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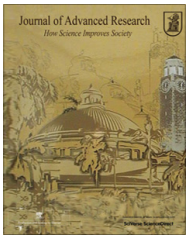

MINI REVIEW

Chemical and biological profile of *Cespitularia* species: A mini review

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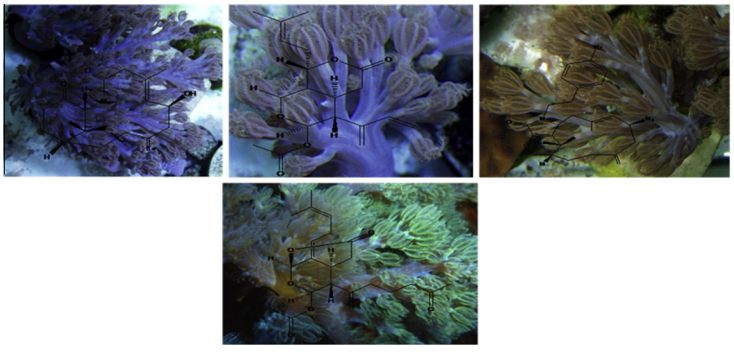
GRAPHICAL ABSTRACT



This review furnishes an overview of all naturally isolated compounds, especially diterpenoids as well as biological activities of these species such as anticancer, immunomodulatory, antiviral, antimicrobial, and anti-inflammatory activities.

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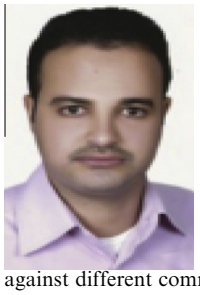
ABSTRACT

Soft corals belonging to the genus *Cespitularia* have been well recognized as a rich source of bioactive secondary metabolites especially diterpenoids. This review furnishes an overview of all naturally isolated compounds from *Cespitularia* genus as, diterpenoids, nitrogen-containing diterpenes, sesquiterpenoids and steroids as well as biological activities of these species. *Cespitularia* species have been studied for their anticancer, immunomodulatory, antiviral, antimicrobial, and anti-inflammatory activities. This work is the first review published on this topic.

Abdelsamed I. Elshamy, Researcher in National Research Centre, Egypt. The research experiences focused on isolation and identification of phenanthrenes, flavonoids, sterols, terpenes, coumarines, volatile oils, ceramides from medicinal plants and marines by different isolation and identification methods such as structural elucidation by modern techniques of spectroscopic analysis, MS, HRMS, 1D and 2D NMR and X-ray. Synthesis of derivatives of natural products. Bioactive assay *in vivo* and *in vitro* of natural products against different diseases.

Mahmoud I. Nassar, Professor of Natural Products Chemistry, National Research Centre, Egypt. His research experiences focused on isolation, identification of phenanthrenes, flavonoids, sterols, coumarines, volatile oils, and ceramides from medicinal plants and marines. Bioactive evaluation of natural products such as plant extracts and compounds.



Tarik A. Mohamed, Researcher in National Research Centre, Egypt. His research interest focused on Chemical Constituents of Medicinal Plants and Marine Organisms, Extraction, Isolation and Purification of Natural Bioactive Compounds, Structural Elucidation of Natural Products by Modern Techniques of Spectroscopic Analysis, MS, HRMS, 1D and 2D NMR and X-ray analysis, Biological Activities of Natural Products against different common diseases and Biotransformation for Natural Compounds.

Mohamed-Elamir F. Hegazy, Associate Professor in Chemistry of Medicinal plant Department, National Research Center, who has two Ph.D. degrees: A Ph.D. degree from Hiroshima University, Japan, and a Ph.D. degree from Minia University, Egypt. Dr. Hegazy is working in the field of natural products chemistry and biotransformation of natural compounds with cultured plant cells ten years ago and he had a strong experience in the isolation, purification and identification of natural compounds from medicinal plants and marine organisms using high technique for identification (1D and 2D NMR analysis).

Introduction

Marine organisms have developed a variety of bioactive secondary metabolites [1]. Chemically, the bioactive metabolites isolated from marine animals could be divided into steroids, terpenoids, isoprenoids, nonisoprenoids, quinones, halogenated compounds, nitrogen heterocyclics, and nitrogen sulfur heterocyclics [2–5]. The bioactive metabolites that are adjectives of that kind of interest have been mainly isolated from corals, marine sponges, jellyfish, sea anemones, bryozoans, molluscs, echinoderms, tunicates and crustaceans [3].

Octocorals (phylum Cnidaria) have been widely studied, as they are responsible for the production of a huge array of skeletal different classes of secondary metabolites. Family Xeniidae (order Alcyonacea) which involves 17 genera of soft corals such as *Heteroxenia*, *Cespitularia*, *Xenia*, *Anthelia*, *Asterospicularia*, *Bayerxenia*, *Sympodium*, is a very large family distributed in all over the marine environments [6,7].

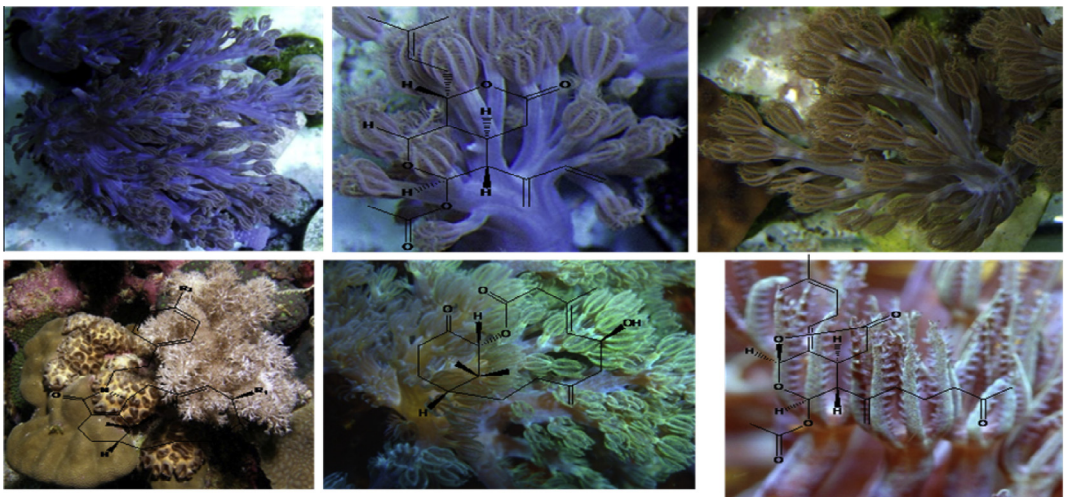


Fig. 1 Photographs of some *Cespitularia* species.

Cespitularia genus involves almost 18 species such as *C. erecta*, *C. hypotentaculata*, *C subviridus*, *C. taeniata*, *C. infirmata* [8] (Fig. 1). They live in tropical reefs, in areas with strong currents and with good light intensity like in the Indo-Pacific Ocean from the East African coast to Australia, New Guinea and southern Japan [8].

Several biological studies on different extracts and isolated secondary metabolites from *Cespitularia* species have reported activities such as anticancer, immunomodulatory, antiviral, antimicrobial, and anti-inflammatory [9–11]. Soft corals of the genus *Cespitularia* are rich in novel and diverse chemical structures with interesting biological activities [12]. Reports related metabolites chemistry of the genus *Cespitularia* is scarce. Earlier studies of the genus *Cespitularia* led to the isolation of a diverse array of diterpenoids including alcyonolides, caryophyllanoids, cembranolides, cespitularanoids, dolabellanoids, norverticillanoids, verticillanoids, and xenicanoids [3,9–30].

Biological activities of *Cespitularia* species

Anticancer activity

It was reported that some isolated compounds from *C. taeniata* have significant cytotoxic activity. Cespitulactone A (**60**) exhibited significant cytotoxicity against human cervical epithelioid carcinoma (HeLa) and colon adenocarcinoma (DLD-1) cancer cells with IC_{50} of 3.69 and 9.98 μg/ml, respectively. Flaccidoxide-13-acetate (**62**) showed mild activity against human medulloblastoma (Daoy) and colon (WiDr) cancer cells 16.9 and 13.8 μg/ml, respectively [10,16].

Cheng et al. [14] have reported that some isolated sesquiterpene lactams from EtOH extract of the soft coral *C taeniata* exhibited cytotoxic activity. 8β-methoxyatractylenolide (**83**) was also reported to exhibit cytotoxicity against KB and Daoy cancer cell lines with ED_{50} values of 10.71 and 7.93 μg/ml [14,17].

Some isolated cespitulactams from *C. taeniata* have been reported to exhibit significant cytotoxicity against some human cancer cells. Cespitulactam A (**19**) was reported to exhibit significant cytotoxicity against human Widr and Daoy cancer cells with the IC_{50} values of 2.72 and 6.34 μg/ml, respectively [18]. Duh et al. [9] have reported that some of isolated cespitularin derivatives showed cytotoxic activity against A-549; P-388 and HT-29. Cespitularin B (**33**) and D (**35**) showed moderate cytotoxicity against P-388 cells with ED_{50} values of 3.23 and 3.86 μg/ml respectively. Cespitularin C (**34**) was stated to exhibit potent cytotoxicity against P-388 and A-549 cells at ED_{50} values of 0.12 and 0.01 μg/ml respectively while cespitularin E (**36**) exhibits potent cytotoxicity against A-549 cells at ED_{50} value of 0.034 μg/ml [9].

Shen et al. [19], stated that some isolated cespihypotin diterpene derivatives showed significant cytotoxic activity against human Daoy and WiDr tumor cell lines. Cespihypotin T (**18**), a *Cespitularia* norditerpene with a keto and two adjacent hydroxy groups, showed significant cytotoxic activity against human tumor cells exhibited significant cytotoxicity against Daoy and WiDr cell lines with ED_{50} values of 9.3 and 7.5 μg/ml, respectively [19].

Some of nitrogen-containing verticillene diterpenoids from the soft coral *C. taeniata* were reported to exhibit *in vitro* antitumor activity against human oral epidermoid carcinoma (KB) and murine L1210 leukemia tumor cell lines. Cespitulactam K (**31**) was stated to have a significant *in vitro* cytotoxic activity against both human cancer cell lines at 3.7 and 5.1 μg/ml respectively [12].

Duh et al. [11] reported that some isolated cespitularin diterpenoids and secosteroids exhibited cytotoxic activity. It was stated that cespitularin O (**47**) showed cytotoxicity against P-388 cells with ED_{50} value of 3.4 μg/ml. While 3*β*,11-dihydroxy-5*β*,6*β*-epoxy-9,11-secocholestan-9-one (**83**) exhibited cytotoxicity against HT-29 cells with an ED_{50} of 1.0 μg/ml [11]. Some of reported cespitularines and cespihypotins from *C. hypotentaculata* have exhibited cytotoxicity against leukemia (P-388 and A-549) cells [9,11,18,20]. Recently, Roy et al. [29] stated that the two alcyonolide derivatives, trisnorditerpenoid 1 (**72**) and 2 (**73**), showed cytotoxicity against HCT116 cancer cells with the IC_{50} values of 6.04 and 47.0 μM, respectively, and a dose dependent [21].

Recently, Lin et al. [15] stated that the isolated diterpenoid from CH_2Cl_2/EtOH extract of *C. taeniata,* cespitulon A (**74**), exhibited significant cytotoxicity against human medulloblastoma and colon adenocarcinoma cancer cells with IC_{50} values

Table 1 Diterpenoids of *Cespitularia species*.

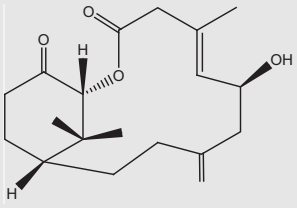
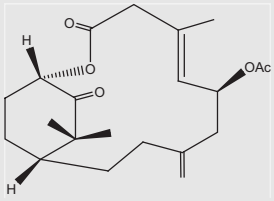
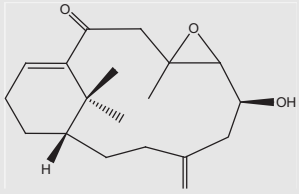
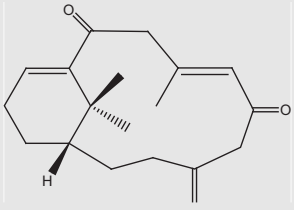
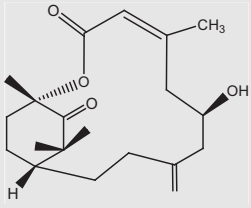
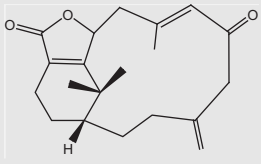
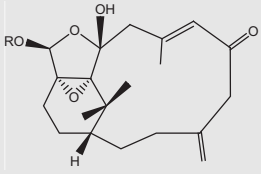
Source	Structure	Compd. name
C. hypotentaculata [11,24]		**1**: Cespihypotin A
		**2**: Cespihypotin B
		**3**: Cespihypotin C
		**4**: Cespihypotin D
		**5**: Cespihypotin E
C. hypotentaculata [20]		**6**: Cespihypotin F
		**7**: R═H – Cespihypotin G **8**: R═COCH═CH_2 – Cespihypotin H **9**: R═Ac – Cespihypotin I

Table 1 (*continued*)

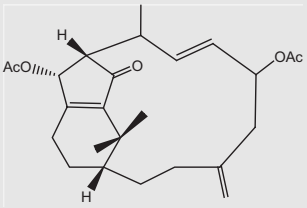
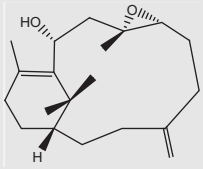
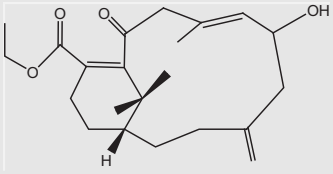
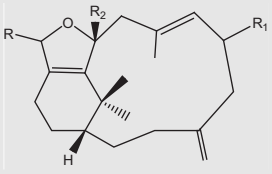
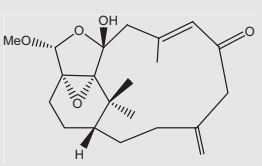
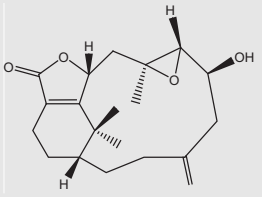
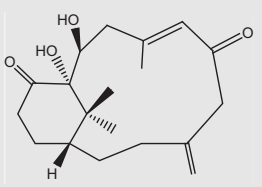
Source	Structure	Compd. name
		**10**: Cespihypotin J
		**11**: Cespihypotin K
		**12**: Cespihypotin L
C. hypotentaculata [19]		**13**: R═R_1═OMe, R_2═OH – Cespihypotin Q **14**: R═R_2═OMe, R_1═H – Cespihypotin R **15**: R═O, R_1═R_2═OH – Cespihypotin V
		**16**: Cespihypotin S
		**17**: Cespihypotin U
		**18**: Cespihypotin T

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Table 1 (*continued*)

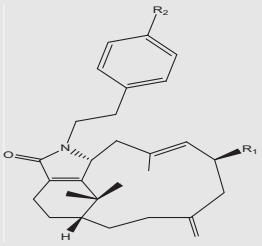
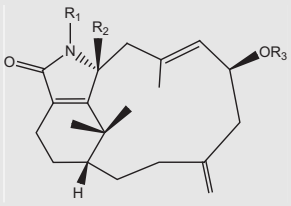
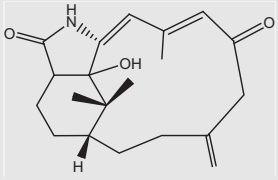
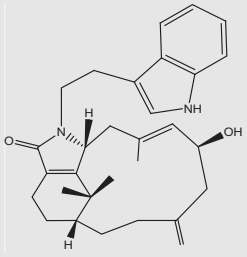
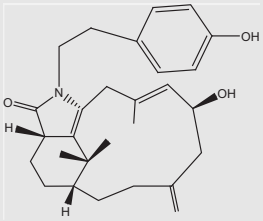
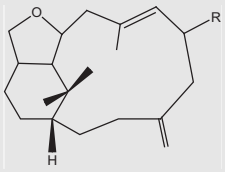
Source	Structure	Compd. name
C. taeniata [20,16,25]		**19**: R_1═OH, R_2═H – Cespitulactam A **20**: R_1═R_2═OH – Cespitulactam C **21**: R_1═OAc, R_2═H – Cespitulactam A-monoacetate **22**: R_1═R_2═OAc – Cespitulactam A-diacetate **23**: R_1═H, R_2═H – Cespitulactam B
		**24**: R_1═R_2═R_3═H – Cespitulactam D **25**: R_1═R_2═H, R_3═Ac – Cespitulactam E **26**: R_1═R_3═H, R_2═OH – Cespitulactam F **27**: R_1═CH_2CH_3, R_2═OH, R_3═H – Cespitulactam G **28**: R_1═CH_3, R_2═R_3═H – Cespitulactam H
		**29**: Cespitulactam I
C. taeniata [12]		**30**: Cespitulactam J
		**31**: Cespitulactam K
C. hypotentaculata and *C. taeniata* [9,12]		**32**: R═OH – Cespitularin A **33**: R═H – Cespitularin B

Table 1 (*continued*)

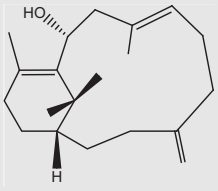
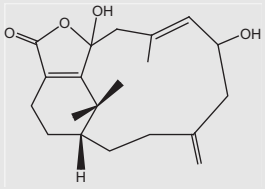
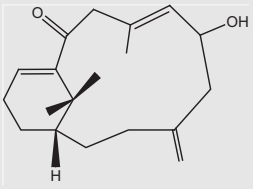
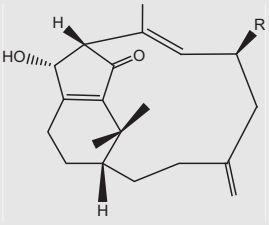
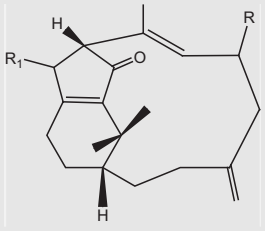
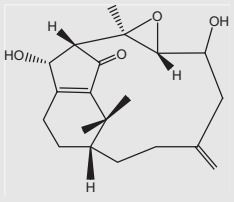
Source	Structure	Compd. name
		**34**: Cespitularin C
C. hypotentaculata and *C. taeniata* [9,12,20,24]		**35**: Cespitularin D
		**36**: Cespitularin E
		**37**: R═OH – Cespitularin F **38**: R═OAc – 6-O-acetylcespitularin F **39**: R═H – Cespitularin G **40**: R═O – Cespitularin H
		**41**: R═OH, R_1═O – Cespitularin I **42**: R═OAc, R_1═α-OH – Cespitularin J **43**: R═OAc, R_1═O –Cespitularin K
C. hypotentaculata [11,22]		**44**: Cespitularin L

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Table 1 (*continued*)

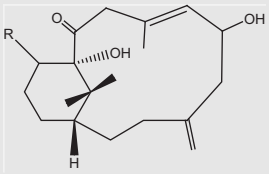
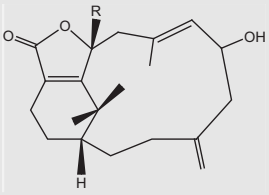
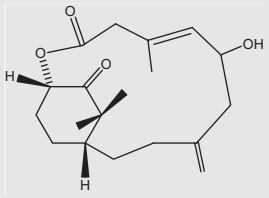
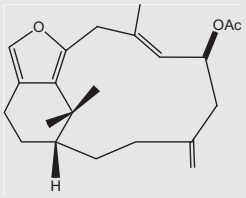
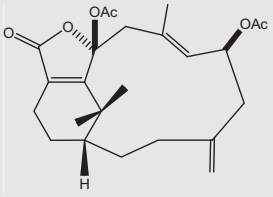
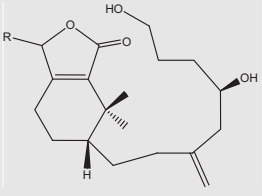
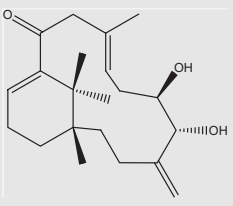
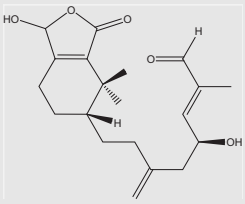
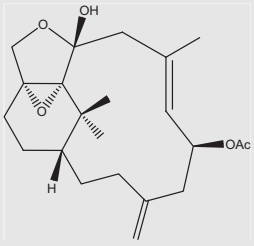
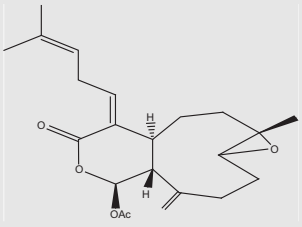
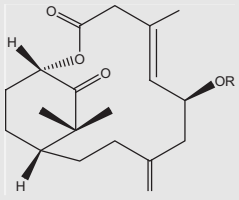
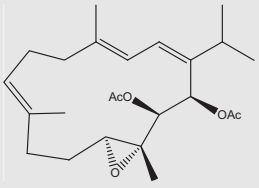
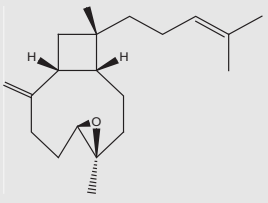
Source	Structure	Compd. name
		**45**: R═α-OH – Cespitularin M **46**: R═β-OH – Cespitularin N
		**47**: R═H – Cespitularin O **48**: R═OMe – Cespitularin P
		**49**: Cespitularin Q
		**50**: Cespitularin R
C. hypotentaculata [22]		**51**: Cespitularin S
C. taeniata [25]		**52**: R═α-OH – Cespitulin A **53**: R═β-OH – Cespitulin B **54**: R═α-OEt – Cespitulin C **55**: R═β-OEt – Cespitulin D
C. taeniata [26]		**56:** Cespitulin E

Table 1 (*continued*)

Source	Structure	Compd. name
		**57:** Cespitulin F
		**58:** Cespitulin G
C. hypotentaculata [22,24]		**59**: Cespitolide
		**60**: R═H – Cespitulactone A **61**: R═Bz – Cespitulactone B
		**62**: Flaccidoxide-13-acetate
C. sp [28]		**63**: 4β,5β-epoxyxeniaphylla-8(19),14-diene

(*continued on next page*)

Table 1 (*continued*)

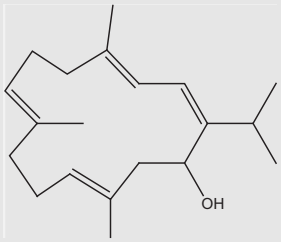
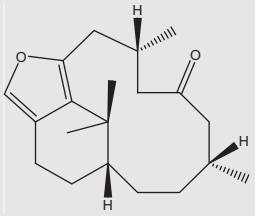
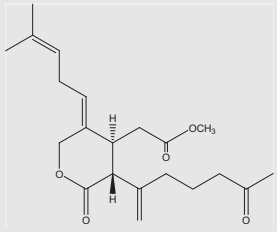
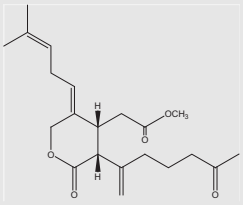
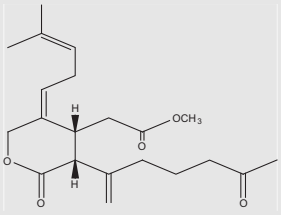
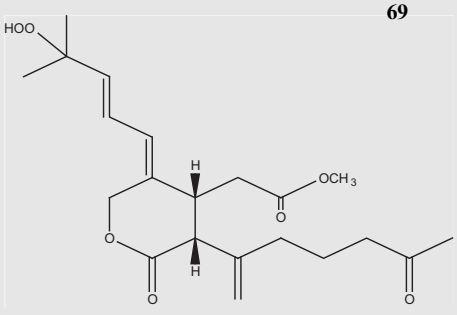
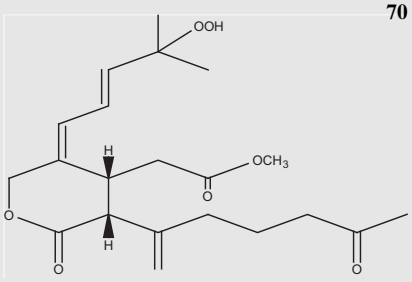
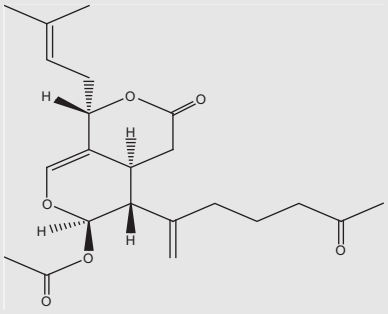
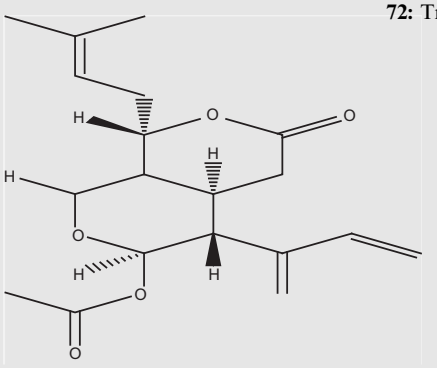
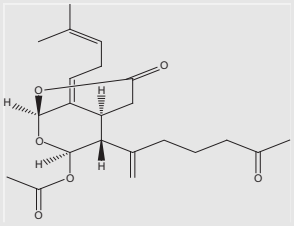
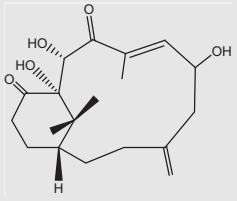
Source	Structure	Compd. name
C. erecta [29]		**64**: Sarcophytol A
C. erecta [29]		**65**
C. sp [21]		**66**
		**67**
		**68**
C. sp [21]		**69**

Table 1 (*continued*)

Source	Structure	Compd. name
		**70**
		**71:** Alcyonolide
C. sp [21,29]		**72:** Trisnorditerpenoid 1
		**73:** Trisnorditerpenoid 2
C. taeniata (15)		**74:** Cespitulone A

(*continued on next page*)

Table 1 (*continued*)

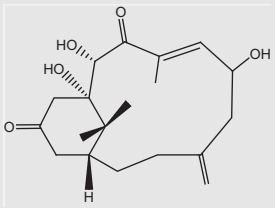
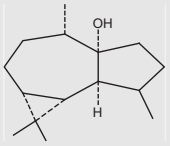
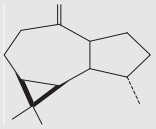
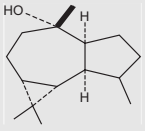
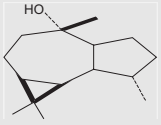
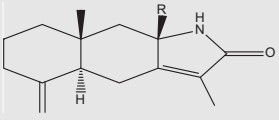
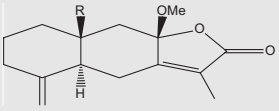
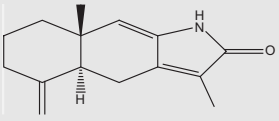
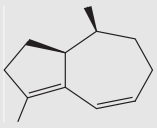
Source	Structure	Compd. name
		**75:** Cespitulone B

Table 2 Sesquiterpenoids of *Cespitularia* species.

Source	Structure	Compd. name
C. aff. subviridis [23,27]		**76**: (+)Palustrol
		**77**: (−)Alloaromadendrene
		**78**: (−)Viridiflorol
		**79**: (+)Ledol
C. taeniata [14]		**80**: R═H – Taenialactam A **81**: R═OH – Taenialactam B
		**82**: R═α-Me – Taenialactone A **83**: R═β-Me – 8β-methoxyatractylenolide
		**84**: Atractylenolactam
C. sp [26,30]		**85**: Trinorsesquiterpene

of 8.7 and 6.7 μM, respectively by a comparison with a positive control with IC_{50} at 0.3 μM [15].

Immunomodulatory and antiviral activities

Some isolated cespihypotin diterpenes from *C. hypotentaculata* have exhibited weak antiviral activity. Cespihypotin K (**11**) showed significant enhancement of cell proliferation, while cespihypotin L (**12**) exhibited inhibition on peripheral blood mononuclear cells (PBMC) proliferation induced by phytohemagglutinin (PHA). The antiviral activities of these compounds were achieved by a comparison with the positive control, cyclosporine A [20].

Anti-inflammatory activity

Some isolated compounds from *C. hypotentaculata* were reported to have a significant anti-inflammatory activity *in vitro*. Cespitularin F (**37**), cespitularines I (**41**) and cespitularin S (**51**) showed significant inhibition of iNOS protein expression [21]. Roy et al. [29] stated that the two alcyonolide derivatives, trisnorditerpenoid 1 (**72**) and 2 (**73**), showed anti-inflammatory effect in LPS/IFN-c-stimulated inflammatory RAW 264.7 macrophage cells and showed anti-inflammatory activity in low concentrations and a dose dependent of 2–8 μM. The lack of cytotoxicity against RAW 264.7 macrophage cells in the test concentration range indicated that inhibition of nitric oxide production was due to the effects of these compounds [21].

The isolated compounds from *C. taeniata*, cespitulins E–G (**56–58**) were reported to have inhibitory effects of superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB. Cespitulin G (**56**) exhibited significant inhibitory activity against elastase release with an IC_{50} value of 2.7 μg/ml and inhibition of superoxide anion with an IC_{50} value of 6.2 μg/ml. Cespitulin E (**58**) exhibited moderate activities at the concentration of 10 μg/ml (30.6 ± 6.0 and 33.8 ± 4.1% inhibition, respectively) with the use of genistein as a positive control [26].

Antimicrobial activity

Some of the isolated nitrogen-containing verticillene diterpenoids isolated from the Taiwanese soft coral *C. taeniata* were reported to exhibit a antimicrobial activity [12]. Cespitulactam G (27) was stated to exhibit potent antimicrobial activity against *Trichophyton mentagrophytes* (IFM45110) with an MIC value of 2.08 μg/ml. Cespitulactam D (**24**), cespitulactam J (**30**), and cespitulactam K (**31**) were reported to have significant antimicrobial activity against *M. luteus* (IFM2066) and *C. neoformans* (IFM46914) (**6–8**) and *T. mentagrophytes* (**2** and **7**) with MIC value of 4.16 μg/ml [12,20]

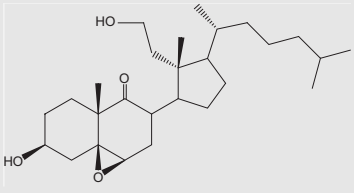
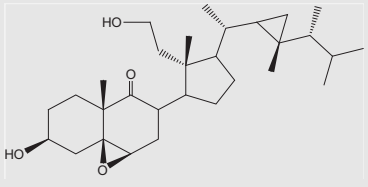
Chemical constituents of *Cespitularia* species

Soft corals of the genus *Cespitularia* are rich in novel and diverse chemical structures with interesting biological activities. This genus elaborates varied diterpenoids of cembrane, neodolabellane, cespitularane, and verticillane skeleton [9–21]. Few numbers of sesquiterpenes were also reported [23]. The previously isolated diterpenoids, sesquiterpenoids and steroids from *Cespitularia* species are summarized in Tables 1–3.

Diterpenoids

Marine invertebrates are a rich source of structurally unique terpenoids with interesting biological activities. The biological activity of some isolated *Cespitularia* diterpenoids has demonstrated remarkable cytotoxicity against various cancer cell lines. Several chemical studies on the *Cespitularia* species led to the isolation of a diverse array of diterpenoids as shown in Table 1, including alcyonolides, caryophyllanoids, cembranolides, cespitularanoids, dolabellanoids, norverticillanoids, verticillanoids, and xenicanoids.

Table 3 Steroids of *Cespitularia* species.

Source	Structure	Compd. Name
C. hypotentaculata [12,37]		**86**: 3β,11-dihydroxy-5β,6β-epoxy-9,11-secocholestan-9-one
		**87**: 3β,11-dihydroxy-5β,6β-epoxy-9,11-secogorgostan-9-one

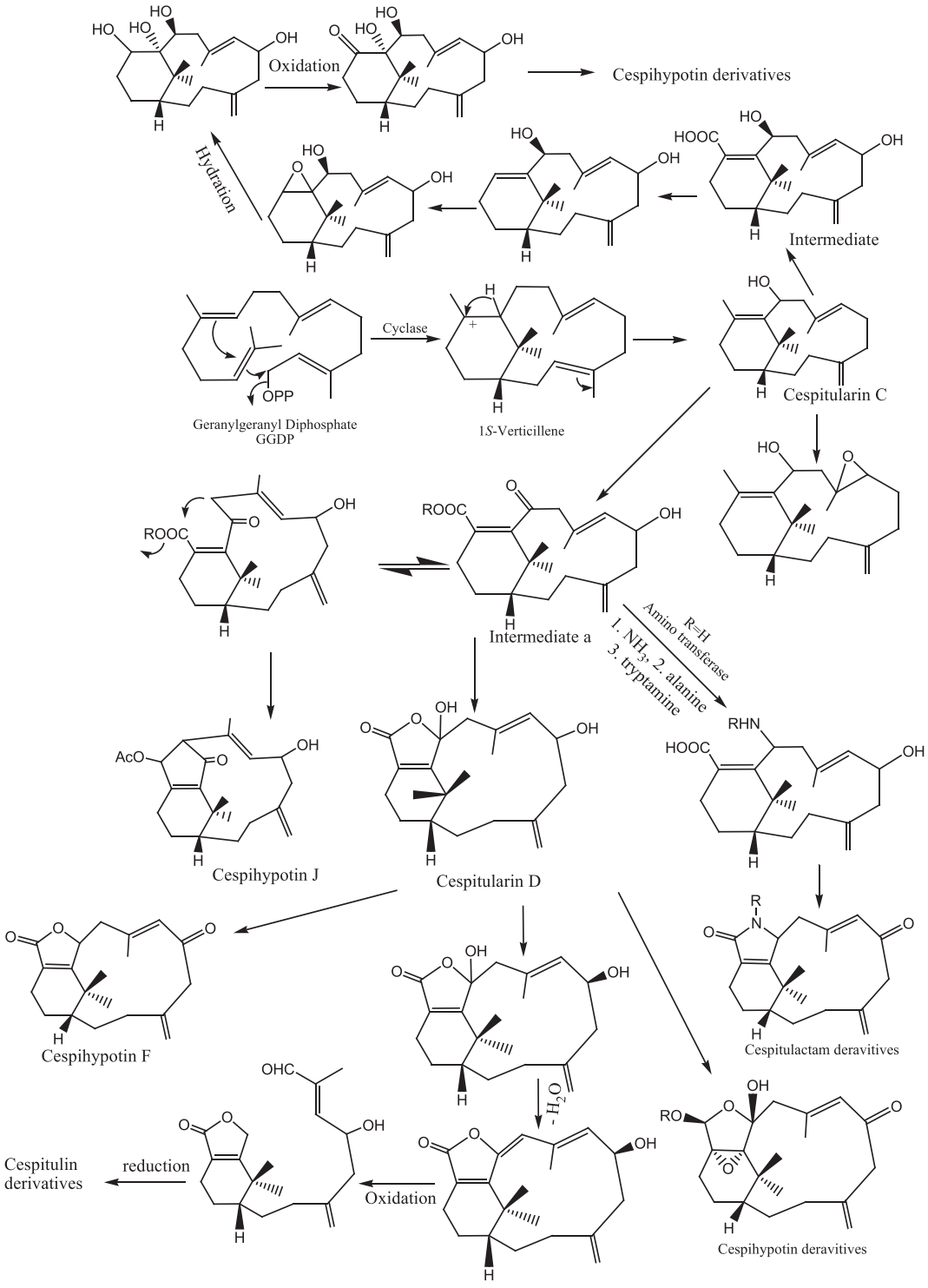


Fig. 2 Biogenetic pathways of *Cespitularia* diterpenoids.

Biogenetic pathways of Cespitularia diterpenoids

The *Cespitularia* species are characterized with a special type of diterpenoids such as cespitularia, cespihypotin, cespitulactam, cespitularin, and cespitulons. The biogenetic pathways of these diterpenoids were described in few reports [15,16]. The biogenetic pathways of *Cespitularia* diterpenoids, as shown in Fig. 2, were derived from the starting amino acid geranylgeranyl diphosphate (GGDP). The amino acid (GGDP) was enzymatically converted by cyclization to 1*S*-verticillene that might be the main precursor of all *Cespitularia* diterpenoids. Firstly, cespitularin C, a basic diterpenoid for biogenesis of *Cespitularia* diterpenoids, was synthesized from 1*S*-verticillene via biogenetically rearrangement. Then cespitularin

C was biogenetically rearranged to give the intermediate **a** that could be converted to different *Cespitularia* diterpenes such as cespitularin, cespihypotin and cespitulactams [16,19,20,26].

Sesquiterpenoids

A few reported sesquiterpenoids were identified from *Cespitularia* species that include sesquiterpenoids, N-containing sesquiterpenes (sesquiterpene lactams), and sesquiterpene lactones (Table 2). Cheng et al. [10] stated the biogenesis of the *Cespitularia* sesquiterpenoids starting by (*E,E*)-Farnesyl cation [10].

Steroids

Soft corals belonging to family Xeniidae have been shown to be an extraordinarily rich source of sterols displaying unconventional nuclear structures and side chains, as well as unusual oxygenation patterns of the A-D rings such as petrosterols [31], gorgosterols [32], cholesterols, ergosterols [33,34] and secosteroids [35–37]. The first marine secosteroid to be described was encountered in the gorgonian *Pseudopterogorgia americana* in 1972 [36]. *Cespitularia* species are not rich soft corals with steroids. Only two cytotoxic 9,11-secosteroids were isolated from *C. hypotentaculata* [11].

Conclusions

Cespitularia species (family Xeniidae) are interesting marine organisms as rich sources in novel and diverse chemical structures such as terpenoids and steroids. These species are characterized by special types of diterpenoids that may be named *Cespitularia* diterpenoids such as cespitulins, cespitularines, cespitulactams, cespitulactones and cespihypotins. As well as *Cespitularia* species are characterized by a very rare type of sesquiterpene lactams. Biologically, *Cespitularia* species produce novel secondary metabolites with very interesting biological activities especially anticancer activity.

Conflict of Interest

The authors have declare no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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