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Recent Researches of Bioactive Metabolites in Marine Organisms-associated Microorganisms

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Abstract Recent researches have shown that some compounds isolated from marine organisms have striking structural similarities with the metabolites from known microorganisms. It is inferred from the researches that the symbiotic or associated marine microorganisms may be the true sources of those compounds or at least involved in the biosynthesizing process. This view has been further evidenced by the researches for many sponges and sponge-associated microorganisms. Importantly, growing evidence has highlighted that the symbiotic or associated marine microorganisms live in the microenvironment within the hosts, and they also produce secondary metabolites which are new and original in structure and unique in activity. All these suggest that the microorganisms associated with marine organisms are the sources with very high potential to be new natural bioactive agents. This article reviews briefly the research advances in the study of new bioactive metabolites from marine organisms-associated microorganisms since 2000.

Key words marine microorganism; symbiont; bioactive; metabolite

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1 Introduction

Since the early 1960s, ocean has been considered as a new and untouched source of potentially useful compounds. The results from the researches on the organisms such as sponges, soft corals, algae, ascidians, bryozoans and mollusks, have demonstrated that marine organisms can produce unique secondary metabolites different from those found in terrestrial organisms (Murray *et al.*, 1999). In recent years, marine microorganisms have attracted increasing attention in the search for new pharmaceutical or agrochemical lead structures (Faulkner, 2001). Indeed, marine microorganisms have been shown to be able to produce a large number of bioactive substances. This might be due to their living conditions and functions in the ecosystem. Many marine microorganisms are symbiotic with marine sponges and other invertebrates. Their secondary metabolites might contribute to protecting their hosts by chemically mediated defense mechanisms from dangers like predation. In some cases, there are evidences that symbiotic or associated marine microorganisms are the true sources of bioactive metabolites originally isolated from their hosts. Thus, the microorganisms associated with marine plants and animals are expected to be potential sources for new natural bioactive agents. The purpose of this article is to review the studies on the secondary metabolites and biological activities of bacteria and fungus which have been isolated from marine organisms.

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2 Bioactive Metabolites from Marine Organisms-associated Bacteria

Recent researches have demonstrated that bacteria isolated from marine organisms have greater antitumor activities than those isolated from sediments. Below is a summary of these researches.

Lomaiviticins A and B (1 and 2 in Fig.1) are two potent antitumor antibiotics with the structure of dimeric diazobenzo-fluorene glycoside. They were isolated from an actinomycete strain identified as a new species of the genus *Micromonospora* on the basis of its morphological characteristic and 16S DNA sequence, *Micromonospora lomaivitiensis* (He *et al.*, 2001). This actinomycete strain was isolated from the inner core of the host ascidian. Lomaiviticins A and B were demonstrated potent DNA damaging agents by BIA, both with a minimum induction concentration less than or

equal to 0.1 ng per spot. The more abundant lomaiviticin A was also tested against a number of cancer cell lines and showed cytotoxicity with IC_{50} values ranging from 0.01 to 98 ng mL^{-1}. Lomaiviticins A and B were also potent antibiotics against Gram-positive bacteria, *Staphylococcus aureus* and *Enterococcus faecium* with MIC values from 6 to 25 ng per spot in a plate assay. The discovery of the potent antitumor lomaiviticins provides an example of a marine-invertebrate-associated microorganism as an excellent resource for new bioactive natural products.

Three new cytotoxic 3, 6-disubstituted indoles (3–5 in Fig.1) were isolated from the mycelium of a strain identified as *Streptomyces* sp. (BL-49-58-005), which was obtained from a Mexican marine invertebrate (Jose *et al.*, 2003). Cytotoxic assays for these compounds were performed against 14 different tumor cell lines. Compound (3) showed significant cytotoxicity against K-562 (leukemia) with a GI_{50} value of 8.46 μmol L^{-1}. Aldoxime mixture (4) showed activity with GI_{50} values within 1 micromolar range against LN-caP (prostate cancer), HMEC1 (endothelial cancer), K-562 (leukemia), PANC1 (pancreas cancer), and LOVO and LOVO-DOX (colon cancer). It showed slightly higher values against the rest of the tumor cell lines, without any particular specificity. Bioassays performed with nitrile (5) showed no activity.

An acidic polysaccharide isolated from *Pseudoalteromonas distincta* from a marine sponge contained two unusual acidic amino sugars, 2-acetamido-2- deoxy-D-galacturonic acid and 5-acetamido-3, 5, 7, 9-tetradeoxy-7-formamido-L-*glycero*-L-*manno*-nonulosonic acid (Muldoon and Shashkov, 2001). However, the bioactivities of these compounds were not reported.

The alkaloid Harman (6 in Fig.1), previously obtained from some marine invertebrates, was identified as the antibiotic substance of the tunicate-associated bacterium, *Enterococcus faecium* (Assila and Bourguet-Kondracki, 2003). It exhibited the antibacterial activity (MIC, 0.017 mmol L^{-1}) against the ichthyopathogenic strain *Vibrio anguillarum*.

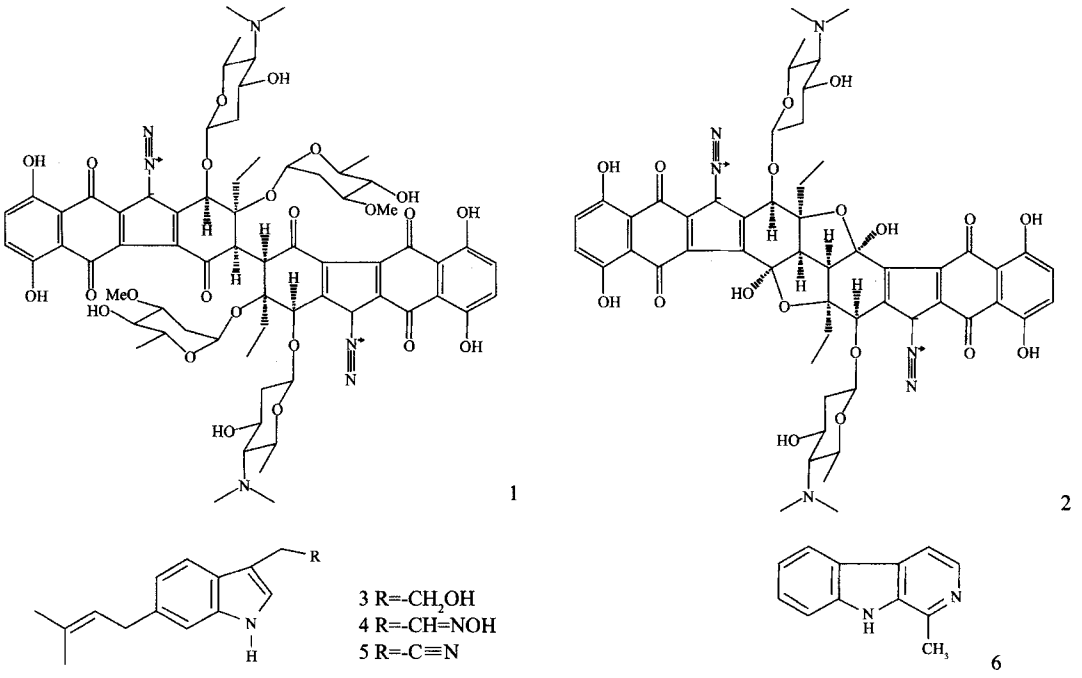


Fig.1 Compounds isolated from marine organisms-associated bacteria

3 Bioactive Metabolites from Marine Organisms-associated Fungi

3.1 Bioactive Metabolites from Fungi Isolated from Sponges

Fungi obtained from marine invertebrates, especially sponges, have yielded novel metabolites with potent antibacterial, anticancer or other bioactivities.

Xestodecalactones A, B and C (7–9 in Fig.2) were purified from the fungus *Penicillium cf. montanense* isolated from marine sponge *Xestospongia exigua* (Edrada, 2002). Compound 8 was found to be active against the yeast *Candida albicans*. In the agar diffusion assay, it caused inhibition zones of 25, 12 and 7 mm at concentrations of 100, 50 and 20 μmol L^{-1} respectively. All the isolated compounds were found to be inactive toward the bacteria *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli*. According to the similar lactones from microorganisms, the xestodecalactones should be formed via an acetogenic pathway, as evidenced from the periodically arranged oxygen atoms, which should be the remainders of a polyketide precursor. From *X. exigua* collected in In-

donesia, the fungus *Aspergillus versicolor* was isolated. Seven new angular tricyclic chromone derivatives (10–16 in Fig.2) were obtained from the culture of the fungus (Lin *et al.*, 2003). Compound 10 displayed only moderate antibacterial activity against *B. subtilis* and was inactive against *E. coli* and *S. cerevisiae*.

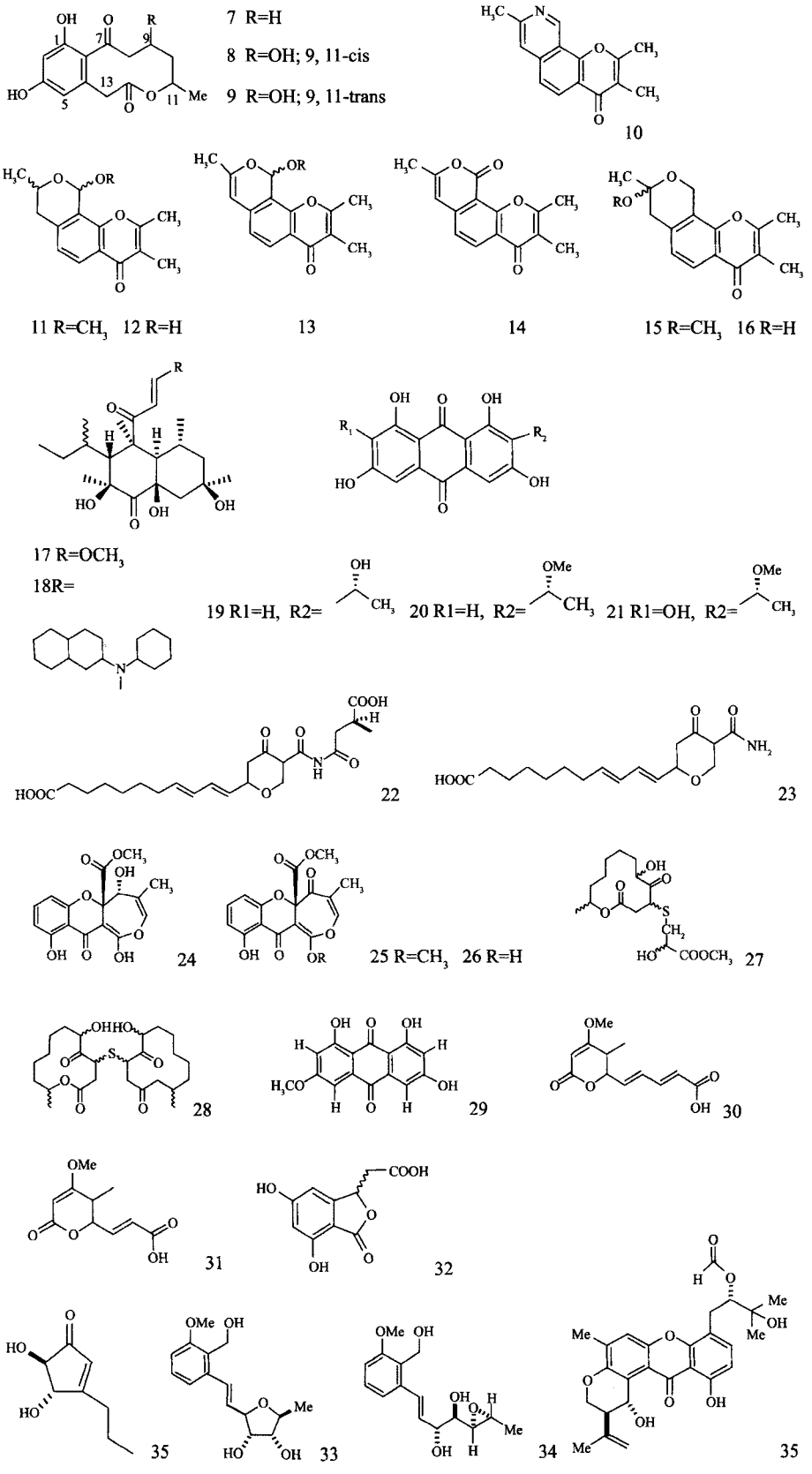


Fig.2 Compounds isolated from sponges-associated fungi

An undescribed fungus of the genus *Microsphaeropsis*, isolated from the Mediterranean sponge *Aplysina aerophoba*, produced two new betaenone derivatives (17 and 18 in Fig.2) and three new 1, 3, 6, 8-tetrahydroxyanthra-quinone congeners (19–21 in Fig.2) (Brauers *et al.*, 2000). Moreover, it was shown that compounds 17, 19, 20 and 21 are inhibitors of PKC-, CDK4- and EGF receptor tyrosine kinases. The range of the IC_{50} values was from 18.5 to 54.0 μmol L^{-1}.

Two new metabolites, microsphaerones A and B (22 and 23 in Fig.2), were identified from the acetic ether extract of the culture of an undescribed fungus of the genus *Microsphaeropsis*, which was isolated from the Mediterranean sponge *Aplysina aerophoba* (Wang *et al.*, 2002). Both compounds, 22 and 23, exhibited no significant antiproliferative activity against HL-60 and NB-4 cell lines. When tested against larvae of polyphageous pest insect *Spodoptera littoralis* and brine shrimp, *Artemia salina*, both compounds displayed no or only moderate activity.

Chemical investigations were conducted for a *Penicillium brocae* obtained from a tissue sample of a Fijian sponge *Zyzyya* sp. The results indicated that the extract yielded three novel cytotoxic polyketides, brocaenols A-C (24–26 in Fig.2) (Bugni *et al.*, 2003 a, Bugni *et al.*, 2003 b). All the three compounds were tested in HCT-116 cell line with MTT assay and showed moderate cytotoxicity. The IC_{50} values for 24, 25, and 26 were 20, 50 and beyond 50 μgmL^{-1} respectively.

Two new macrolide metabolites, pandangolide (27 and 28 in Fig.2), were identified from the organic extract of *Cladosporium herbarum* isolated from marine sponge *Callyspongia aerizusa* (Jadulco *et al.*, 2001). The two compounds were inactive when tested against Gram-positive and Gram-negative bacteria.

One new anthraquinone (29 in Fig.2) was isolated from *Curvularia lunata*; two new R-pyrones (30 and 31 in Fig.2) and one new phthalide (32 in Fig.2) were obtained respectively from two strains of *Cladosporium herbarum* isolated from two sponges, *Aplysina aerophoba* and *Callyspongia aerizusa* (Jadulco *et al.*, 2002). Compound 29 was found active against *S. aureus*, *E. coli*, and *B. subtilis* but inactive against *C. albicans*. Compounds 30 and 31 showed activity against *Artemia salina*. Compound 30 gave mortality rates of 85% and 75% at 100 μg and 50 μg dose levels, respectively, while compound 31 gave 80% and 65% mortality rates at the two dose levels, respectively. However, compound 32 showed no activity in the test against *A. salina* and human leukemia cell line HL-60.

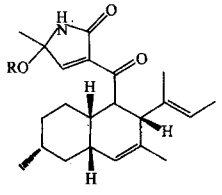
New compounds, varitriol, varioxirane, dihydroterrein and varixanthone (33–36 in Fig.2), were isolated from a marine-derived strain of fungus *Emericella variecolor* isolated from a sponge collected in the Venezuelan waters of the Caribbean Sea (Malmstrøm *et al.*, 2002). Varitriol (33) displayed increasing potency of activity toward selected renal, CNS, and breast cancer cell lines but was inactive against the remaining cell lines at a concentration of 10^{-4}mol L^{-1}. When tested in an antimicrobial assay, varitriol did not inhibit the growth of bacteria and yeast at 100 μg mL^{-1}. Varixanthone (36) was tested toward P388 (mouse lymphoma), A549 (human lung carcinoma) and HT29 (human colon carcinoma) cell lines and found inactive at 1 μg mL^{-1}. However, varixanthone displayed antimicrobial potency against Gram-positive and Gram-negative bacteria.

3.2 Bioactive Metabolites from the Fungi Associated with Other Marine Animals and Plants

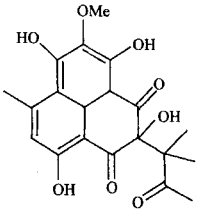
In addition to sponges, many other invertebrates such as mollusks, tunicates, crustacean and algae are also rich sources of fungus isolates.

From the green alga *Ulva* sp., the endophytic marine fungus *Ascochyta salicorniae* was isolated (Osterhage *et al.*, 2002). *A. salicorniae* was mass cultivated and found to produce the unprecedented and structurally unusual tetramic acid containing metabolites ascosalipyrrolidinones A, B (37 a and 37 b in Fig.3). Additionally, a new natural product ascosalipyrone (38 in Fig.3) and many known metabolites were obtained. Ascosalipyrrolidinone A (37 a) had antiplasmodial activity toward *Plasmodium falciparum* strains K1 and NF 54, antimicrobial activity and inhibiting activity toward tyrosine kinase p56lck.

Two phenalenone-skeleton-based compounds, sculezonone-A (SCUL-A) and sculezonone-B (SCUL-B) (39 and 40 in Fig.3), were purified from a broth of the fungus *Penicillium* sp. isolated from Okinawa marine bivalve *Mytilus coruscus* (Perpelescu *et al.*, 2002). Both compounds inhibited bovine DNA polymerases α and γ and moderately affected the activity of DNA polymerase ε. However, they had almost no effect on HIV-reverse transcriptase and *E. coli* DNA polymerase I Klenow fragment. Most notably, SCUL-A inhibited pol β (IC_{50} = 17 μmol L^{-1}), while SCUL-B had only a weak influence upon this polymerase (IC_{50} = 90 μmol L^{-1}). Kinetic studies also showed that SCUL-A or SCUL-B could inhibit DNA polymerases α and γ, and the inhibitive action was competitive with respect to dTTP substrate and noncompetitive with the template-primer. Whereas polymerases α inhibition by SCUL-B was competitive with respect to dATP, the inhibition by SCUL-A was found to be a mixed type with dATP substrate. The calculated *Ki* values of SCUL-B were 1.8 and 6.8 μmol L^{-1} for DNA polymerases α and ε, respectively. The *Ki* of DNA polymerase γ for SCUL-Awas 12 μmol L^{-1} and that for DNA polymerase α was 16 μmol L^{-1}. Therefore, removal of the OH-group at C12 enhanced the inhibition of DNA polymerase β.



37 a R=$CH_2CH_2CH_2CH_3$
37 b R=CH_3



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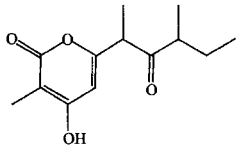

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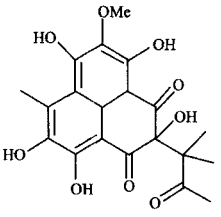

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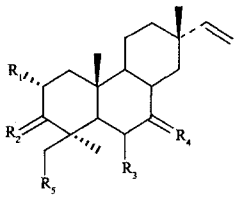
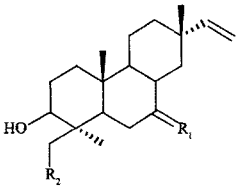
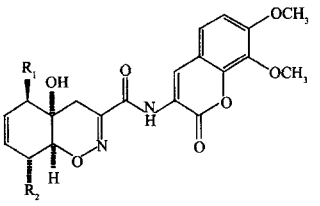


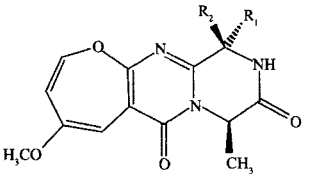
41 R1=OH, R2=H, β -OH, R3=H, R4=O, R5= β -D-altropyranosyl-
42 R1=OH, R2=H, β -OH, R3= β -OH, R4=H,H, R5= β -D-altropyranosyl-



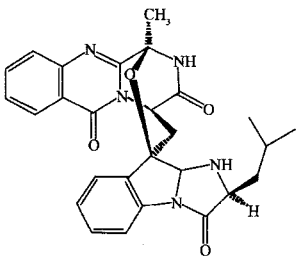
43 R1=H, α -OH, R2= β -D-altropyranosyl-
44 R1=O, R2= β -D-altropyranosyl-
45 R1=H, R2= β -D-mannopyranosyl-



46 R1=R2=OH
47 R1=Cl, R2=OH



48 R1=$CH(CH_3)CH_2CH_3$, R2=OH
49 R1=OH, R2=$CH(CH_3)CH_2CH_3$
50 R1=$CH_2CH(CH_3)_2$, R2=OCH_3



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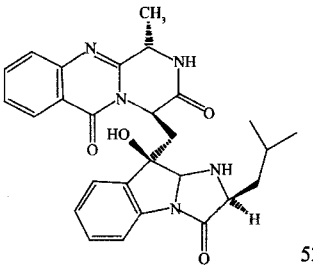

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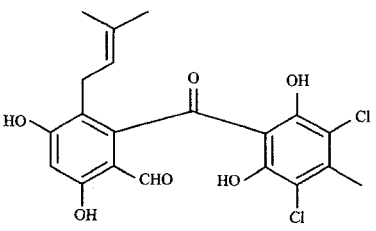

53

Fig.3 Compounds isolated from fungi associated with marine animals and plants

Two new diterpenic altrosides, virescenosides M and N (41 and 42 in Fig.3), have been isolated from a marine strain of *Acremonium striatisporum* KMM 4401 associated with the holothurian *Eupentacta fraudatrix* (Afiyatullov *et al.*, 2000). In addition to the new compounds, three other known diterpenic altrosides, virescenosides A, B and C, have also been isolated. Virescenosides A, B, C, M and N showed cytotoxic effects on developing eggs of sea urchin *Strongylocentrotus intermedius* with MIC_{50} range from 2.7 to 20 $\mu mol\,L^{-1}$, and their activities decreased in the order of C, M, B, A and N. It was shown that these glycosides exhibited cytotoxic action against tumor cells of Ehrlich carcinoma (IC_{50} range from 10 to 100 $\mu mol\,L^{-1}$) *in vitro*. Further investigations for metabolites of this fungal strain *Acremonium striatisporum* KMM 4401 led to the isolation of three new cytotoxic glycosides, virescenosides O, P and Q (43–45 in Fig.3) (Afiyatullov *et al.*, 2002). It was shown that virescenosides O, P and Q exhibited cytotoxic action against tumor cells of Ehrlich carcinoma with IC_{50} range from 20 to 100 $\mu mol\,L^{-1}$ *in vitro*. Virescenoside P showed cytotoxic effects on the developing eggs of the sea urchin *Strongylocentrotus intermedius* (MIC_{50} equal to 5.0 $\mu mol\,L^{-1}$).

Trichodermamides A and B (46 and 47 in Fig.3), two modified dipeptides, have been isolated from the cultures of marine fungus *Trichoderma virens* (Garo *et al.*, 2003). The fungal strains were obtained from a sample of marine ascidian *Didemnum molle* and green alga *Halimeda* sp. respectively. Compound 47 displayed significant cytotoxicity against HCT-116 human colon carcinoma with an IC_{50} of 0.32 $\mu g\,mL^{-1}$ *in vitro*. This metabolite also exhibited moderate antimicrobial activities against amphoterocinresistant *C. albicans*, methacillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* with MIC values of about 15 $\mu g\,mL^{-1}$. Compound 46 was completely inactive in all these bioassays, suggesting that the chlorine atom was an essential part of pharmacophore.

Three new oxepin-containing metabolites, named oxepinamides A-C (48–50 in Fig.3), as well as two new members of the fumiquinazoline class of compounds, fumiquinazolines H and I (51 and 52 in Fig.3), were purified from a fungus of genus *Acremonium* isolated from the surface of Caribbean tunicate *Ecteinascidia turbinate* collected in Bahamas (Belofsky *et al.*, 2000). Compounds 51 and 52 were found to have weak antifungal activities toward *Candida albicans* in broth microdilution assay and exhibit the activities in a dilution of 0.5 $mg\,mL^{-1}$ (1 mm). Oxepinamide A (48) showed good topical anti-inflammatory activity in the resiniferatoxin (RTX)-induced mouse ear edema assay, a test for neurogenic inflammation. Oxepinamide A exhibited 82% inhibition of edema (induced by RTX at 0.1 μg per ear) at the standard testing dose of 50 μg per ear.

Pestalone (53 in Fig.3), a new chlorinated benzophenone antibiotic, was produced by cultured marine fungus (Cueto *et al.*, 2001). The fungus, isolated from the surface of brown alga *Rosenvingea* sp. collected in Bahamas Islands, was identified as an undescribed member of the genus *Pestalotia*. Compound 53 was found to exhibit moderate cytotoxicity *in vitro* in the National Cancer Institute's human tumor cell line screen (mean $GI_{50} = 6.0\,\mu mL^{-1}$). More importantly, it showed potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* ($MIC = 37\,ng\,mL^{-1}$) and vancomycin-resistant *Enterococcus faecium* ($MIC = 78\,ng\,mL^{-1}$).

4 Conclusion

Marine organism-associated microorganisms produce rich secondary metabolites with chemical diversities. These metabolites include alkaloids, glycosides, diones, peptides, polyketides, macrolides, unusual aroma rings and so on. Many of them show antibacterial or antitumor activities. It is well known that the ocean is a source of a large group of structurally unique natural products that are mainly accumulated in invertebrates such as sponges, tunicates, bryozoans and molluscs. Some of these compounds show pronounced pharmacological activities and are interesting candidates for new drugs primarily in the area of cancer treatment. Numerous natural products from marine invertebrates show striking structural similarities to known metabolites of microbial origin, suggesting that microorganisms are at least involved in their biosynthesis or are in fact the true sources of these respective metabolites. This observation has been corroborated by several studies on natural products from sponges, which prove that these compounds are localized in symbiotic microorganisms. However, it is a challenge to develop and apply the novel bioactive natural products because it is very difficult to collect the marine sample, the content of active compounds in samples is extremely low, and the chemical structures of these active compounds are too complex to be synthesized. A large number of novel bioactive products are to be explored and research on the active components found in marine microorganisms has become a hot area of marine natural product. In particular, fungi obtained from marine invertebrates have yielded novel metabolites with potent antibacterial and anticancer activities.

The authors have been working on novel bioactive natural products from marine microorganisms since 2001. In our continuous search for natural products with potential anticancer activity, extracts of microorganisms associated with marine plants and animals are screened for novel cell cycle inhibitors and apoptosis inducers by using mouse *cdc*2 mutant cell lines, ts-FT210. Several strains of fungi and actinomycetes showed inhibitory activities and apoptosis inducers

against the cell cycle of tsFT210. Now, bioassay-guided fractionation of the ethyl esters extract of isolated strains is under investigation in our laboratory.

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