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Antifungal and antiviral products of marine organisms

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Abstract

Marine organisms including bacteria, fungi, algae, sponges, echinoderms, mollusks, and cephalochordates produce a variety of products with antifungal activity including bacterial chitinases, lipopeptides, and lactones; fungal (–)-sclerotiorin and peptaibols, purpurides B and C, berkedrimane B and purpuride; algal gambieric acids A and B, phlorotannins; 3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol, spongistatin 1, eurysterols A and B, nortetillapyrone, bromotyrosine alkaloids, bis-indole alkaloid, ageloxime B and (–)-ageloxime D, haliscosamine, hamigeran G, hippolachnin A from sponges; echinoderm triterpene glycosides and alkene sulfates; molluscan kahalalide F and a 1485-Da peptide with a sequence SRSELIVHQR; and cephalochordate chitotriosidase and a 5026.9-Da antifungal peptide. The antiviral compounds from marine organisms include bacterial polysaccharide and furan-2-yl acetate; fungal macrolide, purpurester A, purpurquinone B, isoindolone derivatives, alterporriol Q, tetrahydroaltersolanol C and asperterrestide A, algal diterpenes, xylogalactofucan, alginic acid, glycolipid sulfoquinovosyldiacylglycerol, sulfated polysaccharide p-KG03, meroditerpenoids, methyl ester derivative of vatomaric acid, lectins, polysaccharides, tannins, cnidarian zoanthoxanthin alkaloids, norditerpenoid and capilloquinol; crustacean antilipopopolysaccharide factors, molluscan hemocyanin; echinoderm triterpenoid glycosides; tunicate didemnin B, tamandarins A and B and; tilapia hepcidin 1–5 (TH 1–5), seabream SauMx1, SauMx2, and SauMx3, and orange-spotted grouper β -defensin. Although the mechanisms of antifungal and antiviral activities of only some of the afore-mentioned compounds have been elucidated, the possibility to use those known to have distinctly different mechanisms, good bioavailability, and minimal toxicity in combination therapy remains to be investigated. It is also worthwhile to test the marine antimicrobials for possible synergism with existing drugs. The prospects of employing them in clinical practice are promising in view of the wealth of these compounds from marine organisms. The compounds may also be used in agriculture and the food industry.

Keywords

Antifungal; Antiviral; Products; Marine organisms

Introduction

Fungi and viruses produce devastating damage to humans, animals, and plants, leading to serious diseases. Due to the use of invasive medical procedures, immunosuppressives, and frequent application of wide-spectrum antibiotics, infections caused by pathogenic *Candida* spp. is on the rise. The pathogenic yeast *Candida albicans* causes nosocomial infections with high mortality. *C. albicans* forms drug-resistant biofilms on mucosal surfaces and implanted medical devices (Taff et al. 2013). Hitherto, there are several major antifungal drugs targeting *C. albicans* as follows: pyrimidines like 5-fluorocytosine, polyenes including amphotericin B and nystatin, azoles such as fluconazole, and echinocandins such as caspofungin. Due to drug resistance encountered during treatments with all four types of drugs and the reported side effects, a search for more potential antifungal agents is warranted (Bondaryk et al. 2013; Geronikaki et al. 2013; Hamill 2013; Silva et al. 2014). Lung infections caused by non-*Aspergillus* molds are increasing in specific populations, and new problems of susceptibility and resistance have emerged (Paiva and Pereira 2013). The systemic mycosis cryptococcosis is a prevalent infection usually involving drug-resistant

biofilms in human immunodeficiency virus-positive individuals (Gullo et al. 2013). Similarly, the development of viral resistance to antiviral drugs and drug toxicity are problems encountered in antiviral therapy. Drug resistance of herpes simplex virus, HIV-1, HIV-2, and human cytomegalovirus has been reported (Kukhanova 2012; Andrei and Snoeck 2013; Megens and Laethem 2013; Menéndez-Arias and Alvarez 2013; Komatsu et al. 2014). In view of the development of resistance by microbial pathogens to existing antifungal and antiviral drugs, numerous investigators have put in considerable time and energy to search for new drugs in order to circumvent the problem. It is well documented that humans, animals, plants, fungi, and bacteria produce substances of peptidic and/or nonpeptidic nature to protect themselves against the various pathogens. Antifungal and antiviral biomolecules with disparate chemical natures including peptides, terpenoids, diacylglycerols, steroids, polysaccharides, and others have been reported from a diversity of marine organisms such as bacteria, fungi, seaweeds, corals, and sponges (Fan et al. 2013; Gong et al. 2013; He et al. 2013; Manivasagan et al. 2013; Plouguerné et al. 2013; Tajima et al. 2013; Wang et al. 2012). Search for marine products with antifungal and antiviral activities and thus potential therapeutic value is a worthwhile undertaking for many investigators. The intent of the present article is to review biomolecules of marine origin with a defense action against pathogenic fungi and viruses.

Antifungal products

Antifungal activity of bacterial products against yeast

The 34 kDa chitinase from marine *Streptomyces* sp. DA11 associated with South China sponge *Craniella australiensis* belongs to ChiC type with 80 % homology to chitinase C precursor from *Streptomyces peucetius*. The chitinase activity may contribute to chitin degradation and antifungal defense. The chitinase manifested antifungal activity against *C. albicans*. The optimal conditions for the chitinase activity were pH 8.0, 50 °C, and a salinity of 45 g‰ psu, respectively, which may contribute to a unique application of this chitinase originating from a marine microbe compared with terrestrial chitinases. The chitinase activity was augmented in the presence of Mn^{2+} , Mg^{2+} , and Cu^{2+} ions, but potently suppressed by Ba^{2+} and Fe^{2+} ions, and significantly inhibited by ethyleneglycoltetraacetic acid, ethylenediaminetetraacetic acid, urea, and SDS. An elevated V_{max} and a lower K_m were obtained using colloidal chitin as substrates in lieu of powdered chitin (Han et al. 2009b).

Antimycins A₁₉ and A₂₀ (antimycin antibiotics), which inhibited *C. albicans* with an MIC of about 5–10 µg/ml, were isolated from a culture broth of marine actinomycete *Streptomyces antibioticus* H74-18 (Xu et al. 2011a).

Surfactin is a lipopeptide biosurfactant with broad-spectrum antimicrobial and antiviral activity. C(15)-surfactin from *Bacillus amyloliquefaciens* (6.25 µg/ml) synergized with the antifungal drug ketoconazole (0.004 µg/ml) in antifungal effect toward *C. albicans* SC5314. Optimum production of C(15)-surfactin (134.2 mg/l) with a 1.52-fold increase was achieved by employing the response surface methodology in shaker flask cultivation in medium (Liu et al. 2012b).

Bahamaolides A and B (1 and 2), two new 36-membered macrocyclic lactones, were isolated from the culture of the marine actinomycete *Streptomyces* sp. derived from a sediment sample collected at North Cat Cay in the Bahamas. The planar structures of 1 and 2, bearing a hexaenone and nine consecutive skipped hydroxyl groups, were determined spectroscopically. Bahamaolide A inhibited *C. albicans* isocitrate lyase and manifested suppressive activity against a number of fungal pathogens (Kim et al. 2012a).

A secondary metabolite, *N*-(2-hydroxyphenyl)-2-phenazinamine has been isolated from the saline culture broth of the marine actinomycete *Nocardia dassonvillei* strain BM-17 isolated from a sediment sample collected in the Arctic Ocean, following incubation at 28 °C in soy bean media for 7 days. The metabolite demonstrated antifungal activity against *C. albicans*, with an MIC of 64 µg/ml and potent cytotoxicity against A549, COC1, HCT-116, and HepG2 cells (Gao et al. 2012).

The bacterium *B. amyloliquefaciens* anti-CA isolated from a mangrove system manifested fungicidal activity against a clinical strain of *C. albicans*. The main bioactive substance was a cyclic lipopeptide containing a heptapeptide, AspLeuLeuValValGluLeu, and a 3-OH fatty acid with 15 carbon atoms. The lipopeptide also killed other yeast strains including *Candida tropicalis*, *Metschnikowia bicuspidate*, *Saccharomyces cerevisiae*, and *Yarrowia lipolytica* (Song et al. 2013).

Antifungal activity of bacterial products against other fungi

The 34 kDa chitinase from marine *Streptomyces* sp. DA11 associated with South China sponge *C. australiensis* exhibited antifungal activity against *Aspergillus niger* (Han et al. 2009b).

Two new cyclic lipopeptides maribasins A and B from the fermentation broth of the marine microorganism *Bacillus marinus* B-9987 isolated from *Suaeda salsa* in Bohai coastline of China displayed the structures cyclo (D-Pro-L-Gln-L-Asn-L-Ser-D-Asn¹-D-Tyr-D-Asn²-D-β-aminoisopentadecanoic acid) and cyclo (D-Pro-L-Gln-L-Asn-L-Ser-D-Asn¹-D-Tyr-D-Asn²-D-β-aminoanteisopentadecanoic acid), respectively. The lipopeptides demonstrated activity against a spectrum of phytopathogenic fungi (Zhang et al. 2010).

From the fermentation broth of *Bacillus mojavensis* B0621A, three lipopeptides designated as mojavensin A, iso-C16 fengycin B, and anteiso-C17 fengycin B, respectively, were purified. Mojavensin A was characterized by the possession of a peptide backbone of L-Asn(1), D-Tyr(2), D-Asn(3), L-Gln(4), L-Pro(5), D-Asn(6), L-Asn(7), and an anteiso-type of the saturated β-fatty acid side chain. The three lipopeptides inhibited a variety of phytopathogenic fungi (Ma et al. 2012).

Preclinical evaluation and molecular docking for 4-phenyl-1-naphthyl phenyl acetamide (4P1NPA), isolated from marine *Streptomyces* sp. DPTB16, against cytochrome P450 51 (CYP 51) were executed with the help of in silico pharmacology and docking tools. The results, which disclosed the drug likeliness of 4P1NPA and satisfactory interaction of 4P1NPA with CYP 51, will facilitate the design of 4P1NPA as an antifungal drug to combat the emerging fungal resistance (Saha et al. 2012).

Schulz et al. (2010) discovered that volatile compounds released from marine bacteria possessed antiproliferative activity against medically important microorganisms like *Aspergillus fumigatus* and *Botrytis cinerea*. These compounds include octanoic acid, 3-methyl-*N*-(2-phenylethyl)pentanamide, γ -butyrolactones, (*Z*)-15-methylhexadec-12-en-2-one, *S*-methyl benzothioate, and furfuryl isovalerate.

Antifungal activity of fungal products against yeasts

Purpurides B and C, two new sesquiterpene alcohol esters generated from a drimane-type sesquiterpenoid lactone and an amino acid, together with two known analogs, berkedrimane B and purpuride, were isolated from the aciduric fungus *Penicillium purpurogenum* JS03-21. All of them had modest antifungal activities against *C. albicans* (MIC values=1.2–3.3 μ M) (Wang et al. 2013).

(–)-Sclerotiorin from the fermented broth of an unidentified marine fungus (98F134) exerted an antifungal action against *S. cerevisiae*, with IC₅₀ values below 20 μ g/ml (Bao et al. 2010).

Antifungal activity of fungal products against other fungi

(–)-Sclerotiorin exhibited inhibitory activity against a variety of fungi including *Alternaria longipes*, *A. fumigatus*, *Fusarium culmorum*, *Fusarium nivale*, *Piricularia oryzae*, and *Verticillium albo-atrum*, with IC₅₀ values below 20 μ g/ml (Bao et al. 2010).

Peptaibols are a large family of antimicrobial peptides produced by *Trichoderma* spp. Trichokonin VI, a peptaibol from *Trichoderma pseudokoningii* SMF2, induced metacaspase-independent apoptosis in fungal phytopathogens such as *Fusarium oxysporum* as evidenced by externalization of phosphatidylserine, generation of reactive oxygen species, and nuclear DNA fragmentation. Trichokonin VI elicited a cellular accumulation of cytoplasmic vacuoles and loss of the mitochondrial transmembrane potential (Shi et al. 2012).

Pestalone first obtained from fermentation of a marine fungus together with a marine bacterium possessed a reported MIC of 37 ng/ml against methicillin-resistant *Staphylococcus aureus* which disagreed with the value of 3–10 μ g/ml for synthetic pestalone reported by Augner et al. (2013). Synthetic pestalone derivatives including pestalachloride A and other isoindolinones (produced from pestalone by reaction with amines) were not more potent than pestalone in activity against methicillin-resistant *S. aureus* and phytopathogenic fungi like *Alternaria mali*, *Septoria tritici*, *Pyrenophora teres*, and *F. culmorum*. The variations in the data in the literature regarding the antibiotic activity of pestalone was attributed to the different sensitivities of the clinical isolates used and the production of a highly active pestalone derivative due to the reactivity of pestalone (Augner et al. 2013).

Antifungal activity of algal products against yeast

The bromophenol, 2,3,6-tribromo-4,5-dihydroxybenzyl methyl sulphoxide isolated from the ethanolic extract of the marine alga *Symphyocladia latiuscula* inhibited *C. albicans* with an MIC value of 37.5 μ g/ml (Xu et al. 2012).

Seaweed obtained from the Riacho Doce beach, Alagoas (Brazil) exhibited antifungal activity against the yeasts *C. albicans*, *Candida krusei*, *Candida guilliermondii*, and *Candida parapsilosis* (Guedes et al. 2012).

Phlorotannins from the brown seaweeds *Fucus spiralis*, *Cystoseira nodicaulis*, and *Cystoseira usneoides* exerted a fungistatic effect against yeast with *C. albicans* being the most susceptible (Lopes et al. 2013). The mechanism of action involved altering the ergosterol composition of the yeast cell membrane. Phlorotannins augmented the activity of mitochondria dehydrogenases and the incorporation of rhodamine 123 by yeast cells, and inhibited the dimorphic transition of *C. albicans*, leading to the formation of pseudohyphae with diminished ability to adhere to epithelial cells associated with a decline of *C. albicans* virulence and ability to attack host cells (Lopes et al. 2013).

Caulerprenylols A and B were prenylated paraxylenes from the green alga *Caulerpa racemosa*, the latter with a unique indane ring system. They demonstrated an antifungal action toward *Candida glabrata* (537) and *Cryptococcus neoformans* (32609) in vitro which were less potent than that of amphotericin B (Liu et al. 2013).

Antifungal activity of algal products against other fungi

Caulerprenylols A and B exhibited an antifungal activity toward *Trichophyton rubrum* (Cmccftla) in vitro with a potency lower than that of amphotericin B (Liu et al. 2013).

Seaweed obtained from the Riacho Doce beach, Alagoas (Brazil) exhibited antifungal activity against the dermatophytes *T. rubrum*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Microsporum canis*, and *Microsporum gypseum* (Guedes et al. 2012).

Phlorotannins from the brown seaweeds *F. spiralis*, *C. nodicaulis*, and *C. usneoides* also demonstrated a fungicidal action against dermatophytes with *Epidermophyton floccosum* and *T. rubrum*. The mechanism of action involved altering the ergosterol composition of the dermatophyte cell membrane. *F. spiralis* phlorotannin reduced the chitin level of dermatophyte cell wall (Lopes et al. 2013).

A convergent synthetic route to the CDEFG-ring system of gambieric acids A and B from a marine dinoflagellate *Gambierdiscus toxicus*, which are polycyclic ethers with potent antifungal activity against *A. niger*, has been developed (Sato and Sasaki 2005).

Callophycoic acids and bromophycolides from the red macroalga *Callophycus serratus* extracts exerted a growth inhibitory action on *Lindra thalassiae*, a marine pathogenic fungus (Lane et al. 2009).

Antifungal activity of sponge products against yeasts

The compound 3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol isolated from the marine sponge *Dysidea herbacea* inhibited *C. albicans* in vitro. The compound permeabilized the cell membrane, causing potassium ions to leak out from the cells. Two other bromodiphenyl ethers had similar activity (Sionov et al. 2005).

Spongistatin 1, a macrocyclic lactone polyether from the marine sponge *Hyrtios erecta*, exerted fungicidal activity toward the bulk of the 74 reference strains and clinical isolates tested, including strains showing resistance to fluconazole, flucytosine, or ketoconazole. Its antifungal activity was preserved when the pH was reduced and when human serum was present. Spongistatin 1 was more potent than amphotericin B in lowering renal infection burden in a mouse model of disseminated candidiasis, and in lessening the lung infection burden in a murine model of pulmonary cryptococcosis. Spongistatin 1 disrupted cytoplasmic and subsequently spindle microtubules in cryptococcal microtubules in a time- and dose-dependent way. An aberrant distribution of nuclei took place in budding cells, and cell division was inhibited, leading to cell arrest in a large-budded stage (Pettit et al. 2005).

Eurysterols A and B, steroidal sulfates from a marine sponge (*Euryspongia* sp.), inhibited amphotericin B-resistant and wild-type strains of *C. albicans* with MIC values of 15.6 and 62.5 µg/ml, respectively (Boonlarpradab and Faulkner 2007).

Plakortide F acid, a marine-derived polyketide endoperoxide, strongly inhibited the opportunistic fungal pathogens *C. albicans* and *C. neoformans*. *S. cerevisiae* was employed as a model organism to elucidate the mechanism of its antifungal action. Abundant evidence described in the following supported the contention that plakortide F acid mediates its antifungal activity via a unique mechanism involving perturbation of Ca²⁺ homeostasis. Plakortide F acid elicited a transcriptome response signifying a Ca²⁺ imbalance, modifying the expression of genes responsive to changes in cellular calcium levels. Mutants deficient in calcineurin and Ca²⁺ transporters, pumps (Pmr1 and Pmc1), and channels (Cch 1 and Mid 1) manifested heightened sensitivity to plakortide F acid. The calcineurin inhibitors cyclosporine and FK506 markedly elevated the activity of plakortide F acid in wild-type cells. Plakortide F acid induced transcription of a lacZ reporter gene activated by the calcineurin-dependent response element. A rise in intracellular calcium levels occurred in response to plakortide F acid (Xu et al. 2011b).

Crude methanolic extract of the Indian sponge *Clathria indica* and its aqueous, n-butanol and chloroform fractions expressed antifungal activity against *C. albicans* and *C. neoformans* (Ravichandran et al. 2011).

Aurantoxide K, a tetramic acid glycoside from a marine sponge belonging to the genus *Melophlus*, demonstrated antifungal activity against wild-type *C. albicans*, amphotericin-resistant *C. albicans*, and *C. neoformans* (Kumar et al. 2012).

Ageloxime B and (–)-ageloxime D from the marine sponge *Agelas mauritiana* possessed antifungal activity against *C. neoformans* (Yang et al. 2012).

Haliscosamine ((9Z)-2-amino-docos-9-ene-1,3,13,14-tetraol) is a sphingosine derivative from the Moroccan sea sponge *Haliclona viscosa* with antifungal activity against *Candida* and *Cryptococcus* sp. (El-Amraoui et al. 2013).

Terpenoid hamigeran G from the New Zealand marine sponge *Hamigera tarangaensis* displayed antifungal activity toward *S. cerevisiae*. Homozygous deletion profiling analysis disclosed Golgi apparatus as its potential target (Singh et al. 2013).

Hippolachnin A, a polyketide possessing an unprecedented carbon skeleton with a four-membered ring, was isolated from the South China Sea sponge *Hippospongia lachne*. Hippolachnin A demonstrated potent antifungal activity against *C. neoformans* with a MIC value of 0.41 μ M (Piao et al. 2013).

Two bromotyrosine alkaloids, ceratinadins A and B, isolated from an Okinawan marine sponge *Pseudoceratina* sp., demonstrated antifungal activity against *C. neoformans* and *C. albicans* (Kon et al. 2010).

Antifungal activity of sponge products against other fungi

3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol and two other bromodiphenyl ethers inhibited *Aspergillus* (mainly *A. fumigatus*) sp. in vitro by compromising the permeability of fungal cell membrane (Sionov et al. 2005).

Plakortide F acid inhibited *A. fumigatus* (Xu et al. 2011b).

Nortetillapyrone isolated from the ethyl acetate extract of the marine sponge *Haliclona cymaeformis* collected from the Gulf of Thailand evinced antifungal activity, especially toward the dermatophytes (Wattanadilok et al. 2007).

Synthetic analogs of the marine-derived phloeodictines with potent fungicidal activity against a diversity of fungal pathogens including drug-resistant strains have been prepared. The 6-hydroxy-2,3,4,6-tetrahydropyrrolo[1,2-a]pyrimidinium structural moiety with a C12 to C16 aliphatic side chain at C-6 is the antifungal pharmacophore and may serve as a new antifungal template for further lead optimization (Li et al. 2011b).

Aurantoside K demonstrated antifungal activity against *A. niger*, *Penicillium* sp., *Rhizopus sporangia*, and *Sordaria* sp. (Kumar et al. 2012).

Hippolachnin A demonstrated potent antifungal activity against the pathogenic fungi *T. rubrum* and *M. gypseum*, with a MIC value of 0.41 μ M for each fungus (Piao et al. 2013).

Antifungal activity of echinoderm products against yeasts

Two triterpene glycosides, namely impatienside A and bivittoside D, and two holostan-type triterpene glycosides, including marmoratoside A and 17 α -hydroxy impatienside A, were isolated from the sea cucumber *Bohadschia marmorata* Jaeger. They all manifested antifungal activity against *C. albicans*, *C. neoformans*, *C. tropicalis*, and *C. krusei* (Yuan et al. 2009).

Antifungal activity of echinoderm products against other fungi

Three antifungal triterpene glycosides, including scabraside A, echinoidea A, and holothurin A1, were isolated from *Holothuria scabra* (Han et al. 2009a).

(5Z)-dec-5-en-1-yl sulfate and (3E)-dec-3-en-1-yl sulfate, alkene sulfates isolated from the sea cucumber *Apostichopus japonicus*, demonstrated antifungal activity against *S. tritici* (La et al. 2012).

Antifungal activity of molluscan products against yeasts

Kahalalide F (KF) isolated from the Indopacific mollusc *Elysia rufescens* and its regioisomer isoKF are two new KF analogs, in which the primary amine hydrogen of ornithine in KF has been replaced with 4-fluoro-3-methylbenzyl and morpholin-4-yl-benzyl by reductive N-alkylation. These compounds displayed antifungal activities against *C. albicans* and *C. neoformans* both in vitro and in vivo (Shilabin and Hamann 2011).

Antifungal activity of molluscan products against other fungi

The extract of the marine mollusk *Melo melo* exhibited maximum antifungal activity against *Trichophyton mentagrophytes* and minimum activity against *Aspergillus flavus* (Kanagasabapathy et al. 2011).

A 1485-Da peptide with a sequence SRSELIVHQR, which impeded the development of *T. rubrum*, was isolated from a crude extract of the marine snail *Cenchritis muricatus*. It probably forms a single hydrophilic α -helix, and the probable cationic residue involved in antifungal action has been proposed (López-Abarrategui et al. 2012).

Roch et al. (2004) selected 3 nonapeptide fragments (B, D, and E) and two 19-residue fragments (P and Q) from the 19 fragments of Mediterranean mussel (*Mytilus galloprovincialis*) defensin previously reported by Romestand et al. (2003) for their antibacterial and antifungal activities. Fragments D and P were similar to fragments B and Q except for the presence of two additional positive charges. The peptides exhibited antifungal action on *F. oxysporum*. Peptide M (with one disulfide bond 25–33) demonstrated anti-*Candida* activity but peptide K (with one disulfide bond 21–38) and peptide Q (with two disulfide bonds) were devoid of similar activity. There was no activity toward human lymphomyeloid K563 cell line. Hence, the peptides exerted preferential toxicity toward prokaryotic cells and fungi (Roch et al. 2004).

Antifungal activity of cephalochord products against yeasts

The mammalian chitinase family 18 comprises two members, chitotriosidases and acidic chitinases. A chitotriosidase-like gene designated as BjChTl, which was composed of a signal peptide, a catalytic domain, a Ser/Thr-rich linker region, and a chitin-binding domain, was reported from the amphioxus *Branchiostoma japonicum*. BjChTl, the common ancestor of chitotriosidases and acidic chitinases, was expressed in the hind gut and hepatic caecum in a tissue-specific manner. Similar to human chitotriosidase, recombinant BjChTl is capable of binding to chitin particles, hydrolyzing the artificial chitin substrate 4-methylumbelliferyl- β -D-N,N',N''-triacetylchitotrioside, and impeding the growth of *C. albicans*. Recombinant BjChTl-CD devoid of the chitin-binding domain possessed partial chitin binding activity, but its enzymatic activity was nearly totally abolished. The chitin-binding domain is crucial to both enzymatic and antifungal activities of recombinant BjChTl. This is the first report of the presence of a chitotriosidase-like homolog with both chitinolytic activity and fungistatic activity in an invertebrate (Xu and Zhang 2012).

Antifungal activity of cephalochord products against other fungi

A 5026.9-Da antifungal peptide devoid of sequence resemblance to any antimicrobial peptide in the databank was identified by functional screening of a marine metagenomic library. The 108 bp ORF designated as mmgp1 was cloned and expressed in *Escherichia coli* BL21 (DE3) using a pET expression system. The recombinant peptide hampered the growth of *A. niger*. It predicted α -helical conformation with an extended coil containing an *N*-acetyl-D-glucosamine binding site which was demonstrated by circular dichroism spectroscopy in the presence of chitin or the membrane mimicking solvent, trifluoroethanol. Its chitin-binding activity was corroborated by fast-performance liquid chromatography (Pushpanathan et al. 2012).

Antiviral activity of bacterial products

Anti-herpes simplex virus activity of bacterial products

Subsequent to the administration of an extracellular polysaccharide from *Geobacillus thermodenitrificans*, HSV-2 replication in human peripheral blood mononuclear cells but not that in WISH cells was repressed. An upregulation of the concentrations of interferon-alpha, interferon-gamma, interleukin-12, interleukin-18, and tumor necrosis factor-alpha in human peripheral blood mononuclear cells was observed (Arena et al. 2009).

Anti-fish nodavirus activity of bacterial products

After exposure to furan-2-yl acetate ($C_6H_5O_3$) extracted from *Streptomyces* VITSDK1 spp., replication of the fish nodavirus-infected Sahul Indian Grouper eye cell lines was suppressed and the vial titer underwent a decline (Suthindhiran et al., 2011).

Antiviral activity of fungal products

Anti-herpes simplex virus activity of fungal products

A 12-membered macrolide from the ethyl acetate extract of the culture broth of Ascomycota fungal strain 222, (3R,11R), (4E,8E)-3-hydroxy-11-methyloxacyclododeca-4,8-diene-1,7-dione, inhibited HSV-1 with an IC_{50} value of 0.45 μ M (Shushni et al. 2011).

Anti-influenza activity of fungal products

Purpurester A, purpurquinone B, and TAN-931 from the ethyl acetate extract of an acid-tolerant fungus, *P. purpurogenum* JS03-21, exerted anti-influenza A (anti-H1N1) activity with IC_{50} values below 90 μ M (Wang et al. 2011).

The anti-H1N1 activities of products including isoindolone derivatives (emerimidine A and B and emeriphenolicins A and D), and the compounds aspernidine A and B, austin, austinol, dehydroaustin, and acetoxydehydroaustin, from the endophytic fungus *Emericella* sp. (HK-ZJ) isolated from the mangrove plant *Aegiceras corniculatum*, have been demonstrated with the cytopathic effect inhibition assay (Zhang et al. 2011).

Asperterrestide A, a new cyclic tetrapeptide with a rare 3- OH-N-CH₃-Phe residue, isolated from the fermentation broth of the marine-derived fungus *Aspergillus terreus* SCSG

AF0162, showed inhibitory effects on influenza virus strains H1N1 and H3N2 and cytotoxicity against U937 and MOLT4 human carcinoma cell lines (He et al. 2013).

A gyantrypine derivative and a pyrazinoquinazoline derivative, both of which are indole alkaloids, together with three alkaloids, derived from the culture of the mangrove-derived fungus *Cladosporium* sp. PJX-41, exhibited antiinfluenza virus A (H1N1) activity, with IC₅₀ values in the range of 82–89 µM (Peng et al. 2013).

Anti-respiratory syndrome virus and anti-porcine reproductive virus activities of fungal products

Alterporriol Q and tetrahydroaltersolanol C, isolated from the culture broth and mycelia of *Alternaria* sp. ZJ-2008003, which was collected from a soft coral (*Sarcophyton* sp.) from the South China Sea, expressed antiviral activity against the porcine reproductive virus and respiratory syndrome virus, with IC₅₀ values of 39 and 65 µM, respectively (Zheng et al. 2012).

Anti-tobacco mosaic virus activity of fungal products

Crude methanolic extracts of the two marine fungi, *Neosartorya fischeri* and *Penicillium oxalicum*, manifested inhibitory activity toward tobacco mosaic virus (Shen et al. 2009).

Antiviral activity of algal products

Anti-herpes simplex virus activity of algal products

Extracts of *Gigartina atropurpurea*, *Plocamium cartilagineum*, *Splachnidium rugosum*, and *Undaria pinnatifida* inhibited herpes simplex virus types 1 and 2 (HSV-1, HSV-2) when administered during the first hour of viral infection (Harden et al. 2009).

The diterpenes 8,10,18-trihydroxy-2,6-dolabelladiene from the Brazilian brown algae *Dictyota pfaffii* and (6 R)-6-hydroxydichotoma-4,14-diene-1,17-dial from *Dictyota menstrualis* suppressed HSV-1 infection in Vero cells with a noncytotoxic EC₅₀ value of 5.10 and 5.90 µM, respectively. There was no effect on HSV-1 adsorption and penetration. Nevertheless, some HSV-1 early proteins, including UL-8, UL-9, UL-12, UL-30, and RL-1 were downregulated (Abrantes et al. 2010).

The 26 kDa xylogalactofucan from the marine alga *Sphacelaria indica* contained (1→3)-linked L-fucopyranosyl and D-galactopyranosyl residues. The 21 kDa algin from *S. indica* owned 41 % guluronic and 59 % mannuronic acid residues. They and their chemically sulfated derivatives displayed IC₅₀ values of 0.6–10 µg/ml against HSV-1 and the inhibition was attributed to direct interaction of polysaccharides with viral particles (Bandyopadhyay et al. 2011).

The glycolipid sulfoquinovosyldiacylglycerol from the red alga *Osmundaria obtusiloba* collected from Southeastern Brazilian coast demonstrated antiviral activity with EC₅₀ values of 42 µg/ml HSV-1 and 12 µg/ml against HSV-2, respectively (de Souza et al. 2012).

Anti-influenza activity of algal products

The sulfated polysaccharide p-KG03 from the marine microalga, *Gyrodinium impudium*, possessed galactose units conjugated to uronic acid and sulfated groups. It obstructed infection by encephalomyocarditis virus and tumor cell proliferation. In a cytopathic effect reduction assay utilizing MDCK cells, p-KG03 demonstrated the 50 % effective concentration EC₅₀ values of 0.19– 0.48 µg/ml against influenza type A virus infection but not against influenza type B viruses. p-KG03 mainly targeted viral adsorption and internalization steps. Its antiviral activity of p-KG03 is attributed to interaction with viral particles (Kim et al. 2012b).

Anti-human metapneumovirus (HMPV) activity of algal products

The crude extract of the marine algae *Stypopodium zonale* and two meroditerpenoids (atomaric acid and epitaondiol) derived from it, and amethyl ester derivative of vatomeric acid exerted antiviral activity against HMPV replication with a selectivity index of 20.78, >56.81, 49.26, and 12.82, respectively (Mendes et al. 2011).

Anti-human herpesvirus-6 activity of algal products

The anti-human herpesvirus-6 (HHV-6) activity was tested in human T lymphoblasts, using HHV-6A (GS)-infected HSB-2 cells, HHV-6B (Z29)-infected MOLT-3 cells, and HHV-6B (HST)-infected MT4 cells. “Red marine algae” (an extract abundant in sulfated polysaccharides) was the only one among the 15 natural compounds examined that when added during viral adsorption, demonstrated strong antiviral activity (Naesens et al. 2006).

Anti-HIV-1 activity of algal products

Lectins, polysaccharides, and tannins with anti-HIV-1 activity have been isolated from marine macroalgae (Kim and Karadeniz 2011).

Anti-tobacco mosaic virus activity of algal products

The number of necrotic lesions on Xanthi-nc tobacco leaves was lessened by concurrent inoculation with tobacco mosaic virus and kappa/beta-carrageenan from the red marine alga *Tichocarpus crinitus*, compared to virus-inoculated leaves (Nagorskaia et al. 2008).

The methanolic extract of *Codium fragile*-possessed activities such as antiviral, antibacterial, antidegranulation in eosinophils, and anti-edema activities. The expression and secretion of lipopolysaccharide-induced inflammatory mediators was reduced after the administration of methanolic extract due to inhibition of NF-κB activity (Kang et al. 2012).

Fucoidan, a sulfated polysaccharide with a myriad of bioactivities encompassing antiviral, antibacterial, antitumor, and anticoagulant activities, is produced by many marine organisms, in particular the brown algae (Morya et al. 2012).

The structural chemistry of main sulfated polysaccharides synthesized by seaweeds including the galactans (e.g., agarans and carrageenans), ulvans, and fucans, as well as

recent findings on the antiviral activities of sulfated polysaccharides and their potential for therapeutic application, have been reviewed (Jiao et al. 2011).

Anti-Newcastle disease virus activity of algal products

Fucoidan from *Cladosiphon okamuranus* inhibits Newcastle disease virus in the Vero cell line at the early stages of infection (within the first hour postinfection). The inhibition of viral penetration was demonstrated. Syncytial decline (70 % inhibition) was observed when fucoidan was introduced prior to cleavage of the fusion protein, suggesting an interaction between fucoidan and the F0 protein. Ribavirin manifested a weaker antiviral potency than fucoidan (Elizondo-Gonzalez et al. 2012).

Anti-dengue virus activity of algal products

Some seaweed extracts (Chlorophyta: *Caulerpa racemosa*; Phaeophyta: *Canistrocarpus cervicornis*, *Padina gymnospora*; Rhodophyta: *Palisada perforate*) attenuated dengue virus infection probably by acting at an early stage of the cycle of infection, like binding or internalization (Koishi et al. 2012).

Antiviral activity of sponge products

Anti-hepatitis C virus activity of sponge products

The hepatitis C virus (HCV) is a causative agent of hepatitis C, which develops into cirrhosis and eventually liver cancer. The NS3 protein of the virus exhibited nucleoside triphosphatase (NTPase) and RNA helicase activities crucial to viral replication. NS3 is a target for antiviral drug development. Manoalide isolated from marine sponge extracts inhibited the RNA helicase and ATPase activities of NS3, with IC₅₀ values of 15 and 70 µM, respectively. Manoalide reduced the helicase, ATPase, and RNA binding activities of NS3 by targeting the helicase core domain conserved in both HCV NS3 and putative RNA helicase human DHX36/RHAU (Salam et al. 2012).

Psammaplin A, an inhibitor of NS3 helicase, which plays a role in hepatitis C virus replication, was identified from sponge extracts by high-throughput screening using a photo-induced electron transfer system. Psammaplin A inhibited hepatitis C virus by inhibiting helicase, RNA binding, and ATPase activities of NS3 (Salam et al. 2013).

Anti-herpes simplex virus activity of sponge products

An important antiviral lead of marine origin is nucleoside Ara-A (vidarabine) isolated from the sponge *Tethya crypta* which suppresses DNA polymerase activity and DNA synthesis in herpes, vaccinia, and varicella zoster virus (Sagar et al. 2010).

Antiviral activity of cnidarian products

Anti-herpes simplex virus activity of cnidarian products

Pseudozoanthoxanthins III and another zoanthoxanthin alkaloid which showed mild anti-HSV-1 activity was isolated from the South China Sea gorgonian *Echinogorgia pseudossapo* (Gao et al. 2011).

Anti-human cytomegalovirus activity of cnidarian products

A norditerpenoid from the soft coral *Sinularia gyrosa* expressed antiviral activity against cells with an IC₅₀ of 1.9 µg/ml (Cheng et al. 2010).

Capilloquinol with a farnesyl quinoid skeleton and displaying cytotoxicity and antiviral activity against human cytomegalovirus in vitro was isolated from the Dongsha Atoll soft coral *Sinularia capillosa* (Cheng et al. 2011).

Antiviral activity of crustacean products

Anti-white spot syndrome virus activity of crustacean products

A hemocyte protein isolated from the mud crab (*Scylla paramamosain*) designated as antilipopolysaccharide factor (Sp-ALF) interacted with the bacterium *Vibrio parahaemolyticus*. Its isoforms exhibited substantial amino acid sequence homology with other crustacean antilipopolysaccharide factors. Recombinant rSp-ALFs and sSp-ALFs expressed potent activity against white spot syndrome virus in crustaceans (Liu et al. 2012a).

The antibacterial peptide scygonadin from the crab *S. paramamosain* probably plays a physiological role of reproductive immunity. Scygonadin could interfere with the replication of white spot syndrome virus in cultured crayfish haematopoietic cells (Peng et al. 2012).

Antiviral activity of molluscan products

Anti-herpes simplex virus activity of molluscan products

Both RtH, native hemocyanin from the Bulgarian marine mollusk *Rapana thomasiana* and its structural isoform RtH2, exerted suppressive effects on replication of two wild-type strains, TM (HSV 1) and Bja (HSV 2), and one ACVR mutant with tk gene mutation, DD (HSV 2). Both hemocyanins did not affect the infectious virus yield on ACVR mutant. The functional unit of native hemocyanin-RtH2 was a selective anti-HSV, especially anti-genital herpes virus, agent. RtH2 did not induce apoptosis/necrosis 8 h after viral infection. The viral DNA but not the host cell DNA was the target of its action (Genova-Kalou et al. 2008).

An abalone herpes virus causes abalone viral ganglioneuritis, a neurotropic infection in abalone. Administration of either the hemolymph or lipophilic extract of the digestive gland of the abalone *Haliotis laevis* reduced the number and size of plaques when assessed against another neurotropic herpes virus, herpes simplex virus type 1. The hemolymph inhibited viral infection at an early stage, whereas the lipophilic extract acted at an intracellular stage of infection. The results indicated that abalone produces distinct compounds that have different mechanisms of action against herpes simplex virus type 1 (Dang et al. 2011).

Antiviral activity of echinoderm products

Anti-white spot syndrome virus activity of echinoderm products

Triterpenoid glycosides, which are found in abundance in sea cucumbers, are grouped into four major structural categories based on their aglycone structure: 3β-hydroxyholost-9(II)-

ene aglycone skeleton, 3 β -hydroxyholost-7-ene skeleton, other holostane type aglycones and nonholostane aglycone. Most of the triterpenoid glycosides have antiviral and anticancer activities (Kim and Himaya 2012).

Antiviral activity of invertebrate products

Anti-HIV-1 activity of invertebrate products

Lectins from marine invertebrates are promising tools for studying natural glycoconjugates and cell effectors in vitro. The inhibitory activity of some of these lectins against human immunodeficiency virus has been examined (Luk'ianov et al. 2007).

Antiviral activity of tunicate products

The didemnin family of marine depsipeptides manifested antitumor, antiviral, and immunosuppressive activities at low nano- and femtomolar levels. Of the various congeners, didemnin B was the first marine natural product that reached phase II clinical trials in the US. This subsequently spurred the synthesis of many analogs. Tamandarins A and B demonstrated structure and biological activities analogous to those of didemnin B (Lee et al. 2012).

Antiviral activity of fish products

Tilapia hepcidin 1–5 and cyclic shrimp antilipopolysaccharide factor agglutinated nervous necrosis virus, which brought about mass mortality of numerous marine fish larvae, into clumps which were found to be viral proteins by transmission electron microscopy and Western blot. Grouper epinecidin-1 (CP643-1), but neither Tilapia hepcidin 1–5 nor cyclic shrimp antilipopolysaccharide factor, upregulated Mx gene expression in cBB cells. Hence, the three anti-nervous necrosis virus proteins have different mechanisms of actions (Chia et al. 2010).

Tilapia hepcidin 1–5 elevated the rate of survival of Chinook salmon embryo (CHSE)-214 cells infected with infectious pancreatic necrosis virus, and diminished the number of plaques produced by the cytopathic effect of the virus in the embryo cells. Tilapia hepcidin 1–5 brought about modulation of expression of interleukin, annexin, and other infectious pancreatic necrosis virus-responsive genes (Rajanbabu and Chen 2011).

Three Mx proteins designated as SauMx1, SauMx2, and SauMx3, which are crucial effectors of the innate antiviral response mediated by the interferon type I signaling pathway, have been identified in cultured seabream (*Sparus aurata*). Only cells expressing SauMx2 and SauMx3 were resistant to infectious pancreatic necrosis virus infection in the cytopathic and virus yield reduction assays (Fernandez-Trujillo et al. 2011).

Infectious pancreatic necrosis virus and salmon alphavirus were highly sensitive to the presence of rainbow trout Mx in the cells, whereas infectious hematopoietic necrosis virus and epizootic hematopoietic necrosis virus manifested partial resistance indicating dissimilar viral evasion strategies between these viruses (Lester et al. 2012).

EcDefensin, a β -defensin cloned from the liver of orange-spotted grouper, *Epinephelus coioides*, prevented the infection and replication of an enveloped DNA virus of Singapore grouper iridovirus (SGIV) and a nonenveloped RNA virus of viral nervous necrosis virus. It also evoked a type I interferon-related response in vitro. In grouper spleen cells overexpressing EcDefensin, the expression of host immunerelated genes, such as antiviral protein Mx and proinflammatory cytokine interleukin-1 β , was enhanced. Type I interferon and interferon-sensitive response element were upregulated (Guo et al. 2012).

Purified recombinant phosvitin (a fish yolk protein) attenuates the cytopathic effect in cells infected by lymphocystis disease virus, which is infectious to many teleost species and brings about tremendous losses in the aquaculture industry, and suppresses the viral titer in infected cells and infected zebrafish (Sun et al. 2013).

Antiviral activity of microbial extracts

Nine out of 38 microbial extracts from Hawaiian coastal waters demonstrated antiviral activity against herpes simplex virus type one, poliovirus type one, vaccinia virus, and vesicular stomatitis virus in vitro. The secosteroid, 5 α (H),17 α (H),(20R)-beta-acetoxysteroid-8(14)-ene was the active principle in these marine microbial extracts (Tong et al. 2012).

Antiviral activity of herbal-marine products

HESA-A is an active natural biological compound from herbal-marine origin capable of treating psoriasis, vulgaris, and cancers. Madin-Darby canine kidney cells exposed to the effective concentration (EC₅₀) of HESA-A (0.025 mg/ml) and 100 TCID₅₀/0.1 ml of influenza virus sample displayed enhanced viability. The hemagglutination titer and expression of the cytokine tumor necrosis factor- α were reduced (Mehrbod et al. 2012).

Conclusions

Organisms in the marine habitat produce a variety of bioactive compounds which are unique because the aqueous environment calls for molecules with specific and potent biological compounds (Vo et al. 2011). For instance, bryostatins which are potent protein kinase C agonists exhibit antitumor activity neoplastic activity and sensitize some resistant cancer cells to anticancer agent and exert memory enhancing actions (Kollár et al. 2014). A repertoire of marine products with exploitable activities has been reported. The spectrum of activities encompassed anti-inflammatory, antidiabetic, antibacterial, antiviral, antifungal, and antiprotozoal activities (Mayer et al. 2013). Hence, many investigators are dedicated to research on marine organisms with the intent to ascertain biomolecules with the potential of development into therapeutic drugs. From the foregoing account, it can be seen that a spectacular array of peptides/proteins and small molecules with inhibitory activity against phytopathogenic fungi such as *Aspergillus niger*, *Alternaria longipes*, *Aspergillus fumigatus*, *Fusarium culmorum*, *Fusarium nivale*, *Piricularia oryzae*, *Saccharomyces cerevisiae*, and *Verticillium albo-atrum* and also fungi like *Candida albicans*, *Candida krusei*, *Candida guilliermondii* and *Candida parapsilosis*, *Cryptococcus neoformans* and the dermatophytes *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Microsporum*

canis, and *Microsporium gypseum* pathogenic to humans are produced by bacteria, fungi, algae, sponges, echinoderms, mollusks, and cephalochordates. Like plant antifungal proteins (Li et al. 2011a; Ma et al. 2009; Wong et al. 2011c, 2012; Ye and Ng 2009; Ye et al. 2011), some of the antifungal proteins produced by marine organisms display antiproliferative activity toward tumor cells (Boonlarpradab and Faulker 2007; Gao et al. 2012; Ma et al. 2012). Similarly, the mechanism of antifungal action involves permeabilization of the fungal membrane (Sionov et al. 2005; Wong et al. 2012). However, the mechanism has been studied in only a few cases (Shi et al. 2012; Sionov et al. 2005; Xu et al. 2011b). A variety of viruses including herpes simplex virus, fish nodavirus, fish nodavirus, influenza virus A and B, respiratory syndrome virus, porcine reproductive virus, tobacco mosaic virus, human metapneumovirus, human immunodeficiency virus, hepatitis C virus, herpes simplex virus, human cytomegalovirus, and white spot syndrome virus are produced by bacteria, fungi, algae, cnidarians, crustaceans, echinoderms, tunicates, and fish. Again, the mechanism of antiviral action has been examined only in some cases (Bandyopadhyay et al. 2011; Kim et al. 2012b; Wang et al. 2011). Thus, it would be worthwhile to conduct detailed investigations on the mechanisms of antifungal and antiviral actions as well as the structure-function relationship of the marine biomolecules. It is anticipated that structurally disparate molecules may exert their antifungal and antiviral activities through different mechanisms. A variety of antifungal (Bink et al. 2010; Fang et al. 2010; Ferket et al. 2003; Thevissen et al. 2007; 1996; 2012; Wong et al. 2011b) and antiviral mechanisms (Fernandez-Trujillo et al. 2011; Kim et al. 2012; Mandal et al. 2013; Ng et al. 1997; Wong et al. 2011a) for different natural products have been reported, and they are summarized in Table 1. These compounds/proteins of marine origin may be obtained in larger quantities by chemical synthesis or recombinant DNA technology. Availability in large amounts would enable more extensive investigations. More novel molecules await discovery in view of the multitude of marine organisms. Hopefully, drugs of marine origin that are useful for the treatment of fungal and viral diseases will be available in the foreseeable future. Some of these drugs may have exploitable activities other than antifungal and antiviral activities, e.g., anticancer activity like their plant counterparts (Li et al. 2011a; Ye et al. 2011; Wong et al. 2012).

Chitosan is a bioactive, biodegradable, biocompatible, and nontoxic linear polysaccharide derived from crustacean shells by alkaline hydrolysis. It can form matrices or complexes for the controlled release of active compounds, which can be exploited in the pharmaceutical, food, and agriculture industries for the biological control of microbes (Cota-Arriola et al. 2013). Hopefully, some of the aforementioned antifungal and antiviral biomolecules will one day find applications just like chitosan.

Selected marine products with antifungal and antiviral activities described in this manuscript are summarized in Tables 2 and 3. The variety of chemical structures displayed by antifungal and antiviral biomolecules of marine origin is depicted in Fig. 1. Table 4 presents the Amino acid sequences of different antifungal and antiviral proteins.

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Antifungal products	
macrolide bahamaolides A and B (Kim et al. 2012a)	<p style="text-align: center;">Bahamaolides A</p> <p style="text-align: center;">Bahamaolides B</p>
lipopeptide C(15)-surfactin (Liu et al. 2012b)	<p style="text-align: center;">C(15)-surfactin</p>
steroidal sulfates eurysterols A and B (Boonlarpradab and Faulkner 2007)	<p style="text-align: center;">Eurysterols A</p> <p style="text-align: center;">Eurysterols B</p>

Antiviral products	
polysaccharides kappa/beta-carrageenan (Nagorskaia et al. 2008)	<p>kappa/beta-carrageenan subunit</p>
benzofuran purpurester A (Wang et al. 2011a)	<p>Purpurester A</p>
azaphilone purpurquinone B (Wang et al. 2011a)	<p>Purpurquinone B</p>
glycolipid sulfoquinovosyldiacylglycerol	<p>Sulfoquinovosyldiacylglycerol</p>

meroditerpenoids
atomaric acid and epitaondiol
(Mendes et al. 2011)

nucleoside
vidarabine (Sagar et al. 2010)

Fig. 1.
Structures of different marine products with antifungal and antiviral activities

Table 1

Mechanisms of antifungal and antiviral action of some of the compounds of marine origin

Antifungal mechanisms	
i.	Leakage of potassium ions from cells of the fungal pathogens <i>Candida</i> (primarily <i>C. albicans</i>) and <i>Aspergillus</i> (primarily <i>A. fumigatus</i>) induced by compound from the marine sponge <i>Dysidea herbacea</i> (Sionov et al. 2005)
ii.	Chitin-binding domain is necessary for both chitinolytic and antifungal activities of chitotriosidase-like homolog in amphioxus against <i>Candida albicans</i> (Xu and Zhang 2012)
iii.	Interference with calcium homeostasis by the marine sponge-derived polyketide endoperoxide plakortide F acid (Xu et al. 2011b)
iv.	Induction of metacaspase-independent apoptotic cell death in <i>F. oxysporum</i> by peptaibols from <i>Trichoderma pseudokoningii</i> (Shi et al. 2012)
Antiviral mechanisms	
i.	Interference of sulfated polysaccharides from <i>Sphacelaria indica</i> with HSV-1 particles or masking viral structures which are necessary for adsorption or entry into host cells (Bandyopadhyay et al. 2011)
ii.	Interaction of sulfated polysaccharide p-KG03 from the marine microalga, <i>Gyrodinium impudium</i> , with influenza A virus particles and prevention of viral entry (Kim et al. 2012)

Table 2

Antifungal activities of selected marine products

Marine organisms	Antifungal products	Chemical class	Susceptible fungal spp.
<i>Streptomyces</i> sp. DA11 (Han et al. 2009b)	Chitinase	Protein	<i>Candida albicans</i> and <i>Aspergillus niger</i>
<i>Branchiostoma japonicum</i> (Xu and Zhang 2012)	Chitotriosidase-like protein	Protein	<i>Candida albicans</i>
<i>Trichoderma pseudokoningii</i> SMF2 (Shi et al. 2012)	Trichokonin VI	Peptide	<i>Fusarium. oxysporum</i>
<i>Streptomyces antibioticus</i> H74-18 (Xu et al. 2011a)	Antimycins A ₁₉ and A ₂₀	Macrolide	<i>Candida albicans</i>
<i>Streptomyces</i> sp. (Kim et al. 2012a)	Bahamaolides A and B	Macrolide	<i>Candida albicans</i>
<i>Bacillus amyloliquefaciens</i> (Liu et al. 2012b)	C(15)-surfactin	Lipopeptide	Synergized with ketoconazole toward <i>Candida albicans</i> SC5314.
<i>Bacillus amyloliquefaciens</i> (Song et al. 2013)	Cyclic lipopeptide containing a heptapeptide, AspLeuLeuValValGluLeu and a 3-OH fatty acid with 15 carbon atoms	Lipopeptide	<i>Candida tropicalis</i> , <i>Metschnikowia bicuspidata</i> , <i>Saccharomyces cerevisiae</i> , and <i>Yarrowia lipolytica</i>
<i>Penicillium purpurogenum</i> JS03-21 (Wang et al. 2013)	Purpurides B and C	Sesquiterpene alcohol esters	<i>Candida albicans</i>
<i>Callophycus serratus</i> (Lane et al. 2009)	Callophycic acids and bromophycolides	Diterpenoid	<i>Lindra thalassiae</i>
<i>Symphyocladia latiuscula</i> (Xu et al., 2012)	2,3,6-Tribromo-4,5-dihydroxybenzyl methyl sulphoxide	Bromophenol	<i>Candida albicans</i>
<i>Fucus spiralis</i> , <i>Cystoseira nodicaulis</i> , and <i>Cystoseira usneoides</i> (Lopes et al. 2013)	Phlorotannins	Tannin	<i>Candida albicans</i> , <i>Epidermophyton floccosum</i> , and <i>Trichophyton rubrum</i>
<i>Dysidea herbacea</i> (Sionov et al. 2005)	3,5-Dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol	Diphenyl ether	<i>Candida albicans</i> and <i>Aspergillus fumigatus</i>
<i>Euryspongia</i> sp. (Boonlarpradab and Faulkner 2007)	Eurysterols A and B	Steroid sulfates	<i>Candida albicans</i>
<i>Melophlus</i> sp. (Kumar et al. 2012)	Aurantioside K	Tetramic acid glycoside	<i>Aspergillus niger</i> , <i>Candida albicans</i> , <i>Cryptococcus neoformans</i> , <i>Penicillium</i> sp., <i>Rhizopus sporangia</i> , and <i>Sordaria</i> sp.
<i>Haliclona viscose</i> (El-Amraoui et al. 2013)	Haliscosamine	Sphingosine derivative	<i>Candida</i> and <i>Cryptococcus</i> sp.
<i>Hamigera tarangaensis</i> (Singh et al. 2013)	Hamigeran G	Terpenoid	<i>Saccharomyces cerevisiae</i>
<i>Hippospongia lachne</i> (Piao et al. 2013)	Hippolachnin A	Polyketide	<i>Cryptococcus neoformans</i> , <i>Trichophyton rubrum</i> , and <i>Microsporium gypseum</i>

Table 3

Antiviral activities of selected marine products

Marine organisms	Antiviral products	Chemical class	Susceptible viral spp.
<i>Scylla paramamosain</i> (Liu et al. 2012a)	Antilipopolysaccharide factor	Protein	White spot syndrome virus
<i>Scylla paramamosain</i> (Peng et al. 2012)	Scygonadin	Protein	White spot syndrome virus
<i>Rapana thomasiana</i> (Genova-Kalou et al. 2008)	Hemocyanin 1 and 2	Protein	Herpes simplex virus-1 and -2
<i>Epinephelus coioides</i> (Guo et al. 2012)	EcDefensin	Protein	Singapore grouper iridovirus and viral nervous necrosis virus
<i>Dictyota pfaffii</i> (Abrantes et al. 2010)	8,10,18-trihydroxy-2,6-dolabelladiene	Diterpenes	Herpes simplex virus-1
<i>Dictyota menstrualis</i> (Abrantes et al. 2010)	(6 R)-6-hydroxydichotoma-4,14-diene-1,17-dial	Diterpenes	Herpes simplex virus-1
<i>Sphacelaria indica</i> (Bandyopadhyay et al. 2011)	Xylogalactofucan and algin	Polysaccharide	Herpes simplex virus-1
<i>Gyrodinium impudium</i> (Kim et al. 2012b)	Sulfated polysaccharide p-KG03	Polysaccharide	Encephalomyocarditis virus and influenza type A
<i>Tichocarpus crinitus</i> (Nagorskaia et al. 2008)	Kappa/beta-carrageenan	Polysaccharide	Tobacco mosaic virus
<i>Streptomyces</i> VITSDK1 spp. (Suthindhiran et al., 2011).	Furan-2-yl acetate	Ester	Fish nodavirus
Ascomycota fungal strain 222 (Shushni et al. 2011)	(3R,11R), (4E,8E)-3-hydroxy-11-methyloxacyclododeca-4,8-diene-1,7-dione	Macrolide	HSV-1
<i>Penicillium purpurogenum</i> JS03-21 (Wang et al. 2011a)	Purpurester A and purpurquinone B	Benzofuran and azaphilone	Influenza A (H1N1)
<i>Emericella</i> sp. (HK-ZJ) (Zhang et al. 2011)	Emerimidines A and B, emeriphenolicins A and D,	Isoindolone	Influenza A (H1N1)
<i>Aspergillus terreus</i> SCSGAF0162 (He et al. 2013)	Asperterrestide A	Cyclic tetrapeptide	Influenza A H1N1 and H3N2
<i>Osmundaria obtusiloba</i> (de Souza et al. 2012)	Sulfoquinovosyldiacylglycerol	Glycolipid	Herpes simplex virus-1 and -2
<i>Styopodium zonale</i> (Mendes et al. 2011)	Atomaric acid and epitaondiol	Meroditerpenoids	Human metapneumovirus
<i>Sinularia gyrosa</i> (Cheng et al. 2010)	Norditerpenoid	Diterpenoid	Human cytomegalovirus
<i>Tethya crypta</i> (Sagar et al. 2010)	Vidarabine	Nucleoside	Herpes, vaccinica, and varicella zoster virus
<i>Sinularia capillosa</i> (Cheng et al. 2011)	Capilloquinol	Quinones	Human cytomegalovirus

Table 4

Amino acid sequences of different antifungal and antiviral proteins

Chitinase from <i>Streptomyces</i> sp. DA11 (Han et al. 2009b)	IVDTWDQPLR GNFNQLLKLK KMYPHIKVLW SFGGWTWSGG FPDAMKNPAA FAKSCNELVN DPRWQGLFDG IDLDWEYPNA CGLTCDTSGP AVMRTMAQAF RAEFGNQLVT AAITADASSG GKIDSADYGG AAQYLDWYNV MTYDFFGA
Antifungal peptide from <i>Cenchrus muricatus</i> (Lopez-Abarrategui et al. 2012)	SEILIVHQQ QSRSSGS
Chitotriosidase-like protein from <i>Branchiostoma japonicum</i> (Xu and Zhang 2012)	MLTVLALLCV MLSLGQASVI PAQRNTYRRV CYHTNWSQYR HGVGQFFPED IDPTLCTHAI YAFKMTNNQ LQPYEWNDDS TDWSTGMYER FNTHLKPHGV KTLGLGVGWN FGSTAFSDMA ATAAGRRTFV TTSIDFLRQR NFDGLDLDEWE YPAARGGRPS DKQTFLLLRK ELREAFDAEG ARTGRAPLLL TAAMPAGEDN AMNGYEMAEV AGYLDLFLNM AYDLHGQWET YTGLNSPLYA AGDETGDDDR LNQAFAVDMW LAGGVPPSKL NLGMGTYGRS FTTTGDNSIR APANGGNGAG LYTREKGYLA YYEICTMLNQ GATRVFHSEH LSPYAYLGNQ WVGYYDDVESL TYKVEYLKSK NLGGAMVWAY DIDDFSGSSC GQGRYPLMNA IKNLLETGSA GVVLPFGPTH PPINPATQAP NPGVTQGPNP VVTQAPVVVE QGNLAAVTC DSKPDGFHPDP TDCGKYFQCW GGTMWPGHCS NGLQWNQAML GCDWPYNVNC
<i>Scylla paramamosain</i> antilipopolysaccharide factors (Sp-ALFs) I from <i>Scylla paramamosain</i> (Liu et al. 2012a) <i>Scylla paramamosain</i> antilipopolysaccharide factors (Sp-ALFs) II from <i>Scylla paramamosain</i> (Liu et al. 2012a)	MRTKVMAGLC VALVVMCLYM PQPCEAQYEA LVASILGKLS GLWHS DTVDF MGHTCHIRRR PKFRKFKLYH EGKFWCPCGW HLEGNSRSTKS RSGSARDAIK DFVYKALQNK LITENNAAW LKG MRTGVVAGLC VALVVMCLYL PQPCEAQYET LIASVLGKLT GLWHNNSVDF MGHTCHFRRR PKVRKFKLYH EGKFWCPCGWA PFEGRSRSTKS RSGSSREAIK DFVRKALQNG LITQQDATVW VNN
Scygonadin from <i>Scylla paramamosain</i> (Peng et al. 2012)	MRSSLLGLT VVLLGVIVP PCMAGQALNK LMPKIVSAII YMVGP NAGV TFLGHQCLVE STRQPDGFYT AKMSCASWTH DNPIVGEGRS RVELEALKGS ITNFVQTASN YKKFTIDEVE DWIASY
Hemocyanin from <i>Rapana thomasiana</i> (Genova-Kalou et al. 2008)	GHRNLVRKSV RNLSPAERAS LVAALKSLQE DSSADGFQSL ASFHAQPPLC PAPAANKAFA CCVHGMAFP EWHRLYTVQF EDALRRHGSV VGIPYWDTVV PQEDLPAPFN DEIWDDALFH ANFTNPFNGA DIDFNHQAIA RDINVDKLAK EGPKGYDTWS FKQYIYALEQ EDYCDFEVQF EIAHNHAIHAW VGGTEEYSMG HLHYASYDPV FILHHSNTDR LFALWQELQK FRGHPNEVN CALEMMREPL KPFSFGAPYN LNPTTKEHSK PEDTFDYKGH FHYEYDHLEL QGMNVQRLHD YINQQKEADR VFAGFLLEGI GTSALHDFSI CAIDGECTHA GYFDVLGGSL ETPWQFDRLY KYEITDVLES KGLDVHDFVD IKITQTSWDN EDISTDRFPP PSVIYVPK