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A REVIEW ON ANTI HIV AGENTS FROM MARINE SOURCES

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ABSTRACT

HIV infects specific white blood cells by hijacking the CD4 receptor on its surface to gain access to the cell and causes necrosis. HIV-infected patients with weakened immune systems can develop life-threatening infections. According to UNAIDS there were approximately 36.9 million people worldwide living with HIV/AIDS in 2017. Of these 1.8 million were children.[10] The current review focuses on the marine derived compounds which possess anti HIV activity and which can be studied further for development of new anti viral drugs.

KEYWORDS: Marine, anti-HIV agents, natural.

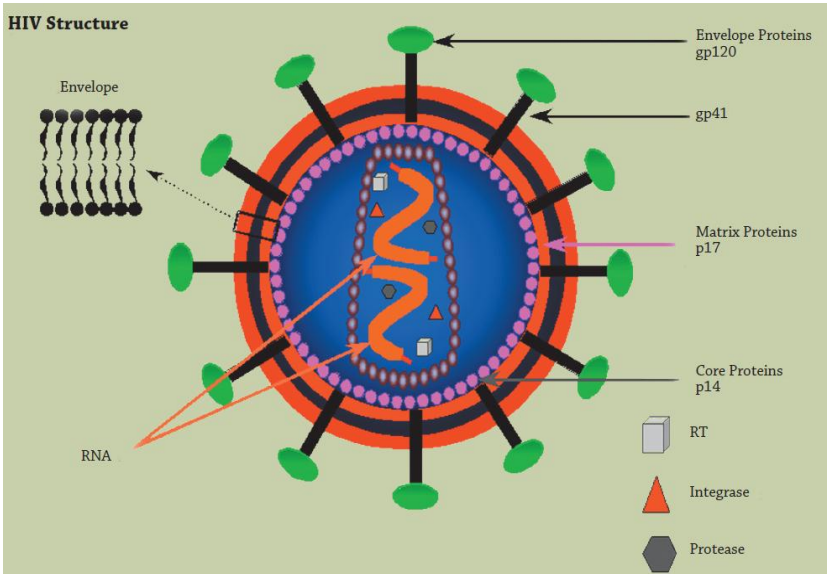
INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus belonging to the family of lentiviruses[8] that infects specific white blood cells with the CD4 receptor on their surface (CD4+ cells). CD4 is hijacked by HIV which uses it to gain access to the cell. Once inside the cell, the virus's genetic material, RNA, is converted to DNA in a process called reverse transcription. The viral DNA is then inserted into the host's DNA where it remains for the lifetime of the cell. The host cell synthesizes viral RNA and proteins, new HIV particles are assembled, which escape and infect other CD4+ cells. As the virus leaves the cell it disrupts the cell membrane leading to host cell death. HIV is so destructive because it infects and destroys the white cells that are responsible for regulating other immune cells. This causes the individual to become severely immune compromised, which leads to acquired immune deficiency syndrome (AIDS). AIDS occurs when the virus has destroyed the immune system, leaving the patient highly susceptible to other life-threatening infections. There are many possible types of experimental HIV vaccines, although none have successfully passed a phase three clinical trial. There is currently no cure for HIV infection, or a vaccine to prevent it.

Treatment consists of a combination of three or more anti-retroviral drugs (ARVs). This combination therapy [also known as Highly Active Anti-Retroviral Therapy (HAART)] slows down the progression of HIV, prolonging the patient's life. There are currently 24 ARVs licensed for use.[9]

Structure of HIV

HIV consists of a cylindrical center surrounded by a sphere-shaped lipid bilayer envelope. There are two major viral glycoproteins in this lipid bilayer, gp120 and gp41. The major function of these proteins is to mediate recognition of CD4+ cells and chemokine receptors, thereby enabling the virus to attach to and invade CD4+ cells. The inner sphere contains two single-strandedcopies of the genomic material, RNA, as well as multiple proteins and enzymes necessary for HIV replication and maturation: p24, p17, reverse transcriptase, integrase, and protease. Unlike other retroviruses, HIV uses nine genes to code for the necessary proteins and enzymes. The three principal genes are gag, pol, and env. The gag gene encodes core proteins. The pol gene encodes the enzymes reverse transcriptase, protease, and integrase. The env gene encodes the HIV structural components known as glycoproteins. The rest of the genes—rev, nef, vif, vpu, vpr, and tat—are important for viral replication and enhancing HIV's infectivity rate.[11] [12]



Anti-HIV drugs from marine sources

Phlorotannins

Tannins are naturally occurring water-soluble polyphenolic compounds. Phlorotannins are tannin derivatives which contain several phloroglucinol units linked to each other in different

ways and formed by the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units and biosynthesis through the acetate–malonate pathway.

Two phlorotannins from brown alga Ecklonia cava Kjellman have been isolated and reported to inhibit the HIV-1 protease and RT. These pholorotannins, 8,8'-bieckol and 8,4'''-dieckol, which are dimers of eckol, isolated from E. cava, inhibited the RT and protease activity efficiently. In case of inhibition of HIV-1 RT, 8,8'-bieckol which has a biaryl linkage showed a 10-fold higher activity than that of 8,4'''-dieckol.

In addition to these results, 6,6'-bieckol from E. cava reduced the cytopathic effects of HIV-1 including HIV-1-induced syncytia formation and viral p24 antigen levels, as well as inhibited RT and HIV-1 entry and activity dependent on the inhibition of production of specific proteins such as p55 and p41.[1]

Another phlorotannin, diphlorethohydroxycarmalol has been isolated from Ishige okamurae Yendo. It was assayed for its inhibitory activity against HIV-1 RT, integrase, and protease. Diphlorethohydroxycarmalol inhibited the RT and protease activity, but it did not show any efficiency against HIV-1 protease. Any study for its HIV-1 activity in vitro has not been carried out.[2]

Polysaccharides

Marine algae are abundant sources of different type of plant-originated bioactive polysaccharides. The chemical structure, amount and bioactivity of these polysaccharides vary according to marine algae species and divisions such as Chlorophyta (green algae), Rhodophyta (red algae), and Phaeophyta (brown algae). It is proposed that polysaccharides are quite efficient in disrupting the viral peptide attachments which are supposed to be highly preserved in the drug-resistance mutation process. Therefore, polysaccharides are directed to affect these peptides as potential anti-HIV targets.

Fucans are sulfated polysaccharides of high molecular weight which can be found widely in various brown algae species. Several fucans from the seaweed species Dictyota mertensii, Lobophora variegata, Spatoglossum schroederi, and Fucus vesiculosus were reported to successfully inhibit the activity of HIV RT. Reserve transcriptase is a common name for an enzyme that functions as an RNA-dependent DNA polymerase. They are encoded by retroviruses, where they copy the viral RNA genome into DNA prior to its integration into

host cells.

An isolated galactofucan with lower sulfate content from L. variegate inhibited the 94% HIV-1 RT activity at a concentration of 1.0 mg/mL. Another isolated fucan with a higher sulfate content and containing mostly fucose units exerted a high inhibitory effect on RT as well.

Same fucan from two different algae, S. schroederi and D. mertensii, showed similar inhibition ratios which are 99.03% and 99.30%, respectively, at 1.0 mg/mL concentration. However, higher sulfate containing fucan from S. schroederi with the units of galactose and fucose could only show a 53.90% inhibitory against the RT activity at the same concentration.[3]

Lectins

Lectins are carbohydrate-binding proteins which are found in a variety of species ranging from prokaryotes to corals, algae, fungi, plants, invertebrates, and vertebrates. Due to their specific carbohydrate-binding properties they are highly involved in crucial biological processes such as host–pathogen interaction, cell–cell communication, induction of intracellular signaling cascades, and cell targeting.

Griffithsin is a novel lectin isolated from the red algae Griffithsia sp. with a molecular weight of kDa. This 121 amino acid protein with no cysteine residues is reported to display promising anti-HIV activity. Griffithsin potently prevented the T-lymphoblastic cells from the cytopathic effects. Griffithsin blocked cell–cell fusion between chronically infected and uninfected cells at sub nanomolar concentrations without any cytotoxic effect.[4]

A high-mannose-binding lectin (BCA) is isolated from green alga Boodlea coacta with potent antiviral activity against HIV-1 and influenza viruses.

Studies showed that BCA inhibited the HIV-1 infection with EC50 value of 8.2 nM. In addition, surface plasmon resonance analysis reported a high affinity between BCA and the HIV envelope glycoprotein gp120 with an association constant of 3.71 *108 M_1.The potent anti-HIV-1 activity of BCA was easily predicted from carbohydrate-binding propensity and similarity with formerly reported antiviral lectins.[5]

Aspernigrins with Anti-HIV-1 Activities

During their continuous chemical study of marine-derived fungi, four 2-benzylpyridin-4-one-

containing metabolites (1-4), including two structurally new aspernigrins C (3) and D (4), and other four known compounds (5-8) were isolated from the marine-derived black aspergilli, Aspergillus niger SCSIO Jcsw6F30.

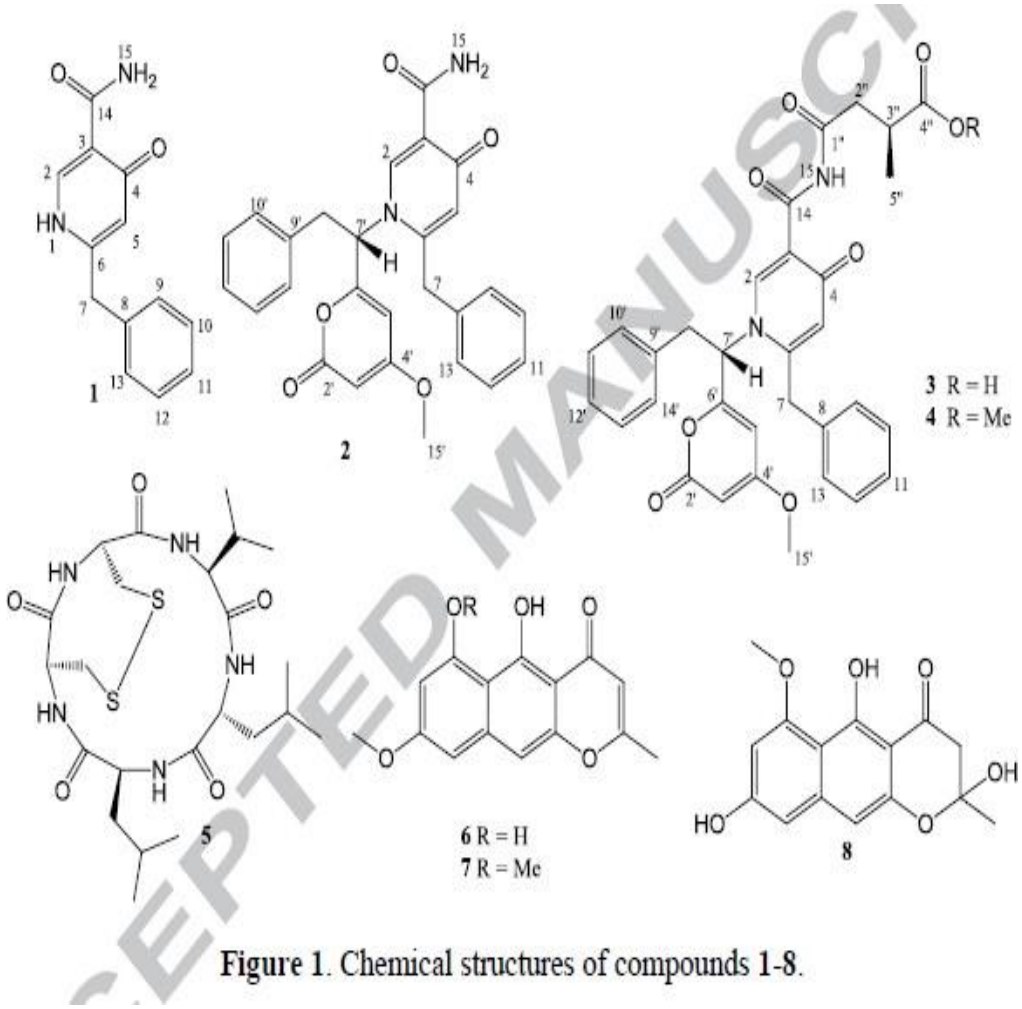


Figure 1. Chemical structures of compounds 1-8.

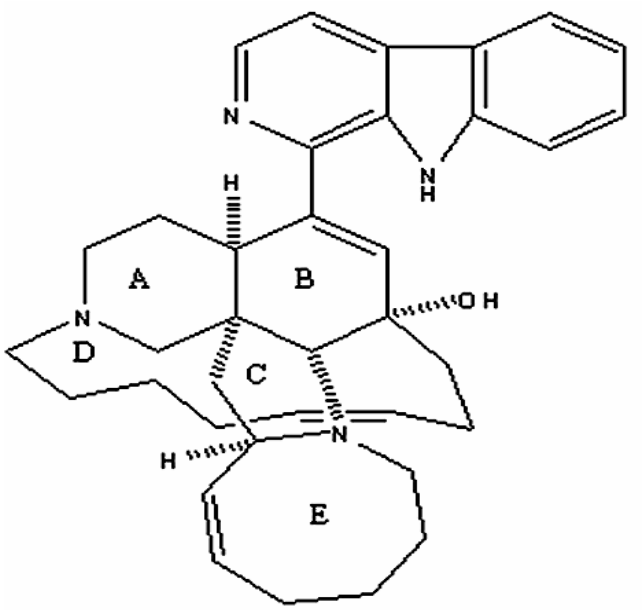
All of the compounds we obtained were tested for their inhibitory activities against chemokine receptor subtype 5 (CCR5) tropic HIV-1 SF162 infection.

They exhibited significant HIV-1 inhibitory activities by SF162 infection in TZM-bl cells. The mechanism of action is on-going and our results suggest these two compounds are potential lead product for the development of anti-HIV therapeutics.[6]

Manzamine

Manzamine A, a beta-carboline alkaloid present in several marine sponge species, has potent anti-HIV-I activities.[7] Oral and intravenous pharmacokinetic studies of manzamine A derivatives in rats indicated that they have low metabolic clearance, a reasonably long

pharmacokinetic half life, and good absolute oral bioavailability which make them as potential leads for preclinical assessment.[13]



CONCLUSION

The drawbacks of these current anti HIV drugs is that the combinations of anti viral drugs are used as specific drug for HIV is not available with good pharmacological activity. Because the combination of drugs are used the side effects may be severe and patients may also develop drug resistance and may not response to the therapy. So there is need to develop new anti HIV agents which have novel structures and also investigations can be focused on the development of new drugs that target the virus directly.

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