton crassocaule	Antitumor	Crassocolides H–M	Cembranoid	TAIW	[35.84]
Sarcophyton crassocaule	Antitumor	Crassocolide N–P	Cembranoid	TAIW	[35.85]
Sarcophyton crassocaule	Anti-inflammatory	Sarcocrassocolide F–L	Cembranoid	TAIW	[35.86]
Sinularia sp.	Antiulcer	Sinulide	Spermine		[35.87]
Sinularia sp.	Antimicrobial	Lipids	Polyketide	RUS	[35.88]
Sinularia capillosa	Antitumor	Capilloquinol	Farnesyl quinoid	TAIW	[35.89]
Sinularia flexibilis	Antitumor	Flexilarin D	Cembranoid	TAIW	[35.90]
Sinularia flexibilis	Antifoulant	11-episinulariolide	Diterpenoid	AUS	[35.91]
Sinularia gibberosa	Anti-inflammatory	Gibberoketosterol	Steroid	TAIW	[35.92]
Sinularia querciformis	Anti-inflammatory	Querciformolide C	Terpenoid	TAIW	[35.93]
Briareidae					
Briareum sp.	Antitumor	Brialalepolide B and C	Diterpenoid	VUT	[35.94]
Briareum sp.	Anti-inflammatory	Brialalepolide B and C	Diterpenoid	VUT	[35.94]
Briareum asbestinum	Antimalarial	Briarellin D, K and L	Diterpenoid	PAN, USA	[35.95]
Briareum excavata	Anti-inflammatory	Briaexcavatin E	Diterpenoid	TAIW	[35.96]
Briareum excavata	Antitumor	Briaexcavatolides L and P	Diterpenoid	TAIW	[35.97]

Table 35.3 (continued)

Family and species	Drug class	Compound	Chemistry	Country	Reference
Clavulariidae					
Clavularia sp.	Nervous system	Stolonidiol	Diterpenoid	JPN	[35.98]
Clavularia koellikeri	Antitumor	Cembrane-type diterpenoid	Diterpenoid	JPN	[35.99]
Clavularia viridis	Antitumor	Claviridic acid	Prostanoid	TAIW	[35.100]
Clavularia viridis	Antitumor	Clavulones	Prostanoid	TAIW	[35.100]
Clavularia viridis	Antitumor	Claviridenone	Prostanoid	TAIW	[35.55]
Clavularia viridis	Antitumor	Halogenated prostanoids	Prostanoid	JPN	[35.101]
Clavularia viridis	Antitumor	Bromovulone III	Prostanoid	TAIW	[35.102, 103]
Clavularia viridis	Antitumor	Yonarasterols	Steroid	JPN	[35.102]
Clavularia viridis	Antitumor	Stoloniferone E	Steroid	TAIW	[35.55]
Clavularia viridis	Antitumor	Claviridin A-D	Prostanoid	TAIW	[35.103]
Carijoa sp.	Anti-inflammatory	carijoside A	steroid	TAIW	[35.104]
Telesto riisei	Antitumor	Punaglandins	Prostaglandin	USA	[35.105]
Ellisellidae					
Junceella fragilis	Anti-inflammatory	Frajunolides B and C	Terpenoid	TAIW	[35.106]
Junceella juncea	Antifoulant	Juncin ZII	Diterpenoid	TAIW	[35.107]
Gorgoniidae					
Antillogorgia acerosa	Antitumor	Bis(pseudopterane) amine	Dialkylamine	BHS	[35.108]
Antillogorgia bipinnata	Antituberculosis	Bipinnapterolide B	Terpenoid	USA	[35.109]
Antillogorgia bipinnata	Antimalarial	Caucanolide A and D	Diterpenoid	COL, PAN, USA	[35.110]
Antillogorgia elisabethae	Antimicrobial	Pseudopterosin X	Diterpenoid	USA	[35.111]
Antillogorgia elisabethae	Antituberculosis	Ileabethoxazole	Diterpenoid	USA	[35.112]
Antillogorgia elisabethae	Antituberculosis	Homopseudopteroxazole	Diterpenoid	USA	[35.113]
Antillogorgia elisabethae	Antituberculosis	Caribenols A and B	Terpenoid	USA	[35.114]
Antillogorgia elisabethae	Antituberculosis	Elisapterosin B	Diterpenoid	USA	[35.115]
Antillogorgia elisabethae	Antimalarial	Aberrarone	Diterpenoid	COL	[35.116]
Antillogorgia kallos	Antimalarial	Bielschowskysin	Diterpenoid	PAN, USA	[35.117]
Antillogorgia kallos	Antitumor	Bielschowskysin	Diterpenoid	PAN, USA	[35.117]
Antillogorgia rigida	Antimicrobial	Curcuphenol	Terpenoid	USA	[35.118]
Leptogorgia setacea	Antifoulant	Homarine	Pyridine	GEO	[35.119]
Leptogorgia virgulata	Antifoulant	Homarine	Pyridine	GEO	[35.119]
Leptogorgia virgulata	Antifoulant	Pukalide	Diterpenoid	USA	[35.120]
Leptogorgia virgulata	Antifoulant	Epoxypukalide	Diterpenoid	USA	[35.120]
Pseudopterogorgia sp.	Antitumor	Secosterols	Steroid	USA	[35.121]
Pseudopterogorgia sp.	Anti-inflammatory	Secosterols	Steroid	USA	[35.121]
Isididae					
Isis hippuris	Antitumor	Polyoxygenated gorgosterol (2-4)	Steroid	JPN	[35.122]
Isis hippuris	Antitumor	Polyoxygenated steroid (3)	Steroid	TAIW	[35.123]
Isis hippuris	Antitumor	Suberosenol B	Terpenoid	TAIW	[35.124]
Isis hippuris	Antitumor	Polyoxygenated steroid	Steroid	IND	[35.125, 126]
Isis hippuris	Antitumor	A –nor-hippuristanol	Steroid	TAIW	[35.127]
Isis hippuris	Antitumor	Isishippuric acid B	Steroid	TAIW	[35.127]

Table 35.3 (continued)

Family and species	Drug class	Compound	Chemistry	Country	Reference
Nephtheidae					
Dendronephthya sp.	Antifoulant	Isogosterones A–D	Steroid	JPN	[35.128]
Dendronephthya rubeola	Antitumor	Capnell-9(12)-ene-8β,10α-diol	Sesquiterpenoid	DE	[35.129, 130]
Lemnalia flava	Anti-inflammatory	Flavalin A and B	Sesquiterpenoid	TAIW	[35.125]
Nephthea chabroli	Antitumor	Chabranol	Terpenoid	TAIW	[35.126]
Nephthea erecta	Anti-inflammatory	Ergostanoids 1 and 3	Ergostanoid	TAIW	[35.131]
Paralemnalia thyrsoides	Anti-inflammatory	Paralemnolin Q and S	Sesquiterpenoid	TAIW	[35.132]
Plexauridae					
Astrogorgia sp.	Antitumor	Astrogorgol F	Secosteroid	TAIW	[35.129]
Echinogorgia pseudosassapo	Antifoulant	3β-methoxyguaian-10(14)-en-2β-ol	Sesquiterpenoid	TAIW	[35.133]
Eunicea sp.	Antimalarial	Sesquiterpenoids	Sesquiterpenoid	COL, PAN, USA	[35.130]
Eunicea sp.	Antimalarial	Dolabellane	Diterpenoid	COL	[35.134]
Eunicea fusca	Anti-inflammatory	Fuscisides	Diterpenoid	USA	[35.135]
Eunicea fusca	Anti-inflammatory	Fuscoside E	Diterpenoid	COL	[35.136]
Euplexaura flava	Anti-inflammatory	Butenolide	Lipid	JPN	[35.137]
Xeniidae					
Asterospicularia laurae	Antitumor	Asterolaurin A	Diterpenoid	TAIW	[35.138]
Cespitularia hypotentaculata	Antitumor	Cespitularin C	Diterpenoid	TAIW	[35.139]
Xenia novaebritanniae	Antibacterial	Xeniolide I	Diterpenoid	ISR	[35.140]
Xenia plicata	Antitumor	Blumiolide C	Diterpenoid	TAIW	[35.54]

exhibit potent neuroprotective effect against the 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in neuroblastoma SH-SY5Y, a human dopaminergic neuron often used for the study of Parkinson's disease. The cytotoxicity of 6-OHDA on SH-SY5Y cells was effectively and dose-dependently inhibited by pretreatment at concentrations of 10^{-3}–10 μM. The ED_{50} was 0.011 ± 0.014 μM [35.65]. Hirsutalins B-D and H, diterpenoids from *Cladiella hirsuta*, at a concentration of 10 μM, displayed significant in vitro anti-inflammatory activity in LPS (LPS)-stimulated RAW 264.7 macrophage cells by inhibiting the expression of the inducible nitric oxide synthase (iNOS), with hirsutalin B also effectively reducing the level of COX-2 (COX) protein. These compounds, in particular hirsutalin B and D, could be promising anti-inflammatory agents [35.66]. Cladielloide B and cladieunicellin C, diterpenoids from a non-identified *Cladiella*, displayed significant inhibitory effects on superoxide anion generation (IC_{50} 5.9 ± 0.7 and IC_{50} 8.1 ± 0.3 μg mL^{-1}, respectively). The first compound also showed significant inhibitory effects against elastase release (IC_{50} 6.5 ± 1.9 μg mL^{-1}) by human neutrophils at 10 μg mL^{-1} [35.63, 64]. The same species that produces cladieunicellin C also produces cladieunicellin B and E, two diterpenoids that exhibited significant cytotoxicity against human colorectal adenocarcinoma (DLD-1, IC_{50} 2.0 μg mL^{-1}) and human promyelocytic leukemia (HL-60, IC_{50} 2.7 μg mL^{-1}) cells, respectively [35.64].

Soft corals of the family Nephtheidae are known for their content of sesquiterpenes and particularly capnellenes [35.41]. Some sesquiterpenes isolated from *Capnella imbricate* [35.142, 152–154] showed anti-inflammatory activity and a dihydroxycapnellene (capnell-9(12)-ene-8β, 10α-diol) from *Dendronephthya rubeola* demonstrated antiproliferative activity against murine fibroblasts cell line (L-929, GI_{50} 6.8 μM L^{-1}) and cytotoxicity against cancer cell lines implicated in human leukemia (K-562, IC_{50} 0.7 μM) and human cervix carcinoma (HeLa, IC_{50} 7.6 μM) [35.143]. Capnell-9(12)-ene-8β, 10α-diol strongly inhibits the interaction of the oncogenic transcription factor Myc with its partner pro-

tein Max [35.155, 156], making it a therapeutically interesting compound in oncology [35.143]. *Nephthea chabroli* also produces a nor-sesquiterpene compound named chabranol, which displays moderate cytotoxicity against mouse lymphocytic leukemia cells (P-388) with an ED_{50} 1.81 $\mu g\,mL^{-1}$ [35.126]. *Nephthea erecta* produces two proteins in mediated inflammatory responses, the oxygenated ergostanoids 1 and 3. At a concentration of 10 μM, these two compounds significantly reduced the levels of the iNOS (45.8 ± 9.9 and $33.6 \pm 20.6\%$, respectively) and COX-2 protein (68.1 ± 2.3 and $10.3 \pm 6.2\%$, respectively), when compared with the control cells stimulated with lipopolysaccharides (LPS) [35.131]. Soft corals of the genus *Paralemnalia* and *Lemnalia* have been found to be rich sources of sesquiterpenoids of nardosinane-type. *Lemnalia flava* produces flavin A, a sesquiterpenoid, that showed significant in vitro anti-inflammatory activity by exhibiting concentration-dependent inhibition of LPS-induced iNOS and COX-2 protein expression (ED_{50} values toward both proteins were $4.8 \pm 0.3\,\mu g\,mL^{-1}$ ($20.5 \pm 1.3\,\mu M$) and $6.2 \pm 0.6\,\mu g\,mL^{-1}$ ($26.5 \pm 2.6\,\mu M$), respectively). This compound and flavin B also exhibited significant neuroprotective activity [35.125]. This neuroprotective activity using 6-OHDA-induced neurotoxicity in neuroblastoma SHSY5Y, a human dopaminergic neuron often used for study of Parkinson's disease, was also demonstrated for paralemnolins Q and S [35.132, 157] and 2-deoxy-7-*O*-methyllemnacarnol [35.157] from *Paralemnalia thyrsoides*. Nonetheless further investigation for their therapeutic potential against neurodegenerative diseases is suggested.

Species in the genus *Xenia* (family Xeniidae) are a rich source of diterpenoids. Xeniolides I, isolated from *Xenia novaebrittanniae* demonstrated antibacterial activity at a concentration of 1.25 $mg\,mL^{-1}$ in *Escherichia coli* ATCC and *Bacillus subtilis* [35.140]. Blumiolide C, a diterpenoid from the *Xenia blumi* (presently accepted as *Xenia plicata*), exhibited potent cytotoxicity against mouse lymphocytic leukemia (P-388, ED_{50} 0.2 $\mu g\,mL^{-1}$) and human colon adenocarcinoma (HT-29, ED_{50} 0.5 $\mu g\,mL^{-1}$) cells [35.54].

Polyoxygenated cembranoids, crassocolides H–P [35.84, 85] from *Sarcophyton crassocaule*, demonstrated cytotoxicity against cancer cell lines of human medulloblastoma (Daoy cells). Crassocolides I, M, and P were found to be more active (IC_{50} 0.8, 1.1, and 1.9 $\mu g\,mL^{-1}$, respectively). Crassocolide H and N inhibited the growth of human oral epidermoid carcinoma (KB) cells (IC_{50} 5.3 and 4.7 $\mu g\,mL^{-1}$, respectively), and crassocolide N and crassocolide L were also active against human cervical epitheloid carcinoma (HeLa) cells (IC_{50} 4.7 and 8.0 $\mu g\,mL^{-1}$, respectively) [35.84, 85]. Other cembrenoids from the same species, sarcocrassocolides F–L, were found to exhibit anti-inflammatory activities by significantly reducing the levels of iNOS protein. Furthermore, sarcocrassocolide I could also effectively reduce COX-2 expression with LPS treatment. All these compounds might be useful anti-inflammatory agents, sarcocrassocolide I being a promising anti-inflammatory lead compound [35.86]. Lobophytone Z, from *Lobophytum pauciflorum*, inhibits NO production in mouse peritoneal macrophages induced by LPS (IC_{50} 2.6 μM) [35.83]. NO is an important signaling molecule that acts in many tissues to regulate a diverse range of physiological and cellular processes. Overproduction of NO is associated with various human diseases, including inflammatory and neuronal disorders [35.158]. The level of NO released may reflect the degree of inflammation and provides an indicator to assess inflammatory processes [35.83].

Lobophytum durum and *Lobophytum crassum* produce durumolides A–C [35.79], durumhemiketalolide A–C [35.80], and crassumolides A and C [35.74], with anti-inflammatory effects. They have been shown to inhibit up-regulation of the proinflammatory iNOS and COX-2 proteins in LPS-stimulated murine macrophage cells at $IC_{50} < 10\,\mu M$ [35.74, 79]. From *Lobophytum crassum*, lobocrassin B displayed significant inhibitory effects on the generation of superoxide anion and the release of elastase by human neutrophils (IC_{50} 4.8 and 4.9 $\mu g\,mL^{-1}$, respectively). Cytotoxicity of this cembrenoid toward tumor cells showed that it exhibited only modest cytotoxicity against human erythromyeloblastoid leukemia (K562), human T-cell acute lymphoblastic leukemia (CCRF-CEM), human acute lymphoblastic leukemia (Molt4), and human hepatocellular liver carcinoma (HepG2) cells [35.76].

Another example of a potential new therapeutic anticancer agent is a cembranolide diterpene from *Lobophytum cristagalli*, which has shown a potent inhibitory activity (IC_{50} 0.15 μM) [35.78] over farnesyl protein transferase (FPT), an important protein in signal transduction and regulation of cell differentiation and proliferation [35.159]). This type of FPT inhibition enhanced interest in this group of metabolites [35.141]. Other species of this genus also showed cembranoids with significant cytotoxic activity against human lung adenocarcinoma (A549, lobophytene [35.72], lobophytosterol [35.82], and 13-

acetoxysarcophytoxide [35.75]), human colon adenocarcinoma (HT-29, lobophytene [35.72]; DLD-1, culobophylin A [35.77], and HCT-116 lobophytosterol [35.82]), and human promyelocytic leukemia (HL60, lobophytosterol [35.82], and culobophylin A and B [35.77]) cell lines. The diterpenoids, lobohedleolide, (7*Z*)-lobohedleolide, and 17-dimethylaminolobohedleolide were isolated from the aqueous extract of *Lobophytum* species and exhibited moderate HIV-inhibitory activity (IC_{50} approximately $7-10\,\mu g\,mL^{-1}$) in a cell-based in vitro anti-HIV assay [35.73]. Additionally, other significant antiviral activity against human cytomegalovirus (IC_{50} of $5.2\,\mu g\,mL^{-1}$) [35.81] was described for the compound durumolide Q produced by *Lobophytum durum*.

Eunicellin-based diterpenoids are secondary metabolites often isolated from the genus *Klyxum*. *Klyxum molle* has been shown to produce molecules (e.g., klymollin F and G) with interesting bioactivities, such as anti-inflammatory agents [35.71]. *Klyxum simplex* also produces diterpene compounds, such as simplexin E, klysimplexins J–N, R, and S, and klysimplexin sulfoxide A–C, which at a concentration of $10\,\mu M$ were found to considerably reduce the levels of iNOS protein. The compounds simplexin E, klysimplexins R and S, and klysimplexin sulfoxide C could also effectively reduce the level of COX-2 protein. These results have shown that this compound significantly inhibits the accumulation of the pro-inflammatory iNOS and COX-2 proteins in LPS-stimulated RAW 264.7 macrophage cells, being potential anti-inflammatory agents [35.67, 69, 70]. This species also produces two diterpenes, klysimplexins B and H, which exhibit moderate cytotoxicity towards human carcinoma cell lines. Klysimplexin B exhibits cytotoxicity toward human hepatocellular carcinoma (Hep G2, IC_{50} $3.0\,\mu g\,mL^{-1}$, and Hep 3B, IC_{50} $3.6\,\mu g\,mL^{-1}$), human breast carcinoma (MDA-MB-231, IC_{50} $6.9\,\mu g\,mL^{-1}$ and MCF-7, IC_{50} $3.0\,\mu g\,mL^{-1}$), human lung carcinoma (A549, IC_{50} $2.0\,\mu g\,mL^{-1}$) ,and human gingival carcinoma (Ca9-22, IC_{50} $1.8\,\mu g\,mL^{-1}$) cell lines. Metabolite klysimplexin H demonstrated cytotoxicity toward human hepatocellular carcinoma (Hep G2, IC_{50} $5.6\,\mu g\,mL^{-1}$, and Hep 3B, IC_{50} $6.9\,\mu g\,mL^{-1}$), human breast carcinoma (MDA-MB-231, IC_{50} $4.4\,\mu g\,mL^{-1}$, and MCF-7, IC_{50} $5.6\,\mu g\,mL^{-1}$), human lung carcinoma (A549, IC_{50} $2.8\,\mu g\,mL^{-1}$), and human gingival carcinoma (Ca9-22, IC_{50} $6.1\,\mu g\,mL^{-1}$) cell lines [35.68].

A tetraprenylated spermine derivative – sinulamide – has been isolated in *Sinularia* sp., which revealed an H,K-ATPase inhibitory activity. H,K-ATPase is a gastric proton pump of the stomach and is the enzyme primarily responsible for the acidification of the stomach contents. Its inhibition is a very common clinical intervention used in diseases including dyspepsia, peptic ulcer, and gastroesophageal reflux (GORD/GERD). Sinulide is a potential antiulcer drug, as it inhibits production of gastric acid by H,K-ATPase (IC_{50} $5.5\,\mu M$) [35.87]. Although it has been chemically synthesized [35.160], no clinical trials seem to have been reported. The steroid gibberoketosterol [35.92], isolated from *Sinularia gibberosa*, and the diterpenoid querciformolide C [35.93] isolated from *Sinularia querciformis*, showed significant inhibition of the up-regulation of the pro-inflammatory iNOS and COX-2 proteins in LPS-stimulated murine macrophages at a concentration of $< 10\,\mu M$ [35.92, 93]. *Paralemnalia thyrsoides* showed significant inhibition of pro-inflammatory iNOS protein expression (70% at IC_{50} $10\,\mu M$) [35.157]. *Sinularia* species produce significant bioactive molecules. Lipids from *Sinularia grandilobata* and another unspecified species of *Sinularia* possess antibacterial and antifungal activity [35.88]. The diterpene 11-episinulariolide from *Sinularia flexibilis* is an interesting antifoulant exhibiting strong algacidal properties [35.91]. This species also produces cembrenoids, named flexilarins, which evidenced cytotoxic activity in cancer cell lines. Flexilarin D exhibited potent cytotoxicity in human hepatocarcinoma (Hep2) cells with IC_{50} $0.07\,\mu g\,mL^{-1}$ and moderate cytotoxic activity against human cervical epitheloid carcinoma (HeLa, IC_{50} $0.41\,\mu g\,mL^{-1}$), human medulloblastoma (Daoy, $1.24\,\mu g\,mL^{-1}$), and human breast carcinoma (MCF-7, $1.24\,\mu g\,mL^{-1}$) cell lines [35.90]. Capilloquinol from *Sinularia capillosa* displayed cytotoxicity against P-388, with an ED_{50} of $3.8\,\mu g\,mL^{-1}$ [35.89].

Antifouling agents from natural sources are of increasing interest since the International Maritime Organization (IMO) banned the use of certain antifouling agents, such as tri-*n*-butyltin (TBT), due to the ecological impacts of these biocides in the marine environment. Several studies have demonstrated that soft corals can yield large quantities of promising antifouling metabolites [35.161, 162]. In fact, 17.95% of potential antifouling natural compounds are from cnidarians (e.g., soft corals) [35.163]. One of the most promising natural antifouling agents identified so far is an isogosterone isolated from an unspecified *Dendronephthya* [35.128]. Also 3β-methoxyguaian-10(14)-en-2β-ol, a sesquiterpene from the gorgonian *Echinogorgia pseudossapo*, was evaluated for its antilarval activity against *Am-*

phibalanus amphitrite and *Bugula neritina* larvae. The results showed that this compound had significant antilarval activity towards *Amphibalanus amphitrite* larvae with an EC50 value of 17.2 $\mu g\,mL^{-1}$ (68.2 μM), and showed 50% inhibition towards the settlement of *Bugula neritina* larvae at concentration of 25 $\mu g\,mL^{-1}$. This EC_{50} value is lower than the standard requirement of an EC_{50} of 25 $\mu g\,mL^{-1}$ established by the US Navy program as an efficacy level for natural antifoulants, indicating that 3β-methoxyguaian-10(14)-en-2β-ol is a potential natural antifouling agent [35.133].

Most of the bioactive substances from the family Clavulariidae with promising biotechnological potential are antitumor molecules from the genus *Clavularia*. Even so, *Carijoa* sp. produces a sterol glycoside, carijoside A, that displayed significant inhibitory effects on superoxide anion generation (IC_{50} 1.8 $\mu g\,mL^{-1}$) and elastase release (IC_{50} 6.8 $\mu g\,mL^{-1}$) by human neutrophils in anti-inflammatory activity testing [35.104]. As was previously mentioned, genus *Clavularia* contains promising secondary metabolites with unique structures and remarkable biological activities. Some of the species in this genus produce prostanoids (icosanoids) [35.55, 101, 103, 164–166], steroids [35.102], and diterpenoids [35.99, 167]. The bioactive marine diterpene, stolonidiol, isolated from an unidentified *Clavularia*, showed potent choline acetyltransferase (ChAT) inducible activity in primary cultured basal forebrain cells and clonal septal SN49 cells, suggesting that it may act as a potent neurotrophic factor-like agent on the cholinergic nervous system [35.98]. Cholinergic neurons in the basal forebrain innervate the cortex and hippocampus, and their function may be closely related to cognitive function and memory. The degeneration of neuronal cells in this brain region is considered to be responsible for several types of dementia, including Alzheimer's disease. One of the neurotransmitters, acetylcholine, is synthesized from acetyl coenzyme A and choline by the action of ChAT. Therefore, induction of ChAT activity in cholinergic neurons may improve the cognitive function in diseases exhibiting cholinergic deficits [35.168–170].

Prostanoids (claviridic acid) isolated from *Clavularia viridis* exhibited potent inhibitory effects on phytohemagglutinin-induced proliferation of peripheral blood mononuclear cells (PBMC, 5 $\mu g\,mL^{-1}$), as well as significant cytotoxic activity against human gastric cancer cells (AGS, IC_{50} 1.73–7.78 $\mu g\,mL^{-1}$) [35.100]. Claviridenone extracts also showed potent cytotoxicity against mouse lymphocytic leukemia (P-388) and human colon adenocarcinoma (HT-29), and exceptionally powerful cytotoxicity against human lung adenocarcinoma (A549) cells, with ED_{50} between 0.52 pg/mL and 1.22 $\mu g\,mL^{-1}$ [35.55]. Claviridins A–D exhibited potent cytotoxicity against four human cancer cell lines: Hep2 (ED_{50} 0.19–0.35 $\mu g\,mL^{-1}$), Doay (ED_{50} 0.18–0.29 $\mu g\,mL^{-1}$), colon adenocarcinoma (WiDr, ED_{50} 0.22–0.34 $\mu g\,mL^{-1}$), and HeLa (ED_{50} 0.31–0.88 $\mu g\,mL^{-1}$) [35.103]. Halogenated prostanoids also showed cytotoxic activity against human T lymphocyte leukemia cells (MOLT-4, IC_{50} 0.52 $\mu g\,mL^{-1}$), human colorectal adenocarcinoma (DLD-1, IC_{50} 0.6 $\mu g\,mL^{-1}$), and human diploid lung fibroblast (IMR-90, IC_{50} 4.5 $\mu g\,mL^{-1}$) cells [35.101]. The cyclopentenone prostanoid, bromovulone III is a promising marine natural compound for the treatment of prostate, colon, and hepatocellular carcinoma, which showed antitumor activity against human prostate (PC-3) and human colon (HT29) cancer cells at an IC_{50} of 0.5 μM [35.164], and induced apoptotic signaling in a sequential manner in Hep3B cells [35.171]. In the case of prostate cancer cells, this compound displayed an antitumor activity 30–100 times more effective than cyclopentenone prostaglandins (known to suppress tumor cell growth and to induce apoptosis in prostate cancer cells), by causing a rapid redistribution and clustering of Fas (member of the tumor necrosis factor (TNF) receptor superfamily). Apoptotic stimulation of Fas by specific ligand or antibodies caused the formation of a membrane-associated complex comprising Fas clustering) in PC-3 cells [35.172]. *Clavularia viridis* also produces steroids that show cytotoxic activity against human colorectal adenocarcinoma (DLD-1, $0.02 < IC_{50} < 50\,\mu g\,mL^{-1}$) and also against human T lymphocyte leukemia cells (MOLT-4, $0.01 < IC_{50} < 10\,\mu g\,mL^{-1}$) in the case of yonarasterols [35.102]. Additionally, stoloniferone displayed potent cytotoxicity against mouse lymphocytic leukemia (P-388), human colon adenocarcinoma (HT-29), and human lung adenocarcinoma (A549) cells [35.55]. This species produces several compounds with antitumor activity in different types of human tumors, although more in vitro studies are needed to determine which compounds are potential anticancer agents. *Clavularia koellikeri* produces diterpenoids as secondary metabolites, which display cytotoxic activity against human colorectal adenocarcinoma (DLD-1, IC_{50} 4.2 $\mu g\,mL^{-1}$) and strong growth inhibition against human T lymphocyte leukemia cells (MOLT-4, IC_{50} 0.9 $\mu g\,mL^{-1}$) [35.99].

In the genus *Cespitularia*, several interesting diterpenes of cembrane and neodolabellane skeletons have

been identified. In *Cespitularia hypotentaculata* (family Xeniidae) a significant production of diterpenoids was detected. Cespitularin C exhibited potent cytotoxicity against mouse lymphocytic leukemia (P-388, ED_{50} 0.01 $\mu g\,mL^{-1}$) and human lung adenocarcinoma (A549, ED_{50} 0.12 $\mu g\,mL^{-1}$) cells, while cespitularin E exhibited potent cytotoxicity against human lung adenocarcinoma (A549, ED_{50} 0.034 $\mu g\,mL^{-1}$) cell cultures [35.139]. A less active diterpene, Asterolaurin A, from *Asterospicularia laurae* (a species from the same family) exhibited cytotoxicity against human hepatocellular carcinoma (HepG2) cells with an IC_{50} of 8.9 μM [35.138].

Telesto riisei produces punaglandins, highly functional cyclopentadienone and cyclopentenone prostaglandins. Cyclopentenone prostaglandins have unique antineoplastic activity and are potent growth inhibitors in a variety of cultured cells. These punaglandins have been shown to inhibit P53 accumulation (a tumor suppressor protein) and ubiquitin isopeptidase activity (IC_{50} between 0.04 and 0.37 μM) (enzyme involved in protein degradation system) in vitro and in vivo [35.105]. Since these proteasome inhibitors exhibit higher antiproliferative effects than other prostaglandins [35.173], they may represent a new class of potent cancer therapeutics.

Sea fans are well-known sources of compounds exhibiting significant biological activity [35.62]. Studies on *Isis hippuris* resulted in the isolation of a series of novel metabolites such as sesquiterpenes [35.124], steroids [35.174], A-nor-hippuristanol [35.127], and isishippuric acid B [35.127]. These compounds exhibit potent cytotoxicity against cancer cell lines of human hepatocellular carcinoma (HepG2 and Hep3B, IC_{50} 0.08–4.64 $\mu g\,mL^{-1}$, and 0.10–1.46 $\mu g\,mL^{-1}$, respectively) [35.127, 175], human breast carcinoma (MCF-7, IC_{50} 0.20–4.54 $\mu g\,mL^{-1}$ and MDA-MB-231, IC_{50} 0.13–2.64 $\mu g\,mL^{-1}$) [35.175], mouse lymphocytic leukemia (P-388), human lung adenocarcinoma (A549), and human colon adenocarcinoma (HT-29) with ED_{50} of values less than 0.1 $\mu g\,mL^{-1}$ [35.127, 174] and IC_{50} of 0.1 $\mu g\,mL^{-1}$ [35.124]. Polyoxygenated steroids were also isolated from this species and showed moderate cytotoxicity against cultured NBT-T2 rat bladder epithelial cells (IC_{50} between 1.8 and 7.5 $\mu g\,mL^{-1}$) [35.122], P-388 and A549 cell lines (ED_{50} 3.2 and 3.86 $\mu g\,mL^{-1}$, respectively), and inhibitory activity against HCMV (EC_{50} 2.0 $\mu g\,mL^{-1}$) [35.123].

Species from the genus *Pseudopterogorgia* (currently accepted as *Antillogorgia* sp.) are a rich source of unusual biologically active diterpenoids, sesquiterpenes, and polyhydroxylated steroids, which exhibit diverse structures [35.109, 176, 177]. A sample of the organic extract of *Antillogorgia bipinnata* (formerly *Pseudopterogorgia bipinnata*) was included in an initial screening carried out as part of an effort in the discovery of new antimalarial agents. This extract was found to be active in inhibiting the growth of *Plasmodium falciparum* (a protozoan parasite responsible for the most severe forms of malaria). Caucanolide A and D demonstrated significant in vitro antiplasmodial activity against chloroquine-resistant *P. falciparum* W2 (IC_{50} 17 $\mu g\,mL^{-1}$ and IC_{50} 15 $\mu g\,mL^{-1}$, respectively) [35.110]. Three secosterols isolated from an unidentified gorgonian from genus *Pseudopterogorgia* inhibited human protein kinase C (PKC) α, βI, βII, γ, δ, ε, η, and ζ, with IC_{50} values in the range 12–50 μM [35.121]. PKC is a key player in cellular signal transduction and has been implicated in cancer, cardiovascular and renal disorders, immunosuppression, and autoimmune diseases such as rheumatoid arthritis [35.159]. Semisynthetic derivatives also showed a similar activity [35.121]. Promising antimicrobial substances were also reported from *Antillogorgia rigida* (formerly *Pseudopterogorgia rigida*) (e.g., curcuphenol) [35.118] and from *Antillogorgia elisabethae* (formerly *Pseudopterogorgia elisabethae*) (e.g., pseudopterosin X and Y) [35.111]. Ileabethoxazole, homopseudopteroxazole, caribenols A and B and elisapterosin B from *A. elisabethae* and bipinnapterolide B from *Antillogorgia bipinnata* inhibit *Mycobacterium tuberculosis* H37Rv at a concentration of 12.5 $\mu g\,mL^{-1}$ [35.113, 115] (for elisapterosin B and homopseudopteroxazole) and at a concentration range of 128–64 $\mu g\,mL^{-1}$ [35.112, 114, 178] (for other compounds). In fact, the inhibition of *Micobacterium tuberculosis* H37Rv is within the range recorded for rifampin [35.112]. *A. elisabethae* and *A. bipinnata* also produce antituberculosis compounds. Bielschowskysin, a naturally occurring diterpene isolated from *Antillogorgia kallos* (formerly *Pseudopterogorgia kallos*) [35.117] and aberrarone isolated from *A. elisabethae* [35.116] exhibited antiplasmodial activity (IC_{50} 10 $\mu g\,mL^{-1}$) when tested against *P. falciparum*. The first compound was also found to display strong and specific in vitro cytotoxicity against the EKVX non-small cell lung cancer ($GI_{50} < 0.01\ \mu M$) and CAKI-1 renal cancer (GI_{50} 0.51 μM) [35.117]. Bis(pseudopterane) amine from *Antillogorgia acerosa* (formerly *Pseudopterogorgia acerosa*) was found to exhibit selective activity against HCT116 (IC_{50} 4 μM)

cell lines [35.108]. Astrogorgol F, a secosteroid produced by *Astrogorgia* sp., showed significant inhibition against protein kinases IGF-1R (insulin-like growth factor receptor-1), SRC and VEGF-R2 with IC_{50} of 3.16, 2.40, and 4.95 μM, respectively. These kinases are currently regarded as very important therapeutic targets for cancer. Protein IGF-1R activates crucial signaling pathways that benefit cancer cells. Inhibition of this protein function has shown to significantly decrease cancer cell proliferation and increase sensitivity to chemotherapy and radiation treatment. Kinase VEGF-R2 plays an important role in tumor angiogenesis, and its relevance as pharmacological target for the treatment of a large variety of solid cancers has been extensively described in the literature. The potent inhibitory activity of secosteroids toward VEGF-R2 indicates that they may induce the inhibition of tumor angiogenesis. SRC family kinases play a critical role in cell adhesion, invasion, proliferation, survival, and angiogenesis during tumor development. It was reported that the three kinds of kinases (SRC, VEGF-R2, and IGF-1R) involved in the different signaling pathways are influenced by crosstalk and interaction with each other [35.129].

Fuscosides, originally isolated from *Eunicea fusca* [35.135], selectively and irreversibly inhibited leukotriene synthesis. Leukotrienes are molecules of the immune system that contribute to inflammation in asthma and allergic rhinitis and their production is usually related to histamine release [35.179]. Pharmacological studies indicated that fuscoside B inhibits the conversion of arachidonic acid (AA) to leukotriene B4 and C4 (LTB4 and LTC4) [35.135, 180] by inhibiting the 5-lipoxygenase (5-LO), in the case of LTB4 with an IC_{50} of 18 μM [35.180]. These selective inhibitors of lipoxygenase isoforms can be useful as pharmacological agents, as nutraceuticals, or as molecular tools [35.159]. Fuscoside B and E were also used in the classical experiment of acute inflammation, the TPA-induced ear edema model, which allows evaluation of the anti-inflammatory properties of some natural products. The topical application on the mouse ear edema of the of these two compounds extracts showed high inflammation inhibition levels of 80.5% and 81.5%, respectively, when compared to the activity shown by the anti-inflammatory commercial drug indomethacin (77.3%) used as reference [35.136]. A diterpenoid, dolabellane, and sesquiterpenoids metabolites isolated from *Eunicea* sp. displayed antiplasmodial activity against the malaria parasite *P. falciparum* W2 (chloroquine-resistant) strain, with IC_{50} values of 9.4 μM, and IC_{50} values ranging from 10–18 $\mu g\,mL^{-1}$, respectively [35.130, 134].

The gorgonian *Junceella fragilis* produces secondary metabolites, frajunolides B and C, with anti-inflammatory effects towards superoxide anion generation and elastase release by human neutrophils, with an $IC_{50} > 10\,\mu g\,mL^{-1}$ [35.106]. When properly stimulated, activated neutrophils secrete a series of cytotoxins, such as the superoxide anion ($O_2^{\bullet -}$), a precursor of other reactive oxygen species (ROS), granule proteases, and bioactive lipids [35.181, 182]. The production of the superoxide anion is linked to the killing of invading microorganisms, but it can also directly or indirectly damage surrounding tissues. In contrast, neutrophil elastase is a major secreted product of stimulated neutrophils and a major contributor to the destruction of tissue in chronic inflammatory disease [35.183]. The anti-inflammatory butenolide lipide [35.184] from the gorgonian *Euplexaura flava* [35.137] can be currently synthesized, which opens the possibility of advancing into a new level of anti-inflammatory pharmaceuticals.

Some of the most interesting compounds identified so far in the on-going search for new antifouling agents have been recorded in the order Gorgonacea. Notable examples of such compounds are juncin ZII from *Junceella juncea* [35.107], homarine from *Leptogorgia virgulata* and *Leptogorgia setacea* [35.119], and pukalide and epoxypukalide so far only recorded from *Leptogorgia virgulata* [35.120].

Species of the genus *Briareum* (family Briareidae) (which commonly exhibit an incrusting appearance rather than the fan-like shape of many gorgonians) are widely abundant in Indo-Pacific and Caribbean coral reefs. These organisms have been recognized as a valuable source of bioactive compounds with novel structural features. Briarane-related natural products are a good example of such promising compounds due to their structural complexity and biological activity [35.185, 186]. Briaexcavatin E, from *Briareum excavata*, also occasionally referred to as *Briarium excavatum*, inhibited human neutrophil elastase (HNE) release with an IC_{50} between 5–10 μM [35.96]. Briaexcavatolides L and P, diterpenoids from the same species, exhibited significant cytotoxicity against mouse lymphocytic leukemia (P-388) tumor cells with ED_{50} of 0.5 [35.97] and 0.9 $\mu g\,mL^{-1}$ [35.187], respectively. Brialalepolides B and C, from a non-identified *Briarium* species, reduced the expression of COX-2 in human colon adenocarcinoma (RAW 264.7) cells, as well as in murine macrophage cells. This is significant because the metabolic products of COX-2 have

been implicated in the pathogenesis of colon cancer and other diseases. Additionally, mouse macrophages cells are used to test the effects of drugs on inflammation pathways. These data support the idea that briaranes such as brialalepolides B and C might be interesting candidates for therapeutic consideration as dual-acting cancer cell cytotoxins and inflammatory response inhibitors [35.94]. Diterpenoids produced from *Briareum polyanthes* (presently accepted as *Briareum asbestinum*), namely Briarellin D, K, and L, exhibited antimalarial activity against *P. falciparum* with an IC_{50} between 9–15 $\mu g\,mL^{-1}$ [35.95].

Other Orders

Sea anemones (order Actiniaria) are a rich source of biologically-active proteins and polypeptides. Several cytolytic toxins, neuropeptides, and protease inhibitors have been identified from this group of organisms [35.56]. In addition to several equinatoxins, potent cytolytic proteins and an inhibitor of papain-like cysteine proteinases (equistatin) were isolated from the sea anemone *Actinia equina* [35.188]. Equistatin has been shown to be a very potent inhibitor of papain and a specific inhibitor of the aspartic proteinase cathepsin D [35.189]. While papain-like cysteine proteases have been implicated in various diseases of the central nervous system, such as brain tumors, Alzheimer's disease, stroke, cerebral lesions, neurological autoimmune diseases, and certain forms of epilepsy [35.190], aspartic proteinase cathepsin D is involved in the pathogenesis of breast cancer [35.191] and possibly Alzheimer's disease [35.192]. An acylamino acid, bunodosine 391 (BDS 391) was isolated from the venom of the sea anemone, *Bunodosoma cangicum*. Intraplantar injection of BDS 391 into the hind paw of a rat induced a potent analgesic effect. This effect was not altered by naloxone (an opioid receptor antagonist), but was completely reversed by methysergide (a serotonin receptor antagonist), indicating that the effect is mediated by activation of serotonin receptors [35.193].

Cycloaplysinopsin C, a bis(indole) alkaloid isolated from *Tubastraea* sp. (order Scleractinia), was found to inhibit growth of two strains of *P. falciparum*, one chloroquine-sensitive (F32/Tanzania) and another chloroquine-resistant (FcB1/Colombia) with IC_{50} 1.48 and 1.2 $\mu g\,mL^{-1}$, respectively [35.59]. Cladocorans A and B, isolated from *Cladocora caespitosa* (order Scleractinia) [35.57], are marine sesterterpenoids that possess a γ-hydroxybutenolide moiety, which is thought to be responsible for the biological activity of these compounds. The potent anti-inflammatory activity of these natural metabolites was attributed to the inhibition of secretory phospholipase A2 (sPLA2, IC_{50} 0.8–1.9 μM). Given the general role of inflammation in diseases that include bronchial asthma and rheumatoid arthritis, the identification and development of potent inhibitors of sPLA2 continues to be of great importance for the pharmaceutical industry, with this type of metabolite being of paramount importance for future research [35.58].

A sphingolipid, 2S*,3S*,(4E,8E)-2N-[35-tetradecanoyl]-4(E),8(E)-icosadiene-1, 3-diol and a steroid (22E)-methylcholesta-5,22-diene-1a,3b,7a-triol, were isolated from the black coral *Antipathes dichotoma* (order Antipatharia) and screened for antibacterial activity against Gram-positive and Gram-negative bacteria at 1 mg/ml concentration. Data obtained showed that the sphingolipid exhibits potent activity against *Bacillus subtilis* and *Pseudomonas aeruginosa* (MIC 0.4 and 0.2 $mg\,mL^{-1}$, respectively), while the trihy droxy steroid showed potent activity against *B. subtilis* (MIC 0.6 $mg\,mL^{-1}$) [35.194].

35.2.2 Class Hydrozoa

The class Hydrozoa includes 7 orders and nearly 3500 valid species (Table 35.1), some of which are solitary while others are colonial. Among the most emblematic species are probably hydroids and the Portuguese man-o-war (*Physalia physalis*). Despite the large number of species in the class Hydrozoa, only a few have yielded interesting marine natural products in the last decade.

Immune escape plays an important role in cancer progression and, although not completely understood, it has been proposed that indoleamine 2,3-dioxygenase (IDO) plays a central role in the evasion of T-cell-mediated immune rejection [35.195]. IDO catalyzes the oxidative cleavage of the 2,3-bond of tryptophan, which is the first and rate-limiting step in the kynurenine pathway of tryptophan catabolism in mammalian cells [35.196]. The polyketides annulins A, B, and C, purified from the marine hydroid *Garveia annulata* (order Anthoathecata), potently inhibited IDO in vitro (Ki 0.12–0.69 μM) [35.197]. These annulins are more powerful than most tryptophan analogs known to be IDO inhibitors. These compounds are active at concentrations higher than $\approx 10\,\mu M$ and are, therefore, more effective than 1-methyltryptophan (Ki 6.6 μM), one of the most potent IDO inhibitors currently available [35.198]. Solandelactones C, D, and G are cyclopropyl oxylipins isolated from the hydroid *Solan-*

deria secunda (order Anthoathecata) and exhibit moderate inhibitory activity against FPT (69, 89, and 61% inhibition, respectively) at a concentration of 100 $\mu g\,mL^{-1}$ [35.199]. Note that FPT is associated with cell differentiation, and proliferation and its inhibition may be a target for novel anticancer agents (as was already mentioned above for the soft coral *Lobophytum cristagalli*).

35.2.3 Class Scyphozoa

Approximately 200 species are currently classified in the three orders of the class Scyphozoa (Table 35.1). However, in the last decade, only a single marine natural product was purified from the mesoglea of the jellyfish *Aurelia aurita* (order Semaeostomeae) and considered to be promising enough to be included in the present overview. This compound, aurelin, is a novel endogenous antibacterial peptide that exhibited activity against Gram-positive and Gram-negative bacteria. As an example, aurelin displayed an IC_{50} of 7.7 $\mu g\,mL^{-1}$ for *Escherichia coli* (Gram-negative bacteria) [35.200].

35.2.4 Other Classes

Staurozoa, Cubozoa, and Polypodiozoa are the classes with the least number of species in the phylum Cnidaria (Table 35.1). This fact may explain the current lack of data on secondary metabolites produced by these organisms. It is possible that with growing bioprospecting efforts new compounds may be revealed once these cnidarian species are screened. Cubozoa (box jellies), for example, produce some of the most harmful cnidarian toxins known to humans [35.201].

35.3 Concluding Remarks and Future Challenges

The intense pressure to find and develop more profitable molecules for all sorts of industries continues to fuel bioprospecting efforts of marine invertebrates. While the phylum Cnidaria is not the most significantly bioprospected at present, this chapter shows that some cnidarian species are promising sources of marine bioactive compounds of medical, economic, and scientific interest. Green fluorescent protein (GFP), GPF-like proteins, red fluorescent, and orange fluorescent protein (OPF) are good examples of biotechnological metabolites derived from cnidarians that are currently employed as molecular biomarkers. They were first purified from a fluorescent hydrozoan medusa [35.202] and have since been recorded in other cnidarian species [35.203–208].

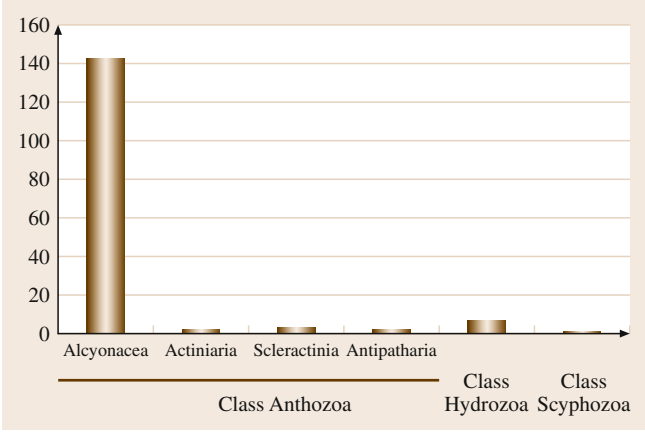

Fig. 35.6 Marine bioactive compounds with high biotechnological potential studied from the phylum Cnidaria in the twenty-first century (after [35.28])

In the present survey of the most promising bioactive marine natural products from cnidarians, only about 0.57% of extant cnidarian species are represented, with the class Anthozoa displaying by far the highest number of promising bioactive marine natural products (91%) (Fig. 35.6). This result is probably due to the fact that this class displays the highest number of species in the phylum (Table 35.1). Additionally, many anthozoans occupy marine habitats that can be readily accessed for the collection of biomass (e.g., coral reefs and intertidal regions), which facilitates bioprospecting. Of all the compounds presented in this review, 89% were detected in cnidarians collected from tropical waters (mostly from Southeast Asia and the Caribbean Sea), with the remaining 11% recorded from species that are mostly present in temperate waters (e.g., European countries and Japan).

Antitumor drugs are the main area of interest in the screening of marine natural products from cnidarians (39%, Fig. 35.7). This is not surprising, as the major financial effort for the screening of new marine compounds is made by cancer research [35.209]. Terpenoids (terpenoids, diterpenoids, sesquiterpenoids, sesterterpenoids, cembranoids) [35.14] (Fig. 35.8) are

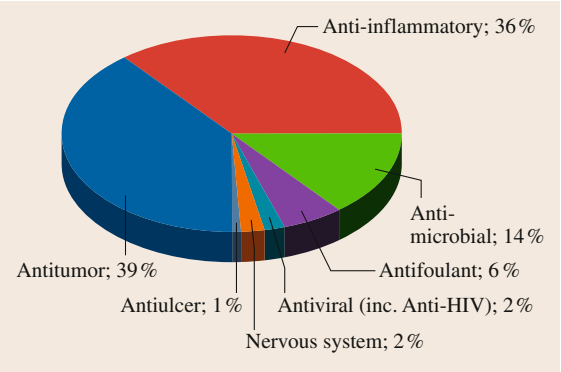

Fig. 35.7 Distribution in drug classes of marine bioactive compounds with high biotechnological potential studied from cnidarian species in the twenty-first century (after [35.28])

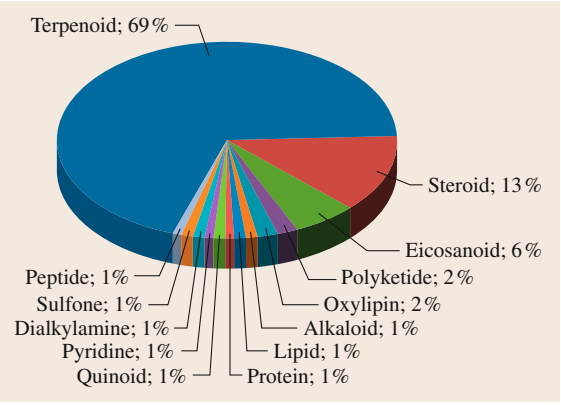

Fig. 35.8 Distribution of chemistry classes of marine bioactive compounds with high biotechnological potential studied from cnidarian species in the twenty-first century (after [35.28])

the main chemistry group in the MNPs analyzed in this survey.

Even though most pharmaceutical industries abandoned their natural product-based discovery programs over a decade ago, the lack of new compounds in their pipelines in some strategic areas (e.g., antibiotics) suggests that a renewed interest in this field is imminent. The establishment of small biotechnology companies can play a decisive role in the initial discovery of promising marine bioactive compounds, as these enterprises will work closely together with academics and governmental agencies to take the initial steps in the discovery of new chemical entities. Collaboration between private companies and public institutions can be of paramount importance for financial support in the discovery process. On the other hand, crude extracts and pure compounds produced by academic laboratories may be screened by diverse bioassays as part of broader collaboration programs, nationally and internationally, with private biotechnology companies. One challenge for universities is to devise mechanisms that protect intellectual property and simultaneously encourage partnerships with the private sector, by recognizing that the chances of a major commercial pay-off are small if drug discovery is pursued by a single institution [35.29].

The commercial use of some promising marine bioactive compounds isolated from cnidarians may still be several years away. However, new compounds other than toxins and venoms produced by members of this highly diverse group of marine invertebrates may soon be discovered in the ongoing quest for new MNP.

As with most marine organisms, the bioprospecting of cnidarians has been mostly limited to shallow habitats accessible either by foot, snorkeling, or SCUBA diving. In recent years, with the advent of deep-sea exploration it has been possible to bioprospect several unique ecosystems that had remained inaccessible to researchers [35.210, 211]. Deep-sea habitats (including hydrothermal vents and cold seeps), as well as seamounts, are commonly colonized by unique cnidarian species [35.212–214] that exhibit remarkable adaptation to extreme environments [35.215] and are promising candidates for the discovery of new MNPs [35.216]. Marine biodiversity conservation has been capturing the growing attention of nations worldwide. The growing concerns towards the conservation of marine habitats are already conditioning the bioprospecting of coral reefs, deep sea and other endangered marine habitats [35.217–219]. Even so, it is likely that in the years to come bioprospecting for new marine natural products will continue to grow and that new cnidarian groups will be targeted by researchers.

Modern screening techniques rely on the use of a significantly lower amount of biomass (micrograms) than what was required a decade ago for the discovery of new chemical compounds [35.18]. The incorporation of modern molecular biology and bioinformatics to complement the use of chemical approaches in the study of biosynthetic pathways has allowed researchers to make significant breakthroughs in the production of marine drugs [35.220]. Nonetheless, the production of such compounds at a commercial level is still a remarkable challenge. Large-scale production of a given com-

pound can be possible either through chemical synthesis or through its extraction from the source organism. Unfortunately, the first option is not always possible, as several complex molecules are simply impossible to produce or incur production costs that cannot be afforded by commercial applications [35.221, 222]. The harvest of the source animal from the wild for the extraction of a compound is invariably an unsustainable practice and rarely a long-term option [35.219]. On the other hand, the production of source organism biomass (either *in* situ or *ex* situ) has been considered as a potential alternative to the collection of wild specimens [35.223]. Additionally, the production of source organisms under controlled conditions may help to control the ecophysiological diversity promoted by environmental interactions and maximize the production of target marine molecules. Unfortunately, the culture of most target organisms has turned out to be more technically challenging and significantly more expensive than initially assumed [35.224, 225].

There is growing evidence that microorganisms associated with marine invertebrates may be the true producers of some of the MNPs isolated from these animals and may even be responsible for the variation of chemical diversity at species level [35.226–228]. The microbiome present in marine invertebrates is likely to shift geographically [35.229, 230], which may enhance the production of different secondary metabolites. Whether this is also the case of most cnidarians remains to be confirmed [35.231]. Nonetheless, it has already been recognized that one of the promising compounds recorded from the gorgonian *Antillogorgia elisabethae* is, in fact, produced by its symbiotic dinoflagellates [35.232]. In this way, it is possible that future bioprospecting efforts may shift from invertebrate hosts towards symbiotic microorganisms. Under this scenario another constraint for the commercial use of these compounds must be overcome, as the culture of symbiotic microorganisms is generally not possible using classic/standardized methodologies. Once isolated from their host symbiotic microorganisms rarely thrive in vitro or no longer produce the desired compound [35.223–228].

The early impetuous of natural product-based discovery programs by pharmaceutical industries has decreased in the twenty-first century [35.233]. Nonetheless, the lack of new compounds in some of the strategic pipelines for drug discovery impels researchers to consider the new tools available for blue biotechnology [35.234] and the importance of joining efforts with academic institutions for the early stages of marine organisms bioprospecting. New drugs derived from MNP isolated from cnidarians may still be several years away, but it is unquestionable that more chemical entities, besides toxins and venoms, will be recorded from cnidarians [35.28]. In conclusion, this diverse group of marine invertebrates is destined to play a major role in the pursuit of new drugs from the sea.

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