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Antiviral Activity of Natural Products Extracted from Marine Organisms

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ABSTRACT

Many epidemics have broken out over the centuries. Hundreds and thousands of humans have died over a disease. Available treatments for infectious diseases have always been limited. Some infections are more deadly than the others, especially viral pathogens. These pathogens have continuously resisted all kinds of medical treatment, due to a need for new treatments to be developed. Drugs are present in nature and are also synthesized *in vitro* and they help in combating diseases and restoring health. Synthesizing drugs is a hard and time consuming task, which requires a lot of man power and financial aid. However, the natural compounds are just lying around on the earth, may it be land or water. Over a thousand novel compounds isolated from marine organisms are used as antiviral agents. Others are being pharmacologically tested. Today, over forty antiviral compounds are present in the pharmacological market. Some of these compounds are undergoing clinical and preclinical stages. Marine compounds are paving the way for a new trend in modern medicine.

Introduction

In the world, animals, plants and microorganisms live together in an ecological niche. Pathogenicity is a liability, which cannot be completely obliterated; however it can be curable (Mayer and Hamann 2004).

Since the dawn of man, he has been vulnerable to microbial attack, from a mild fever to a fatal disease. Scientists have been working diligently to prepare vaccines or to discover cures for various infections. After experimenting with terrestrial life forms, researchers have obtained many antimicrobial compounds, which have been used for patient care (Marin Lit 1998; Cirne-Santos *et al*. 2008; Oku *et al*. 2004; Lee *et al*. 2006; Mayer and Hamann 2002). However, many new diseases have sprung up over the ages, which are resistant to many antibiotic drugs. The world is in need of more pharmacological agents, especially against viral infections.

For nearly one hundred thousand years, it has been known that marine life-forms can be used against microbial attacks. However, serious investigation started nearly half a century ago (Mayer and Hamann 2002). Researchers have opted for screening marine life forms for finding antiviral activity against viruses, such as HIV, HSV (1 and 2), and HCMV, etc. (Mayer and Hamann 2004; Oku *et al*. 2004; de Souza *et al*. 2005; Rodriguez *et al*. 2005).

The first credited work on studying marine natural products against the microbes was of Bergman, over 60 years ago (Bergman and Feeny 1951). During 1970s-1980s, many research papers on marine natural products were published and reviewed (Munro *et al*. 1987). Mostly studied phyla were (in order of preference): Porifera, Cnidaria, Chromophycota, Rhodophycota, Mollusca, Chordata, and Echinodermata (Marin Lit 1998).

After a comparative study between the pharmacological benefits from marine life forms and terrestrial ones, it was reported that marine invertebrates were preferred as their cytotoxic activity was quite high, (Garson 1994). Marine life-forms are under clinical trials since the early 1950s, to find anticancer marine metabolites (Fenical 1996; Nakao *et al*. 2001).

From 1998-2008, a massive amount of marine life forms were studied to extract the antiviral compounds. Many species showed remarkable activities against pathogenic viruses. However, this was observed *in vitro*. Chemical classification of the marine compounds was done to classify them into the following major marine chemical compounds; Polyketides, Terpenes, Nitrogen-containing

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compounds and Polysaccharides (Schimtz 1994). Marine compounds show antibacterial, antifungal, anti-malarial, anticoagulant and antiviral activities. They also affect cardiovascular and nervous systems. During 1999, 21 marine compounds underwent clinical trials. The antiviral pharmacology of the natural products of marine water reached its peak during 1999. Antiviral activity was screened against human immunodeficiency virus-1 (HIV-1), herpes simplex virus-2 (HSV-2), junin virus (JV), polio virus (PV), *molluscum contagiosum* dengue virus, severe acute respiratory syndrome (SARS) virus, measles virus and influenza virus (Comin *et al*. 1999; Hwang *et al*. 1999; Mayer and Lehman 2000; Rowley *et al*. 2002; Rodriguez *et al*. 2005).

Marine compounds from tunicates and sponges

Antiviral compounds, *halichondrin B, homohalichondrin B* and *isohomohalicondrin B;* were derived from the sponge *Lissodendoryx* sp. These compounds inhibited the proliferation of tumor cells after replication. For this purpose in vivo and in vitro trials have been established (Munro *et al*. 1987).

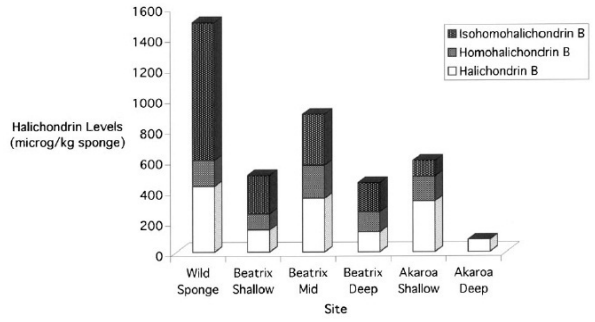

Fig. 1. Halichondrin levels in *Lissodendoryx* samples.

Antiviral bioactive compounds from marine Bacteria, Clam and marine Ascidian species

The causative agents of the most fatal diseases are viruses, such as cancer, anti-acquired immune deficiency syndrome (AIDS), herpes simplex (Mayer *et al*. 1998). Integrase is an integral enzyme of HIV. In 1999, a new compound, "alkaloid lamellarin α 20-sulphate" was discovered in an unidentified ascidian. This compound exhibited inhibition of integrase *in vitro* (Reddy *et al*. 1999). A series of antiviral compounds, "cyclic depsipeptides papuamides A, B, C and D" were derived from a family of sponges, *Theonella mirabilis* and *Theonella swinhoei*. Compounds A and B inhibited the infection of HIV in T-lymphoblastoid cells (Ford *et al*. 1999).

Another aromatic alkaloid, "Polycitone A" was isolated from an ascidian, *Polycitor* sp. It works as a potent inhibitor of reverse transcriptase of HIV and retroviruses as well as an inhibitor of DNA polymerases, (Loya *et al*. 1999). As it is a general inhibitor it cannot be used as an anti-HIV agent. However, with a few modifications and some new derivatives it can be used as such.

A compound glycosaminoglycan was discovered in a *Pseudomonas* sp. This compound exhibited antiviral activity against influenza virus A and B, (Ahmad *et al*. 1999). In some AIDS patients, HIV causes syncitia formation. One infected cell binds with another cell via CD4, resulting in a multinuclear HIV infected cell. Another antiviral compound, Sulphated β-galactan from clam displayed inhibition of HIV binding with CD4, *in vitro* (Amornrut *et al*. 1999).

Hydroxysteroids from marine echinoderms

Poly-hydroxysteroids were isolated from the Brittle Star, *Astrotoma agassizzi*. These compounds caused the reduction of three human pathogenic viruses; HSV-2, JV, and PV-3 *in vitro*, (Comin *et al*. 1999). Sulfated polymannuroguluronate is an anti-AIDS drug candidate which targets CD4 in lymphocytes. Scientists have great hopes for this compound to be used against HIV (Miao et al. 2004).

Antiviral activity shown by marine fungus

An antiviral compound sansalvamide was isolated from a fungus, *Fusarium* sp. Molluscum contagiosum is a poxvirus causing pink bumps (rash) in humans. This compound inhibited the topoisomerase enzyme of the poxvirus (Hwang *et al*. 1999).

Marine sponges

Rudi *et al*. (2001) discovered clathsterol from the Red Sea sponge (*Clathria* sp.). It caused the inhibition of RT-HIV, like the alkaloid compound of 1999 (Loya *et al*.). Microspinosamide was discovered by Rashid *et al*. (2001) and it was originated from a sponge, Sidonops microspinosa. It inhibited HIV growth, *in vitro*. Polyacetylenetriol was derived from a specific sponge (*Petriosa* sp.). This compound inhibited the DNA and RNA directed DNA-polymerases, by reversible, noncompetitive mechanism, involving hydrophobic interaction (Loya *et al*. 2002). Calyceramides, derived from the marine sponge Discodermia calyx, showed inhibition of neuraminidase in influenza virus (Nakao *et al*. 2001).

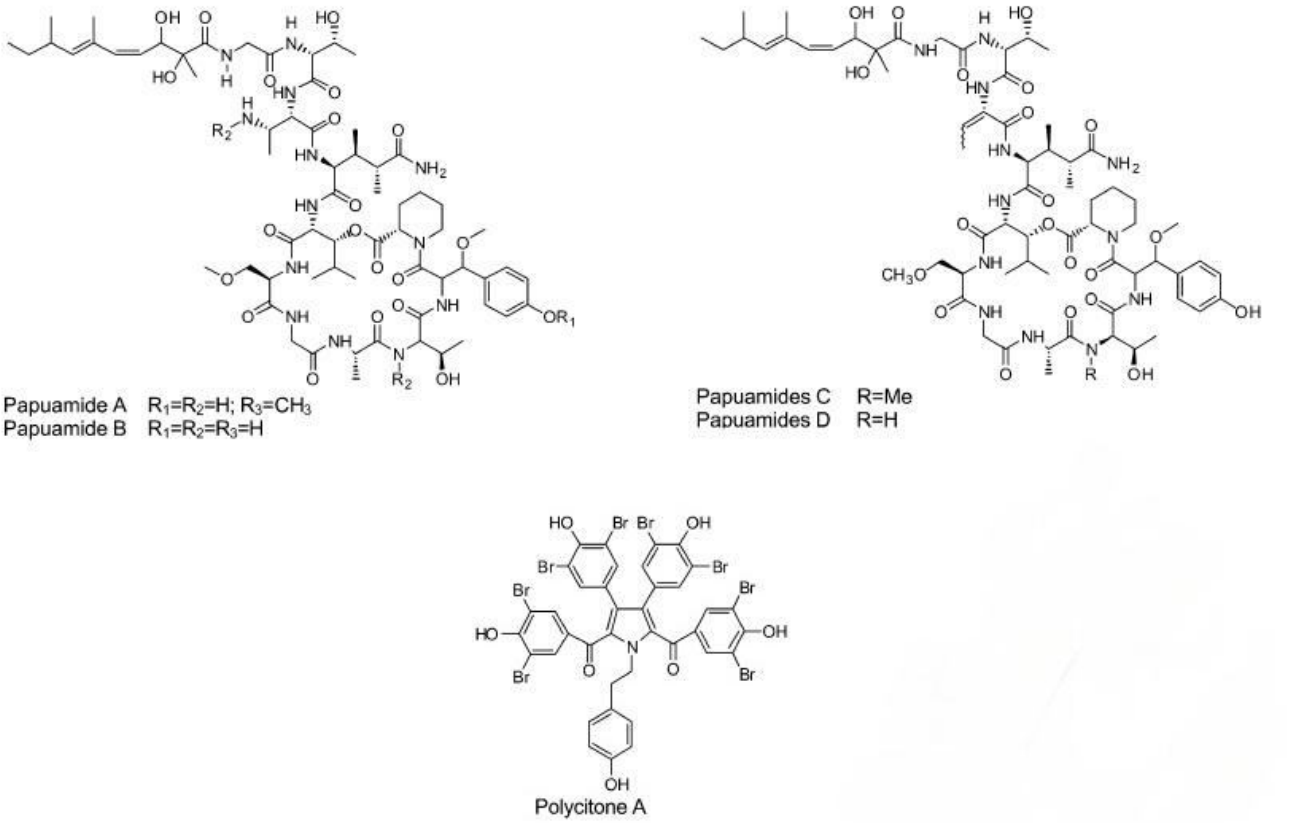

Fig. 2. Natural compounds from marine bacteria, ascidians and clams.

For HIV growth inhibition, neamphamide was discovered that was obtained from a marine sponge, *Neamphius huxleyi* (Oku *et al*. 2004). Crambescidin was isolated from a Monanchora sponge. It inhibited HIV-1 envelope fusion with normal cells, *in vitro* (Chang *et al*. 2003). Chill *et al*. (2004) discovered dehydrofurodendin from a Madagascan sponge, *Lendenfeldia*. It inhibits the RT-RNA and DNA directed DNA polymerases like polyacetylenetriol (Loya *et al*. 2002). *Petrosia similis* is a marine sponge which produces petrosins, for HIV growth inhibition (Venkateshwar Goud *et al*. 2003). Esculetin ethyl ester from sponge (*Axinella* cf. *corrugata*), this compound inhibits the protease 3CL of the SARS enzyme, (de Lira *et al*. 2007). It is effective against Corona virus. *Mirabamides* A, C and D were isolated from a sponge, *Siliquariaspongia mirabilis*. It inhibits the action of HIV-1 cell fusion (Plaza *et al*. 2007).

Seagrass and seaweed

Thalassoilins A, B and C were derived from sea grass, *Thalassia testudinum*. It inhibited HIV growth, HIV enzyme, and integrase, (Rowley *et al*. 2002). This ability was discovered in an ascidian. *Thalassia* A was reported to be the most active compound, (Reddy *et al*. 1999; Rashid *et al*. 2001). *Schizymenia binderi* is derived from marine red seaweed and causes the deactivation of HSV-1 and 2 by interfering with the haparan sulphate residues in the viral cells (Matsuhiro *et al*. 2005). Xylomannan, from red seaweed; *Scinaia hatei,* showed antiviral activity against HSV-1 and HSV-2 (Mandal *et al*. 2008).

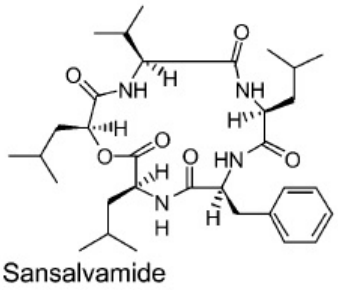

Fig. 3. Natural compound obtained from *Fusarium sp*.

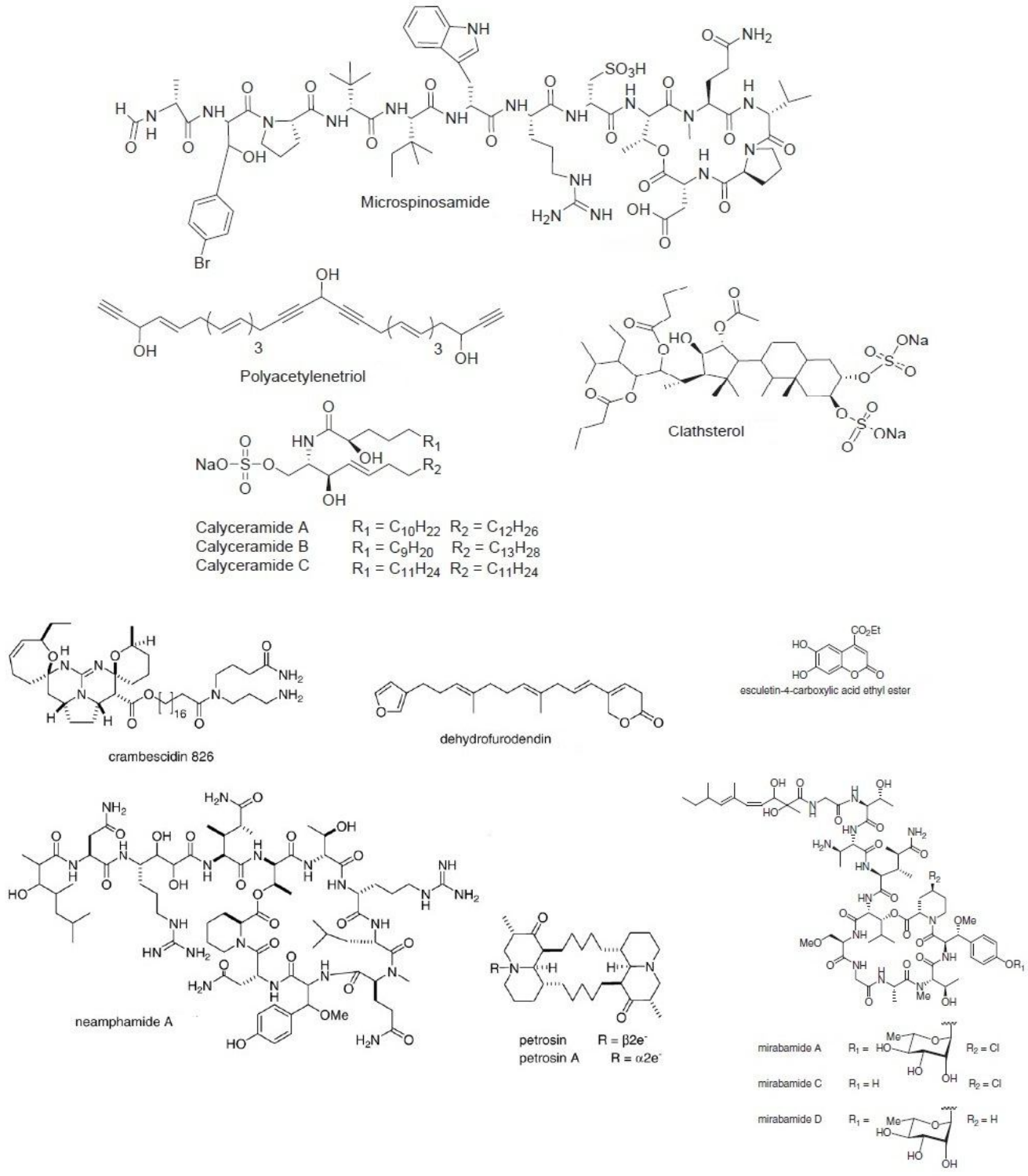

Fig. 4. Natural products extracted from marine sponges.

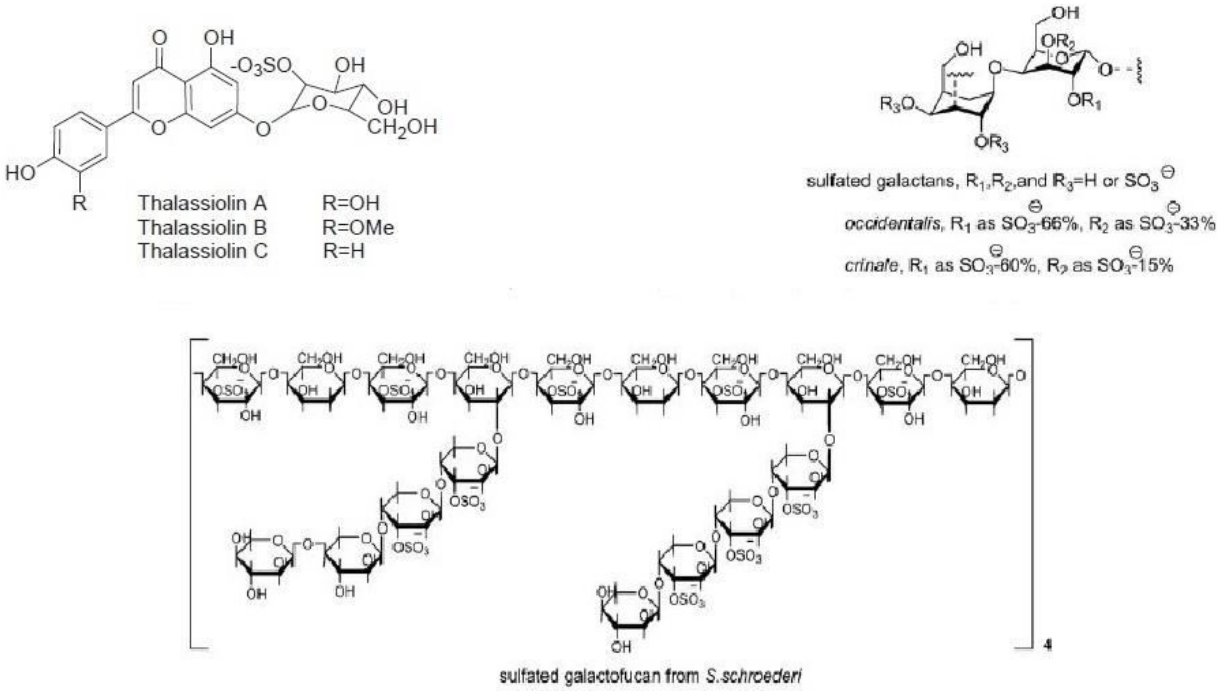

Fig. 5. Compounds obtained from Seaweed and Seagrass.

Marine alga

Extracts of marine microalgae exhibited *in vitro* suppression of the replication of haemorrhagic septicaemia virus (VHSV) and African swine fever virus (ASFV) (Fabregas *et al*. 1999). *Dictyota menstrualis* is an alga, from which, *dictyota* diterpenes was derived for the inhibition of HIV-1 replication in cell lines (Pereira *et al*. 2004). Rodriguez *et al*. (2005) isolated three polysaccharides from the marine alga, *Callophyllis variegata*. It was observed that they displayed antiviral activity against HSV-1 and 2 and dengue type 2. Researchers regarded them as "promising antiviral agents". Three fractions of *sargassam plastiquinones* were isolated from marine alga *Sargassam micracanthum*, for the inhibition of measles and cytomegalovirus, (Iwashima et al. 2005). It was suggested that it can be used as a lead compound in anti-human cytomegalovirus drug. De Souza *et al*. (2005) isolated griffithsin from a marine red alga, *Giffithsia* sp. It showed properties of being a microbiocide to prevent the sexual transmission of HIV and AIDS, *in vitro*. Mori *et al*. (2005) contributed in the characterization of this HIV inactivating protein compound, Griffithsin, which is a new type lectin. This was a remarkable discovery. D, L-galactan hybrid C2S- 3 from the alga *Cryptonemia crenulata* inhibits three strains of dengue type 2; it also inhibits the binding and penetrating the virus (Talarico *et al*. 2007). From the brown alga family, *E. cava* 6, 6'-Bieckol was extracted which is a phlorglucinol derivative suppressing the syncytia formation caused by HIV-1 infection (Artan *et al*. 2008). Cirne-Santos *et al*. (2008) discovered dolabelladienetriol from a family of brown alga, *Dictyota pfaffii*. This compound had the ability to inhibit HIV-1 replication. It inhibits the RT enzyme of the provirus. Lu *et al*. (2007) discovered a novel compound sulphated polymannuroguluronate (SPMG) from the brown alga, *Laminaria aponica*. It has a molecular weight of 8.0 KDa. It deactivated HIV-1 with a very high intensity, *in vitro* (Meiyu *et al*. 2003). It is an anti-AIDS drug candidate and is in the phase II of clinical trials in China. SPMG eliminates viral gene product, transactivator of transcription protein (Tat) - induced transduction. Tat stimulated calcium overload and caused apoptosis of cells. SPMG showed neuroprotective effect, i.e. no apoptosis occurred in the neural cells (Hui *et al*. 2008).

Marine diatoms

Naviculan was derived from a marine diatom *Navicula directa*, for the inhibition of viral replication of HSV-1 and 2 at early stages (Lee *et al*. 2006).

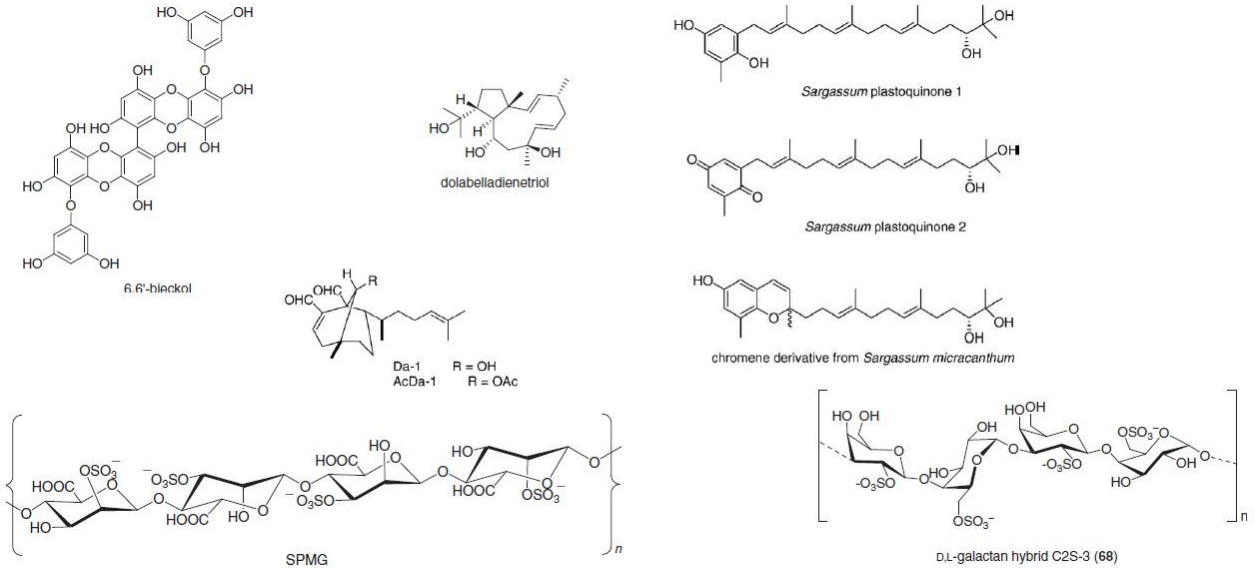

Fig. 6. Natural compounds from marine alga exhibiting antiviral activity.

Table 1. Marine compounds having antiviral pharmacological potential since 1999 to 2008

Compound/organism	Chemistry	Pharmacological activity	Molecular Mechanism of Action	Country	References
Lamellarin a-20- sulfate/Tunicate	Tyrosine-based	*In vitro* HIV infection	HIV integrase	IND, USA	Reddy *et al*. 1999
Papuamides A–D/sponge	Depsipeptide	*In vitro* HIV infection	Undetermined	CAN, USA	Ford *et al*. 1999
Polycitone A /Tunicate	Tyrosine-based	*In vitro* anti-RT inhibition	DNA polymerase inhibition	ISRA	Loya *et al*. 1999
Glycosaminoglycan /Bacterium	Sulfated Polysaccharide	*In vitro* anti- influenza A & B inhibition	influenza A virus inhibition	JPN	Ahmad *et al*. 1999
Sulfated β-galactan /Clam	Sulfated Polysaccharide	*In vitro* syncitia formation inhibition	Inhibition of HIV binding to CD4	S. KOR, JPN, USA	Amornrut *et al.* 1999
Poly-hydroxysteroids /Brittle Star	Sterol	*In vitro* reduction of HSV-2, JV, PV plaque formation	Sulfate at C-21, C-2 and C-3 critical for inhibition	ARG	Comin *et al*. 1999
Sansalvamide /Fungus	Depsipeptide	*Molluscum contagiosum* virus topoisomerase inhibition	DNA binding and relaxation inhibition	USA	Hwang *et al*. 1999
Clathsterol/sponge	Sulfated sterol	HIV reverse transcriptase inhibition	Undetermined	ISRA, S. AFR	Rudi *et al*. 2001
Microspinosamide/sponge	Depsipeptide	HIV-growth inhibition	Undetermined	USA	Rashid *et al*. 2001
Polyacetylenetriol/sponge	Fatty acid	RNA- and DNA-directed DNA polymerase inhibition	Reversible non-competitive inhibition, with hydrophobic interactions	ISRA	Loya *et al*. 2002
Thalassiolins A–C/sea grass Sulfated flavones	Sulfated flavones	HIV-1 integrase inhibition and HIV growth *in vitro*	Binding to catalytic domain of HIV-1 integrase	USA	Rowley *et al*. 2002
Calyceramides A–C/sponge	Fatty acid	Neuraminidase inhibition	Undetermined	JAPN	Nakao *et al*. 2001
Crambescidin/sponge	Alkaloid	HIV-1 envelope-mediated fusion inhibition *in vitro*	Undetermined	USA	Chang *et al*. 2003
Dehydrofurodendin/sponge	Furanoterpene	RT RNAand DNA-directed DNA polymerase inhibition	Undetermined	ISRA, FRA	Chill *et al*. 2004
Neamphamide A/sponge	Depsipeptide	HIV-growth inhibition	Undetermined	USA	Oku *et al*. 2004
Dictyota diterpenes/alga	Diterpene	Inhibition of HIV-1 replication in cell line	RNA-dependent DNA-polymerase RT inhibition	BRA	Pereira *et al*. 2004
Petrosins/sponge	Alkaloid	HIV-growth inhibition	Giant cell formation and RT inhibition	IND	Venkateshwar Goud *et al*. 2003
Callophylis variegate galactans/alga	Polysaccharide	Herpes simplex and dengue type 2 inhibition	Undetermined	ARG	Rodriguez *et al*. 2005
Naviculan/diatom	Polysaccharide	Herpes simplex 1 and 2 inhibition	Undetermined	JPN	Lee *et al*. 2006
Schizymenia binderi sulfated galactan/alga	Polysaccharide	Herpes simplex 1 and 2 inhibition	Interference with HSV-heparan sulfate cellular residues	ARG, CHL	Matsuhiro *et al*. 2005
Sargassum plastoquinones/sponge	Terpenoid	Measles and cytomegalovirus Inhibition	Lipid peroxidation observed	JPN	Iwashima *et al*. 2005
Griffithsin/alga	Protein	T- and M-tropic HIV-1 inhibition	Inhibition of CD4- dependent gp120 binding	USA	De Souza *et al*. 2005
Griffithsin/alga	Protein	HIV inactivation	Binds to viral glycoproteins in a monosaccharide manner	USA	Mori *et al*. 2005
Esculetin ethyl ester/sponge	Polyketide	SARS-Corona virus viral protease 3CL inhibition	Undetermined	BRA, CAN	De Lira *et al*. 2007
Cryptonemia crenulata galactan/alga	Polysaccharide	Dengue type 2 inhibition	Inhibition of viral binding and cell penetration	ARG, BRA	Talarico *et al*. 2007
6,6′-Bieckol/alga	Shikimate	Inhibition of HIV-1 Infection	Viralp24antigen production and reverse transcriptase inhibition	CHN, S. KOR	Artan *et al*. 2008
Dolabelladienetriol/alga	Terpenoid	Inhibition of HIV-1 Replication	Noncompetitive inhibition of reverse transcriptase	BRA	Cirne-Santos *et al*. 2008
Mirabamides A, C and D/sponge	Peptide	Inhibition of HIV-1 fusion	InteractionwithHIV-1 envelope glycoproteins	NZL, USA	Plaza *et al*. 2007
Sulfated SPMG/alga	Polysaccharide	Inhibition of HIV-1 infection	Inhibition of HIV-1 Tat induced angiogenesis	CHN	Lu *et al*. 2007

Conclusion

Since 1940s, scientists have been trying to find cures for fatal viruses like HIV, HSV and HCMV. Marine based antiviral compounds are to be approved for patient use by the US Food and Drug Association. The isolated compounds undergo various stages of preclinical and clinical trials. They pass through different phases before being approved for human use. Then those showing higher activity than the others are subjected to clinical trials, where they are subjected for dry development after QSAR activity.

The clinical trials are still going on and it is expected that antiviral compounds will be used for patients soon, as it will be much better than chemotherapies and radiotherapies. It has little side-effects. 97% of the world is marine water, from which only 5% has been explored and these compounds have been extracted. However, there is a lot of area to cover and it beckons us to work on it.

The future trends show the use of "polymer therapeutics", in which specific target drug designing system is used. Drugs are attached to a water soluble polymer and injected at a specific site of infection/disease. In this process, the pharmacokinetic properties of the drugs are enhanced. It is a huge help in drug designing and cancer chemotherapy (Dumdei *et al*. 1997).

Ethical issues

None to be declared.

Conflict of interests

None to be declared.

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