Emerging Novel Anti HIV biomolecules from marine Algae: An overview

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ABSTRACT

Over the past 3 decades, despite enormous scientific advancements and developments in the field of vaccine development and drugs, HIV-1 is still posing a major challenge to human health. While development of vaccines is still clearly many years ahead, administration of FDA approved drugs leads to severe side effects and toxicity. Marine algae due to its biodiversity has been a rich source of biologically active compounds with varying degree of actions such as anti-viral, anti-cancer, anti-amyloid, anti-inflammatory and anti-oxidant properties. The primary and secondary metabolites obtained from the marine algae have shown potent anti-viral activities in vitro and in animal model. This review focus on the bioactive compounds from marine algae that have been recently identified and studied.

INTRODUCTION

HIV-1, the causative agent of AIDS, is a major human pathogen with >30 million infected people world-wide and several million deaths annually (Osman Sankoha et al., 2015). HIV is a major public health concern not only because it can’t yet be prevented by vaccination, but also because those it infects are infected for life with a virus that targets their immune system making them more prone to other infections (Backus et al., 2005). According to world health organization (WHO) ~35 million peoples in the world are currently living with HIV and 36 millions AIDS related deaths till date (Shafiee et al., 2015). The vast majority of the people living with HIV are in low and middle income countries, two-thirds of them in sub-Saharan Africa (over 25 million peoples) (Figure 1) (Zhang et al., 2015). In the early years of the AIDS epidemic, people infected with the virus faced certain death, often within just a few years after infection. Initially, HIV prevention methods focused primarily on preventing the sexual transmission of HIV through behavior change. Later the biological methods of prevention such as vaccines, microbicide, male circumcision, and pre and post exposure prophylaxis were developed (Bailey et al., 2007). For the past three decades significant progress has been made in the development of vaccines, drugs and neutralizing antibodies for HIV treatment. Despite huge effects, HIV is still posing a major health threat globally.

All the current treatment modalities against HIV offer a marginal increase in the life expectancy as observed during anti HIV treatment. Marine organism offers diverse classes of biological active compounds many of which have been translated into potential drugs for human diseases. More than 60% of the marine drugs are the secondary metabolites from algae and sponges. This review is mainly focused on bioactive compounds from marine sources for anti-viral activity.

Vaccines for HIV

The development of vaccine for HIV-1 after three decades of its discovery is clearly still many years ahead (Wang et al., 2015). Funding for developing HIV-1 vaccine was increased in last decade but now it was steadily decreasing. Developing a vaccine is a very difficult challenge mainly because

1. Lack of natural immunity to HIV
2. Frequent mutation and several subtypes of HIV
3. Lack of animal model.

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Since there are no suitable animal model exist till now, vaccines have to be developed in monkeys using SIV which don’t have exactly the same immune effects as HIV (Velu et al., 2009). Furthermore we don’t know with certainty which immune response will provide protection.

Various vaccines have been tested in clinical trials since the discovery of HIV in 1985, however after 3 decades still HIV remains a difficult target for vaccines. One of the most successful clinical trials to date has been a US Military HIV Research trial in Thailand in 2009, known as the RV144 trial, two vaccines were used together: a “prime” (the ALVAC vaccine) and a “boost” (the AIDSVAX B/E vaccine) (Peter et al., 2011). This combination vaccine was found to be safe and lowered the rate of infection by 31 percent. Another possible vaccine comes from a novel gene therapy that alters the CCR5 co-receptor permanently, preventing HIV from entering cells. A successful vaccine against HIV is yet to be developed though several come strategies are currently being evaluated.

**Drugs for HIV**

The treatment of HIV infection was revolutionized in the mid 1990s by the development of inhibitors for protease and reverse transcriptase two of the three essential enzymes of HIV-1. Due to structural and functional complexity of HIV, single drug is
not sufficient to control HIV infection and therefore a multi prong attack is required. Antiretroviral therapy (ART) serves as one of the prevention strategy for HIV infection patients. People on antiretroviral therapy takes a combination of HIV medicines (called as HIV regimen) everyday. The prevention of HIV transmission from mother to child has highlighted the important use of anti retroviral drugs (Temgoua et al., 2015). Currently there are 26 FDA approved drugs from 6 mechanistic classes based on the phases of retroviral life-cycle that the drugs inhibit which are listed in Table 1. (Kinch and Patridge, 2014).

Limitations of ART

One of the major limitations of ART is its inability to act on viral reservoirs requiring adherence to lifelong treatment. Further, HIV infected individuals on ART are shown to be at elevated risk for an array of "non AIDS" conditions like liver disease, cardiovascular disease, kidney impairment, non-AIDS cancers, osteoporosis, neurocognitive decline, etc (Andrew et al., 2008). Hence, Dr. Dadachova and his researchers have used radioimmunotherapy to destroy the remaining HIV cells in the blood samples of patients treated with ART (Dadachova et al., 2006).

In spite of diverse class of drugs that targets viral enzymes at various stages of virus replication and infectivity, there still remain several powerful drivers to discover and develop new classes of HIV inhibitors. The main reasons are continued acquisition of HIV-1 resistance to currently administered antiretroviral drugs and toxicities associated with the lifelong therapy required for viral suppression (Rebecca Torres and William Lewis 2014). The discovery of compounds that inhibit the replication of HIV-1 via new mechanisms offers the best hope of generating drugs that are active against all HIV-1 variants in the clinic. In principle, viral mutations conferring resistance to any existing drug classes would not confer cross-resistance to drugs targeting a new mechanism.

Natural products from marine sources for anti-viral activity

Natural products have been the source of most of the active ingredients of medicines (Newman et al., 2012; Chin et al., 2006; Fischbach & Clardy, 2007). Almost 50% of the drugs approved since 1994 are based on the natural products including marine sources. Many marine organisms live in challenging and extreme conditions such as low temperature and high pressure, and in adapting to such conditions they produce a wide variety of primary and secondary metabolites which cannot be present in other organisms (Lordan et al., 2011; Ponnambalam et al., 2013). Nearly 58 % of the marine bioactive compounds have been extracted from algae (25%) and sponges (33%). Marine algae due to its biodiversity is a rich natural source of biologically active compounds such as polyphenols, sulphated polysaccharides, terpenes, alkaloids, carotenoids, sterols, proteins and antioxidants (Hamed et al., 2015).

Marine algae are classified into four major groups 1) Blue-green algae (Cyanobacteria) 2) Green Algae (Chlorophyta) 3) Red Algae (Rhodophyta) and 4) Brown Algae (Phaeophyta), based on the chloroplast present in them. These classes of algae are ubiquitous and its primary and secondary metabolites have shown activities against anti-viral, anti-cancer, anti-bacterial and anti-fungal.

Cyanobacteria; Blue-Green Algae

Cyanobacteria are Gram-negative prokaryotes; obtain their energy through photosynthesis with autotrophy as their dominant mode of nutrition. They are ubiquitous, widespread distribution in both aquatic and terrestrial zones including several types of challenging and extreme environmental conditions and stress. They produce different classes of primary and secondary metabolites to adapt themselves to challenging environments. Interest on cyanobacteria as a possible source of pharmaceutical and bioactive compounds emerged within the last 20 years and several compounds of interest which are quite unique and novel to Cyanobacteria have been identified. A variety of secondary metabolites belonging to different chemical groups, such as alkaloids, macrolides, glycosides, peptides etc. have been found to possess different bioactivities (Giromes et al., 1989 and Lau AF et al, 1993). Marine Cyanobacterial being photosynthetic in nature, mass cultivation of the organism that could produced cost effective bioactive metabolites. Furthermore, Cyanobacteria are known for containing novel bioactive compounds including toxins which may have wide pharmaceutical applications. The table 2 represents the bioactive molecules from Cyanobacteria that have shown activity against HIV life cycle.

Table 1: FDA approved drugs for inhibition of HIV-1 replication and infections. These drugs targets viral genome, reverse transcriptase, protease, viral coat protein gp120 and integrase.

<table>
<thead>
<tr>
<th>Nucleoside reverse transcriptase inhibitors (NTRI’s)</th>
<th>Non-nucleoside reverse transcriptase inhibitors (NNTRI’s)</th>
<th>Protease inhibitors</th>
<th>Entry inhibitors</th>
<th>HIV integrase inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Nevirapine</td>
<td>Saquinavir</td>
<td>Enfuvirtide</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Delavirdine</td>
<td>Indinavir</td>
<td>Maraviroc</td>
<td>Elvitegravir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Efavirenz</td>
<td>Ritonavir</td>
<td></td>
<td>Dolutegravir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Etravirine</td>
<td>Nelfinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Rilpivirine</td>
<td>Amprenavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Enfuvirtide</td>
<td>Lopinavir/ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combivir</td>
<td></td>
<td>Atazanavir</td>
<td></td>
<td></td>
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<tr>
<td>Trizivir</td>
<td></td>
<td>Fosamprenavir</td>
<td></td>
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<tr>
<td>Emtricitabine</td>
<td></td>
<td>Tipranavir</td>
<td></td>
<td></td>
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<tr>
<td>Truvada</td>
<td></td>
<td>Darunavir</td>
<td></td>
<td></td>
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<tr>
<td>Epzicom</td>
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</tbody>
</table>
Brown Algae

Brown algae are exclusive to the marine habitat. The body of all brown algae is termed a thallus, indicating that it lacks the complex xylem and phloem of vascular plants. The brown algae are rich in photosynthetic pigments (chlorophyll a & c, carotene, xanthophylls and fucoxanthin) and polysaccharides that possess many biological activities (Ruperez and Saura-Calixto 2001; Siriswardhana et al., 2004). The photosynthetic products of the brown algae are laminaran and mannitol. Food reserves of brown algae are typically complex polysaccharides, principally laminarin, (others - galactans, fucoidan, laminarin, algamines) and higher alcohols (Ferreira et al., 2012).

The various biological properties exhibited by brown algae include immune modulation (Raghavendran et al., 2011); anti-inflammation (Islam et al., 2013); antiviral (Sinha et al., 2010); antioxidative (Balboa et al., 2013); vasodilation (Park et al., 2008); anticoagulant (Arivulsevan et al., 2011); antitumor (Khanavi et al., 2010); anti-vasculogenic (Dias et al. 2008); anti-herpetic (Lee et al., 2010) anti lipidemic (Guangling Jiao et al., 2011), and hepato- protection (Josephine et al., 2008). Brown algae have potential for therapeutic application because they are taxonomically diverse, largely productive, biologically active and chemically unique, thus offering a great scope for discovery of drugs from the ocean. Table 3 represents the anti-viral compounds extracted from brown algae that targets virus at different level.

Red Algae

Several bioactive compounds have been identified from the red marine algae and available in markets as anti-viral foods in assisting body’s specific immune regulatory response. Their sulphated polysaccharides have shown promising activity towards HIV, Ebola, Hepatitis C and HSN1 virus. Current research on red marine algae in the family of Dumontiaceae suggests a breakthrough in the discovery of natural immunomodulatory and antiviral agents.

Further the sulphated polysaccharides extracted from red marine algae suppressed retroviral replications and inhibited viral reverse transcriptases. Table 4 represents anti-viral compounds that have shown promising inhibitory activity against many viruses at entry and replication steps.

Green Algae

The green algae are a large and diverse group of photosynthetic eukaryotes, with more than 7000 species growing in a variety of habitats. Green algae are important components of marine, freshwater and terrestrial ecosystems. Several screening studies have been carried out over few decades with the aim to discover new antibiotic or cytotoxic metabolites (Mayer et al., 2004; 2007).

Sulphated polysaccharide extracts collected by maceration and decoction from Green algae Ulva fasciata possessed 100% inhibitory activity against human metapneumovirus (HMPV). The results from this study have shown the biomolecules acts against two possible mechanisms, virucidal and inhibition of cell entry (Paulo 2010). Further, Ulva fasciata produces a novel sphingosine derivative has been found to have antiviral activity in vivo (Garg et al., 1992). Caulerpa racemosa, collected from the South China Sea showed potent inhibition of herpes simplex virus type 1 (HSV-1) and Coxackie virus B3 (Cox B3). A Sulfoglycosylglycerol (SQDG) exhibited an excellent antiviral effect against HSV-2, with a 50% inhibitory concentration (IC50) of 15.6μg ml⁻¹ against both standard and clinical strains of HSV-2, but showed only moderate antiviral effects against HSV-1 and Cox B3 (Yue-Wei Guo 2014).

Table 2. Biomolecules from Blue-green algae (Cyanobacteria) and its inhibitory activity on viral targets and life cycle.

<table>
<thead>
<tr>
<th>Bioactive molecules</th>
<th>Cyanobacteria</th>
<th>Virus Targets (within the replication cycle)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfolipids</td>
<td>Lyngbya majuscula</td>
<td>Virus particles, infectivity, entry</td>
<td>Boyed MR et al. (1997)</td>
</tr>
<tr>
<td>Spirulan</td>
<td>Spirulina Platensis</td>
<td>HIV-1 and HIV-2 (inhibit reverse transcriptase) HSV, influenza</td>
<td>Hayashi et al. (1996)</td>
</tr>
<tr>
<td>Cyanovirin –N (Hypericin)</td>
<td>Nostoc ellipsoспорum</td>
<td>Interacts with mannose groups of envelope glycoproteins gp 120 and blocks its interaction with target cell receptors</td>
<td>Dey et al:(2000)</td>
</tr>
<tr>
<td>Scytovirin</td>
<td>Scytonema varium</td>
<td>Interacts with oligosaccharides containing alpha1-2 alpha1-2, alpha 1-6 tetramannose units of envelope glycoproteins, gp120, gp160, gp41</td>
<td>Rahul Kunwar Singh et al. (2011)</td>
</tr>
<tr>
<td>Sulfoglycolipid</td>
<td>Scytonema sp.</td>
<td>Inhibits RT and DNA Polymerases</td>
<td>Loya et al. (1998)</td>
</tr>
<tr>
<td>Sulfated polysaccharides</td>
<td>Aghardhiella tenera</td>
<td>Virus adsorption</td>
<td>Boyed MR et al. (1997)</td>
</tr>
</tbody>
</table>

Table 3: Biomolecules from Brown Algae and its inhibitory activity on viral targets and life cycle.

<table>
<thead>
<tr>
<th>Bioactive molecules</th>
<th>Brown Algae</th>
<th>Virus Targets (within the replication cycle)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water extract</td>
<td>Cystoseira myrica</td>
<td>herpes simplex virus type 1 (HSV-1)</td>
<td>Keivan Zandi 2007</td>
</tr>
<tr>
<td>Aqueous/Ether extract (Diterpenes)</td>
<td>Dictyota Pfaffii Schnetter</td>
<td>HSV-1</td>
<td>Jussara et al, 2003</td>
</tr>
<tr>
<td>Sulphated polysaccharide</td>
<td>Padina pavonia</td>
<td>HAV and HSV</td>
<td>Sahera F. Mohamed Fatimah</td>
</tr>
<tr>
<td>Diphlorethohydroxycarmalol</td>
<td>Ishige Okamurae</td>
<td>HIV-1 reverse transcriptase and integrase</td>
<td>Ahn MJ et al. 2006</td>
</tr>
<tr>
<td>Galactofucan Fucose, galactose</td>
<td>Adenocystis articulavis</td>
<td>anti-HIV-1 activity in vitro</td>
<td>Trinchero et al., 2009</td>
</tr>
<tr>
<td>Sulfated polymannorogluuronate Mannuronate</td>
<td>Dictyota mertensii</td>
<td>HIV-1 entry</td>
<td>Meiyou et al, 2003</td>
</tr>
<tr>
<td>Sulfated polymannuronate Mannuronate</td>
<td>Lobophora variegata</td>
<td>HIV-1 entry</td>
<td>Stephan Kremb et al. 2014</td>
</tr>
<tr>
<td>Sulfated fucans Fucose</td>
<td>Fucus vesiculosus</td>
<td>HIV-1 reverse transcriptase</td>
<td>Queiroz et al.</td>
</tr>
</tbody>
</table>
CONCLUSION

The algae derived natural biomolecules has several advantages, such as availability, relatively low production cost and low cytotoxicity. Recent studies demonstrated that biomolecules and extracts from four major classes of marine algae targets HIV, HSV, fish virus, Ebola, SARS, hepatitis C and H5N1 enzymes and inhibits viral entry and replication. These compounds can be used alone or in combination with other ART drugs for anti-viral infections. Although these biomolecules have shown promising anti-viral activity in vitro and in animal models, further studies by chemoinformatics and identification of target binding sites will improve our knowledge to investigate their anti-viral activities in humans.

REFERENCES


