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Chemical constituents and biological activities of the soft corals of genus *Cladiella*: A review

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Dedicated to the late Dr. D. John Faulkner,[1] the late Dr. Paul J. Scheuer,[2] the late Dr. Kenneth L. Rinehart[3] and the late Prof. Dr. C. Bheemasankara Rao[4] for their pioneering work on bioactive marine natural products.

Abstract

In this review, structures of natural products isolated from the soft corals of genus *Cladiella* and their biological activities are described.

Keywords: Soft coral; *Cladiella*; Sesquiterpenes; Diterpenes; Ceramides; Cerebrosides; Sterols; Sterol glycosides; Lipid glycosides; Biological activity

A number of reviews on the chemical and biological perspectives of natural products of marine origin have appeared in *Chemistry of Marine Compounds* (Scheuer, 1973), *Marine Toxins* (Scheuer, 1977), *Interesting Aspects of Marine Natural Products Chemistry* (Faulkner and Fenical, 1977), *Marine Natural Products: Chemical and Biological Perspectives* (Scheuer, 1978–1983), *Bioorganic Marine Chemistry* (Scheuer, 1987–1992), and *Marine Natural Products* (Faulkner, 2002; Blunt et al., 2006). The work of Rinehart at the University of Illinois at Champaign–Urbana and Pettit at Arizona State University opened a new horizon in discovering new biologically active molecules from the marine environment. The specific biological activity of marine natural products was also well reviewed and published in different journals (Faulkner, 2000; El Sayed et al., 2000; Blunden, 2001; Beutler and McKee, 2002; Proksch et al., 2002; Gochfeld et al., 2003; Haefner, 2003; Newman and Cragg, 2004).

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Soft corals are a rich source of bioactive molecules such as terpenes, steroids and steroidal glycosides (Faulkner and Fenical, 1977). It was reported that 50% of the soft coral extracts exhibited ichthyotoxic characteristics (Sammarco and Coll, 1988). Cnidarian–algal symbiotic associations are common in marine environment and are of great ecological importance. Many of the secondary metabolites of cembranoid type diterpenes from the soft corals may be involved in ecological interactions (Coll, 1992), whereas other metabolites have biological activities such as antifungal, antineoplastic, ichthyotoxic (Kashman and Groweiss, 1977), cytotoxic (Duh et al., 2000), HIV-inhibitory (Rashid et al., 2000) and anti-inflammatory activity (Radhika et al., 2005).

Soft corals are widely distributed but have marked preference for tropical waters of a depth between 5 and 30 m than temperate reefs. The genera of *Sinularia*, *Lobophytum* and *Sarcophyton* are the most prolific soft corals, whereas species of *Cladiella* (Phylum: Coelenterata, Family: Alcyoniidae, Class: Anthozoa, Order: Alcyonacea) are found on reefs in the Indo-Pacific region. The chemical constituents and different types of biological activities of 14 species of this genus have been studied by various research groups. The structure and biological activities of these metabolites are described and presented in this review.

1. Sesquiterpenes and diterpenes

Studies on the chemical constituents of soft corals of *Cladiella* were initiated in 1977 with the discovery of two eunicellin type of diterpene metabolites, cladiellin **1** and acetoxycladiellin **2** (Kazlauskas et al., 1977) from a species of *Cladiella*, collected on the Great Barrier Reef near Townsville. They were structurally related to eunicellin, a metabolite isolated from the gorgonian *Eunicella stricta*. The structure of the *m*-chlorobenzoate derivative of cladiellin was determined by X-ray analysis. A diterpene **3** was reported from an unidentified pacific soft coral related to cladiellin **1** by chemical interconversion (Hochlowski and Faulkner, 1980). The soft coral has now been identified as a species of *Cladiella* (identified by Dr. J.C. Coll). An eunicellin-based diterpene **4** has been isolated from a *Cladiella* sp. (Uchio et al., 1989). The structure and relative stereochemistry of metabolite **4** were determined on the basis of spectroscopic (IR, ^{1}H and ^{13}C NMR) and chemical evidences. Its structure was confirmed by a single-crystal X-ray analysis.

Co-occurring with metabolite **4** were three other eunicellin-based diterpenoids **5**, **6** and **7** isolated from an Okinawan *Cladiella* species of soft coral (Uchio et al., 1992). Their structures have been determined by spectral evidence and confirmed by chemical interconversion. The diterpenoid cladiellisin **8** was isolated from the soft coral *Cladiella similis* (Liu et al., 1992). Its structure was determined by IR, NMR, and 2D-COSY. The compounds isoneocembrene-A **9** and 11,12-epoxy isoneocembrene-A **10** were two cembrane diterpenoids reported from the soft coral, *Cladiella klugzingeri* (Hari Babu, 1992), on the coasts of the Andaman and Nicobar Islands. A cembranoid diterpene was isolated from the soft coral, *Cladiella krempfi* (Sarma et al., 1993) from Minicoy Island (India). Its structure was established by X-ray crystallography as sclerophytin F methyl ether **11** with the *R* absolute configuration at all six epimeric centers, assuming a configuration similar to that of sclerophytin C. Seven cladiellane diterpenes, **12**, **13**, **14**, **15**, **16**, **17** and **18** were isolated from the soft coral *Cladiella australis* (Bheemasankara Rao et al., 1994; Sreenivasa Rao et al., 1994) collected on the coasts of the Andaman and Nicobar Islands of the Indian Ocean. The structures of these metabolites were elucidated on the basis of high resolution spectral data and chemical studies. In addition, sclerophytins C **19** and E **20** reported earlier from *Sclerophytum capitalis*, were also isolated from this species. It was reported that compound **11** may be an artifact of the isolation process (Sarma et al., 1995). *Cladiella sphaeroides* (Yamada et al., 1997), a species found in Japan, contained a new bioactive diterpenoid, cladiellaperoxide **21**, together with the eunicellin-type diterpenoid which had the same relative stereostructure as that of the diterpenoid cladiellisin **8**. All the structures were characterized by NMR studies and chemical conversion. The absolute configurations of **8** and **21** have been elucidated by modified Mosher method. Compound **21** showed toxicity in the brine shrimp lethality bioassay at a 30-ppm concentration, while cladiellisin **8** was inactive in this bioassay. Three cembrane diterpenes namely flaccidoxide **22** (1*Z*,3*E*,7*E*,11*S*,12*S*,14*S*)-11,12-epoxy cembra-1,3,7-trien-14-ol **23** and flaccidoxide-13-acetate **24** (Gray et al., 2000) were isolated from the southern African soft coral, *Cladiella kashmani*, collected off Ponto do Oura, Mozambique. Application of the modified Mosher's method established the previously unassigned absolute configuration of **22** as (1*Z*,3*E*,7*E*,11*S*,12*S*,13*S*,14*R*)-14-acetoxy-11,12-epoxy cembra-1,3,7-trien-13-ol. Acetylation of **22** yielded **24** and confirmed the structure of **24** as (1*Z*,3*E*,7*E*,11*S*,12*R*,13*S*,14*R*)-13,14-diacetoxy-11,12-epoxy cembra-1,3,7-triene. The isolation of cembranoids from *C. kashmani* was reported for the first time. All the three diterpenes (**22**, **23** and **24**) were toxic to the brine shrimp *Artemia salina*.