International Journal of Advance Research in Science and Engineering
Volume No.07, Special Issue No.04, March 2018
www.ijarse.com
IJARSE
ISSN: 2319-8354

MARINE FLORA: A SOURCE OF POTENTIAL ANTI-H_1N_1 COMPOUNDS

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ABSTRACT

Commonly known as swine flu, H_1N_1 is caused by a variant of Influenza A, responsible for higher mortality and morbidity throughout the world. The struggle of world against H_1N_1 is completing almost a century now. A serious threat has been posed to human health due to its persist occurrence. In the last decade alone, the number of clinically approved drugs for the treatment of swine flu has escalated from 5 to 30. Pathological analysis has revealed the susceptibility of H_1N_1 influenza A (swine flu) to oseltamivir and zanamivir. However due to problems of increasing resistance and drug toxicity, successful control of infections related to viruses has settled as an unachieved goal. Marine source, being an underexplored source, can be used for development of novel antiviral agents. Many compounds from the marine source have established their identity in the late stages of clinical trials and several have been chosen as likely leads for prolonged preclinical evaluation. Anti influenza compounds have been isolated from different forms of marine life like sea weeds, fungi, corals, sponges. In the current review emphasis has been laid on marine drugs which have shown in-vivo or in-vitro activity against swine flu: the mammoth of century.

Keywords: Fungi, H_1n_1virus, Influenza, Marine, Resistance.

I INTRODUCTION

In 1992, Rob Webster, a virologist was amongst the first few people to predict birds as all the sources of influenza A viruses (IAV). Till date influenza viruses have claimed millions of lives responsible for causation

of annual epidemics and intermittent pandemics Jonathan et al., (2013). To public health and the scientific communities, the emergence of new influenza strains will persist to pose challenges (Gabriele et al., 2009). Influenza viruses belong to the family of Orthomyxoviridae (Sami and Kenneth, 2010). All Influenza viruses adopt almost same route of transmission, the principle route being respiration via large-particle respiratory droplet inhalation or through droplet nuclei. Large particle droplets as the name indicates cannot travel longer distances or remain suspended in the air, therefore large particle droplet transmission requires close contact between persons (< 2 meters). Alternative source of spread is contact with contaminated surfaces. Bodily fluids and respiratory secretions of diseased individuals can pose an infection threat to healthy and susceptible individuals (Ynag et al., 2009; United States Centers for Disease Control and Prevention a & b). Most of the times, disease is mild. The complications however can progress to emergency hospitalization. The afflicted populations of very young children, pregnant women, individuals with persistent cardiac and lung diseases, diabetes, immunosuppression, morbid obesity may require intensive care (Sami and Kenneth, 2010).

70% of the earth's surface is covered by oceans and 95% of earth's biosphere is a home to diverse marine organisms. Nearly each class of marine flora and fauna exhibits a different range of molecules with characteristic organizational qualities because of the special physical and chemical environments in the marine environment. Unfortunately, marine organisms are less studied for their pharmacological activities as compared to terrestrial plants (Schueffler & Anke, 2014). In the present times, microbes from marine cradle have established themselves as chief source of marine natural products (MNPs). Nowadays, they are drawing an enormous quota of attention round the globe as they find their place as important source of unique natural products. The existing cure for several virulent diseases are restricted hence the prime emphasis is laid over marine peptides which display wide range of anti-infective activities like antifungal, antimalarial, antimicrobial, antiprotozoal, anti-tuberculosis, and antiviral activities. Due to the snags of growing resistance to existing treatments, the need of era is to discover the new avenues for treatment of diseases. Marine source is one such gem, which is under evaluation for the discovery of new remedies which can be used as powerful antimicrobial drugs.

II SEA WEEDS AS BUDDING SOURCES FOR TREATMENT OF H_1N_1

The chief components of red seaweed cell walls are carrageenans. They epitomize nearly 30% to 75% of algal dry weight (McCandless & Craigie, 1979). A sulfated polysaccharide extract of red algae, κ-carrageenan apparently holds potential to obstruct replication of SW731 virus. Attachment of haemagglutinin (HA) to Madin-Darby canine kidney (MDCK) cells is particularly hampered thereby leading to clampdown of mRNA and protein expression after *in vitro* internalization. Therefore κ-carrageenan may prove as an appropriate agent against H_1N_1/2009 and other viruses comprising the HA of H_1N_1/2009 (Qiang et al, 2015). Similar kind of study by Wang et al., 2011 has revealed κ-carrageenan oligosaccharide mediated inhibition in proliferation of influenza A H_1N_1 virus. The possible mechanisms behind this effect being inhibition of transcription and protein expression and direct inactivation of virus particles.

Many researchers in the recent past have reported the antiviral activities both *in vivo* and *in vitro* (Schaeffer and Krylov, 2000; Hidari et al., 2008). Red algae polysaccharide is predominantly isolated from definite genres of

red seaweeds such as *Chondrus, Eucheuma, Gigartina, Hypnea* (Lahaye et al., 2001). One of the characteristic features that algal polysaccharides possess is the presence of sulfate and uronic acid groups thus differentiating them from polysaccharides of terrestrial plants. Antiviral efficiency may be attributed to the similar features it shares with mammalian glycosaminoglycan like heparin and chondroitin sulfate. A number of polysaccharides have been acquired from Canadian sea weeds and investigated for antiviral activity. Polysaccharides from three red algae (*Polysiphonia lanosa*, *Furcellaria lumbricalis*, and *Palmaria palmata*), two brown algae (*Ascophyllum nodosum* and *Fucus vesiculosus*), and one green algae (*Ulva lactuca*) have been equated. The reported results reveal that the polysaccharides from brown algae happen to be predominantly effective against influenza A/PR/8/34 (H_1N_1) virus (Guangling et al., 2012)- TABLE 1

Microalga *Gyrodinium impudium*, the source of sulfated polysaccharide p-KG03 has apparently inhibited attachment of H_1N_1 influenza virus. This inhibition is achieved by interfering with HA and cells (Kim et al., 2012). Oligomeric mannuronic acid (OM), a by product of polymannuronic acid polysaccharide having low molecular weight of less than 5 kDa has exhibited useful inhibitory outcomes on influenza A (H_1N_1) virus *in vitro* and *in vivo* (Wang et al., 2011)

III ANTI H_1N_1 COMPOUNDS FROM MARINE FUNGI

The trend on the antiviral potential of compounds isolated from marine fungi started in 1998 after the isolation of stachyflin from *Stachybotrys* sp. RF-7260 by Taishi and colleagues after it had shown promising antiviral activity against influenza A virus (H_1N_1). Stachyflin possesses a pentacyclic moiety which includes cis-fused decalin. Its antiviral activity is mediated through the inhibition of fusion between the viral envelope and the host cell membrane. Such activity is unique among antiviral compounds (Minagawa et al., 2002 a,b). Over the time, marine fungi have evolved as promising source to develop new antivirals against different viruses like the human immunodeficiency virus, the influenza virus and herpes simplex viruses. Marine fungi belong to the phyla Ascomycota, Bacidomycota, Chytridiomycota, Deuteromycota, and Zygomycota. Anti H_1N_1 polyketides sequestered from both marine and terrestrial fungi are sorbicillinoids. Sorbicatechols A and B are the two new sorbicillinoids which are isolated from marine and terrestrial fungus *Penicillium chrysogenum PJX-17*. These compounds have reportedly exhibited anti influenza virus A (H_1N_1) activity (Jixing et al., 2014).

The fermentation broth of the marine-derived fungus *Aspergillus terreus* SCSG AF0162 is a source of a cyclic tetrapeptide recognized as Asperterrestide A. As reported by Hee et al., (2015) Asperterrestide A has displayed inhibitory effects on M2 resistant strain (strain A/WSN/33- H_1N_1) and M2 sensitive strain (strain A/Hong Kong/8/68-H3N2). Another novel indole alkaloid (14*S*)- oxoglyantrypine holding pyrazinoquinazoline derivative framework isolated from culture of mangrove derived fungus *Cladosporium* sp. PJX-41 has exhibited anti H_1N_1 activity (Peng et al., 2013) TABLE 1. Compounds from marine-derived fungus *aspergillus terreus* sequestered from the sediment of the Putian Sea Saltern, Fujian, China have shown to possess adequate anti-H_1N_1 activity (Wang et al., 2011). The OUCMDZ-1925 strain of *Aspergillus terreus* is known to possess rubrolide S which has reportedly exhibited noticeable antiviral activity against influenza A (H_1N_1) virus (Zhu et al., 2014).

Wu and colleagues (2014) evaluated the secondary bioactive metabolites from a deep-sea-derived fungus called *Cladosporium sphaerospermum* 2005-01-E3. As exhibited by its IC value, the novel compound cladosin C has shown to possess sufficient antiviral activity against influenza A (H_1N_1) virus- TABLE 1. Further, the team of Wang et al (2011) were successful in finding six new polyketides with anti- H_1N_1 activity from the aciduric *Penicillium purpurogenum* JS03-21. A rich chemical diversity was observed when fermented at pH 2 as compared to those grown at pH.

IV SPONGES AS POTENTIAL ANTI H_1N_1 CANDIDATES

Marine environment is a host to one of the plush spring of pharmacologically active compounds known as marine sponges. Microbes related to sponges produce composites almost similar anti-influenza compounds. Spongothymidine and spongouridine were the early nucleosidic compounds sequestered from *Tethya crypta.* Further investigation and research gave birth to Ara-C and Ara-A. While Ara-C was an anticancer agent Ara-A proved to be the first antiviral drug. Ara-A exhibits its antiviral activity by acting as viral DNA synthesis inhibitor. Clinically it has been used for management of infection associated to herpes virus (Sunil S et al., 2010)- TABLE 1. A team of researchers led by Zhao explicated 14 compounds from sponge-associated fungus *Truncatella angustata.* The isolated compounds were isoprenylated cyclohexanols and were named truncateols A-N (A-N=1-14). In vitro testing of truncateols against influenza A (H_1N_1) virus revealed the anti H_1N_1 efficacy of Truncateol C, E and M. Truncateol M proved to be the most potent inhibitor as revealed by its IC_{50} value.

On chemical exploration of marine sponge *Pericharax heteroraphis* gathered from the South China Sea, several compounds have been isolated one of which happened to have feeble H1N1 activity (Gong et al., 2016). Another compound Asteltoxin E isolated from a marine sponge–derived fungus, Aspergillus sp. SCSIO XWS02F40 has shown significant inhibitory activity against H_1N_1 (Tian et al, 2016) TABLE 1. Calyceramides are other kind of novel influenza virus neuraminidase inhibitors. Three active sulfated ceramides, calyceramide A–C isolated from the marine sponge *Discodermia calyx* have shown significant activity against H_1N_1 (Nakao et al., 2001)- TABLE 1.

V CORALS AND ANTI H_1N_1 ACTIVITY

Various phyla of marine organisms are known to contain polyhydroxylated steroids. They are renowned for the broad spectrum of activities they possess. One such subclass is Octocorallia, commonly called “soft corals” (Sarma et al., 2009). On chemical exploitation of the soft coral Sarcophyton sp. isolated from the South China Sea several compounds were sequestered, some of which possesed significant anti H_1N_1 activity (Gong et al., 2013). Cheng et al., 2016 reported strong inhibitory effects of some pregnane type steroids without cytotoxicity isolated from a gorgonian coral Subergorgia suberosa. This proposes them to be the novel molecular models for the management of H_1N_1.

TABLE 1: Brief overview of anti H_1N_1 compounds from the marine source

S.No	Microorganism	Compound	Source	Basic skeleton	Reference
1.	*Ascophyllum nodosum*	Sulfated fucans	Brown algae	Polysachharides	Guangling et al., 2012
2.	*Aspergillus sp. SCSIO XWS02F40*	Asteltoxin E	Marine sponge derived fungus	Mycotoxin	Tian et al, 2016
3.	*Aspergillus terreus Gwq-48*	Aspulvinone, Isoaspulvinone, Aspulvinone E, Pulvic acid	Mangrove rhizosphere soil sample	Pulvinones	Gao et al., 2013
4.	*Aspergillus terreus OUCMDZ-1925*	Rubrolide S	Marine fungi	Furanone	Tonghan et al., 2014
5.	*Aspergillus terreus SCSG AF0162*	Asperterrestide A	Marine fungi	Tetrapeptide	He et al., 2013
6.	*Cladosporium sp*	Oxoglyantrypine, Norquinadoline A, Deoxynortryptoquivaline, Deoxytryptoquivaline, Tryptoquivaline, Quinadoline	Mangrove derived fungus	Indole alkaloids	Peng et al., 2013.
7.	*Cladosporium sphaerospermum 2005-01-E3*	Cladosin C	Deep sea derived fungus	Enaminotetramic acid	Wu et al., 2014
8.	*Discodermia calyx*	Calyceramides	Marine sponges	Sulfated ceramides	Nakao et al., 2001
9.	*Emericella sp.*	Emerimidine A & B	Mangrove aegiceras corniculatum	Isoindolone	Zhang et al., 2011
10.	*Fucus vesiculosus*	Sulfated fucans	Brown algae	Polysachharides	Guangling et al., 2012
11.	*Furcellaria lumbricalis*	Sulfated galactans	Red algae	Polysachharides	Guangling et al., 2012
12.	*Gyrodinium Impudium*	pKG03	Marine microalga	Sulfated polysaccharides	Meehyein et al., 2012
13.	*Palmaria palmata*	Xylans	Red algae	Polysachharides	Guangling et al., 2012
14.	*Penicillium chrysogenum PJX-17*	Sorbicatechol A & B	Marine fungi	Polyketides	Peng et al., 2014
15.	*Polysiphonia lanosa*	Sulfated galactans	Red algae	Polysachharides	Guangling et al., 2012
16.	*Stachybotrys sp. RF-7260*	Stachyflin	Marine fungi	Terpenoid	Minagawa et al. (2002a,b)
17.	*Tethya crypta*	Ara-A	Marine sponge	Arabinosyl nucleoside	Sunil et al., 2010
18.	*Truncatella angustata*	Truncateol C, E & M	Sponge associated fungus	Isoprenylated cyclohexanols	Zhao et al., 2015
19.	*Ulva lactuca*	Heteroglycuronans	Green algae	Polysachharides	Guangling et al., 2012

VI CONCLUSION

A challenging problem in antiviral treatment is the swelling rate of pathological resistance and drug toxicity towards available synthetic antiviral drugs. Marine flora and fauna has a rich diversity of anti H_1N_1 compounds. A proper indepth exploitation of these sources is needed so that alternative strategies can be developed for treatment of swine flu.

VII ACKNOWLEDGEMENT

The sincere efforts of all the co-authors in writing this paper are highly appreciated. Heartfelt credits to Rumaisa Rashid, Mudasir Maqbool, Asmat Majeed and Saeima Farooq for all the cooperation.

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