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Microbial based promising natural bioactive compounds as potential inhibitors to combat viral infection

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Abstract: Infections caused by viruses are among the utmost ordinary diseases disturbing individuals worldwide. Novel viruses develop quickly and currently we don't have adequate quantity of vaccines besides merely limited antivirals compounds or agents to fight against viruses. The apparently irresistible viruses pose a human health risk because of the resistant and scarcity of operational therapeutics. With the aim to fight against viruses' lots of investigation had been dedicated for the innovation of novel natural antiviral compounds. Natural bioactive compounds of microbial origin provide stimuli so as to find and get novel drugs. The diversity of organic or natural bioactive compounds offers significant specificity and efficiency to aim different steps of viral infection and provide as an exceptional origin for antiviral compounds or agents. The detection and production of natural bioactive compounds acts as an antiviral agents continue to be a challenge because of paucity in their natural hosts. With the help of biotechnological tools for reconstruction of bioactive compounds with in microorganisms is an encouraging resolution to control this restraint. The scalability and economical production of new antiviral natural bioactive compounds, facilitated by metabolic or genetic engineering, might give the expectation to overcome and eliminate the lethal viruses. Among different bioactive compounds isolated from bacteria, fungi and algae (Carrageenan, Nostaflan, Galactan Sulfate, Alginate, Fucan & Fucoidan, Naviculan, Laminaran), polysaccharides are well-recognized compounds, as they possesses broad antiviral activities. Furthermore, these bioactive compounds use diverse molecular mechanisms, for example inhibition of binding or else virus internalization inside the host cell, suppression of replication of DNA and biosynthesis of proteins. This chapter focused on the present knowledge of microbes, microbial based natural bioactive compounds and their molecular mechanism of action with actual target site so as to produce probable natural bioactive antiviral compounds for future research.
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1. Introduction

Unique viral structures and their complex lifecycles had constructed the innovation of novel therapy in case of viral infection exceptionally challenging. Several viral infections comprising Covid-19 (SARS-CoV2), AIDS, Herpes virus and Hepadnavirus produce a risk to the human healthiness because of the deficiency of operational therapeutics. Regardless of complete research efforts for appropriate vaccines and treatment against particular viral infection, still numerous infections, for example Dengue Virus (DENV), HCV and HIV affect a considerable proportion of the world populations (Murrell et al 2011; Lazarus et al 2014). Development of vaccine against certain viruses for instance HIV and HCV was up to now evidenced to exist as an impulsive scheme. Besides, the problem of toxicity to target cells and drug resistance towards antiviral agents has been a severe impairment to the management of viral infections (Qian et al 2012). Furthermore, the continuous appearance of novel serotype's inside virus clusters with high mutation rate and less accuracy for replication of virus supplements complications in fighting against viral particles. Approximately 7 to 20% of worldwide population have started Antiretroviral Therapy (ART) had resistant HIV in 2010. As per the World Health Organization (WHO) recommendation in the year 2015, every HIV positive person should be on ART. Henceforth, augmented ART resistance is estimated as more individuals start ART.

Natural compounds have used immensely in Chinese and Indian Ayurveda since ancient times. During recent years various modern antiviral drug molecules have been isolated from natural compounds and empirically used to combat virus infections. The antiviral drugs target the specific viral proteins or else the cellular components of host (exploited for

reproduction) to combat virus infections (De Clercq, 2002). Conversely, when viral proteins are used as a target site for drug action the viruses could produce resistant mutants against antiviral drugs (De Palma et al 2008).

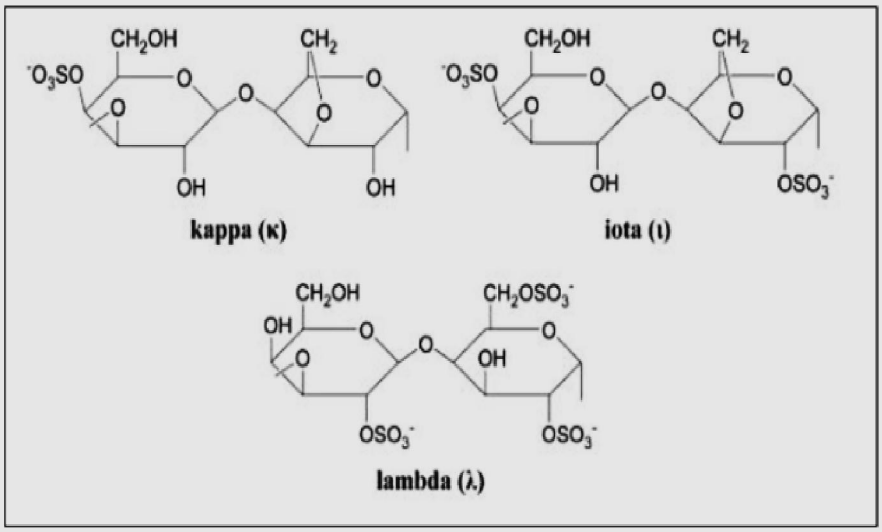
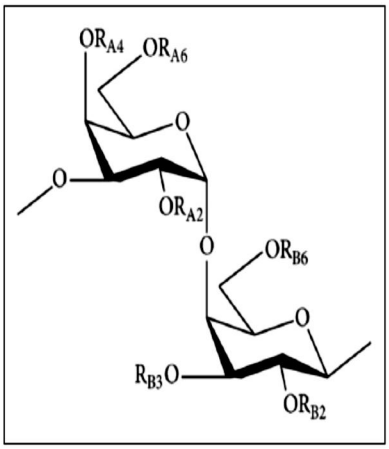


Fig. 1 Structure of Carrageenans



R_{B6}: H, SO_3^-, R_{B3}: H; R_{B2}: CH_3, SO_3^-, H; R_{A6}: H, CH_3, Pyruvic acid, SO_3^-; R_{A4}: SO_3^-, H, pyruvic acid; R_{A2}: H, SO_3^-.

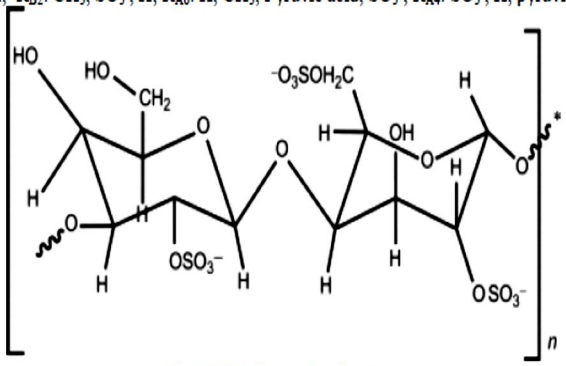


Fig. 2 Galactan unit's structure

During trials an antiviral drugs have to accomplish a set of fundamental requisite such as its effectiveness in virus infection inhibition without affecting host cells and inhibition of virus infection completely as fractional inhibition leads to the production of resistant mutants. As a result, few drugs (<10) have been officially licensed against viral infections till the 21st century. Subsequently, for obtaining complete knowledge of multiplication of viral life cycle, research is going on in order to discover novel antiviral agents or drugs. However, we are so far from monitoring the viral infection. Though, today the emphasis has been shifted toward broad spectrum antiviral drugs designing (Vigant et al 2015). In contrast, diverse bioactive components are obtained from naturally occurring biological sources. These natural products still provide the inexpensive treatment and served as traditional medicine for many threatening diseases (Amzat and Razum, 2018). Amongst microbes, algae is an ample inception of bioactive metabolites having enormous prospective at pharmaceutical level, comprising antiangiogenic, anti-cancer, antioxidant, anti-tumor, neuroprotective, antimicrobial, antiobesity, anti-inflammatory and antinociceptive actions (Pangestuti & Kim 2011; Moghadamtousi et al 2014). The distinctive living environment has remarkable assortment of microorganism (Bacteria, fungi or algae) have encouraged substantial commercial attention as food, fertilizer, agar, iodine source, and potash (Yasuhara-Bell & Lu, 2010). Numerous new natural bioactive metabolites had been extracted from marine fungi and bacteria which have antiviral, anticancer and antibacterial activities (Singh et al 2015). Therefore, the current chapter summarizes the latest advancements where several microbial based natural compounds have been isolated and used empirically to combat virus infections. Consequently, there is a necessity for recognizing agents with different or innovative mechanism of action and enhanced effectiveness. Several in vivo, in vitro, computational studies are further requisite to validate the potential of bioactive components of natural origin.

1 *Bacteria as a source of antiviral agents*

Microbes are promising producers of biologically active metabolites as they can be grown easily in bioreactors from 5ml – 100,000 l scale, able to make the natural products production under controlled environment (Reichenbach, 2001). Large number of marine bacteria produced unique secondary metabolites having new plus different structural formula that might be advantageous for the finding and expansion of new remedies against viruses (Blunt et al 2018). Around 660 novel bacterial natural products have been recognized from marine resources in the period of 1997-2008. Major classes of marine bacteria involved are of the order Actinomycetales, Cyanobacteria, Proteobacteria and few members of the Firmicutes and Bacteroidetes with 40%, 33%, 12% and 5% contribution, respectively (Williams, 2009). In contrast in the year 2016, 179 new products have been recovered from marine bacteria.

Presently, there have been merely a limited compounds (marine exopolysaccharides) extracted from marine bacterial cells with antiviral potential (Table 1). Majority of marine bacterial population produced exopolysaccharides (EPS) as an approach to adhere solid substratum, for growth, and existence in conditions which are highly adverse (extreme environment). Bacterial cells isolated from deepsea hydrothermal vents, for example *Alteromonas infernus, Vibrio diabolicus* and *Alteromonas macleodii* subsp. *fijiensis* could create EPS having unique structural formula that facilitate bacterial species to stay alive in utmost environmental conditions (Arena et al 2009).

Table 1 Marine bacterial antiviral compounds (adapted from Yasuhara-Bell J & Lu Y, 2010)

Antiviral compound	Associated microbe	Viral activity	References
Macrolactin A	Deepsea bacteria	HSV, replication of HIV	Gustafson et al (1989a, b)
Exopolysaccharides-1 (EPS 1) and Exopolysaccharides-2 (EPS-2)	*Blicheniformis* and *Geobacillusthermodenitrificans*	Replication of HSV-2, up regulation of Thl cytokines	Arena et al (2006 and 2009)

Macrolactin-A

It is extracted from deepsea bacterial cells. It comprises lactones, open chain acids and glucose pyranosides. This compound displays the defense to T lymphoblasts in case of HIV replication (Gustafson et al 1989b).

Exopolysaccharides (EPS)

Sulphated EPS are involved in inhibition of several retroviral reverse transcriptase enzymes and create interference with the adsorption and entrance of viral particles inside the host. EPS-1 & 2 was derived from *B.*

licheniformis and *G. thermodenitrificans*, respectively (Table 1) (Arena et al 2006, 2009). The antiviral activities exerted by EPS-1 & 2 (@ concentration 200 & 300g/ml) were able to decrease Herpes simplex virus 2 (HSV) titer.

In addition to above mentioned marine sources, Myxobacteria are known secondary metabolites producers with new mechanism of action (Herrmann et al 2017; Hüttel et al 2017). Myxobacteria (δ proteobacteria) belong to Myxococcales. Recently, majority of the secondary metabolites recovered from myxobacteria have been found with notable antiviral potential against several viruses (Koutsoudakis et al 2015; Herrmann et al 2017). The majority of biologically active components are derived from Non ribosomal peptide synthetases (NPRSs), Polyketide Synthases (PKSs) or else a hybrid of NPRSs and PKSs (Wenzel & Müller 2009;

Table 2 Natural products production inside engineered microbes

Natural Products	Host	Source
Aromatics		
Pinocembrin	*E. coli*	Tao et al 2018
p-Coumaric acid	*S. cerevisiae*	Liu et al 2019
Kaempferol, Quercetin and Caffeic acid	*S. cerevisiae*	Lyu et al 2019; Rodriguez et al 2017; Liu et al 2019a
Resveratrol	*S. cerevisiae, E. coli*	Li et al 2016; Lim et al 2011
Apigenin, Baicalein, Scutellarein	*E. coli*	Lee et al 2015; Li et al 2019
Naringenin, Taxifolin	*Y. lipolytica*	Palmer et al 2020; Lv et al 2019
Terpenoids		
Betulinic acid	*S. cerevisiae, Y. lipolytica*	Huang et al 2019; Sun et al 2019
Glycyrrhetinic acid, Oleanolic acid, Artemisinin	*S. cerevisiae*	Paddon et al 2013; Zhao et al 2018; Wang et al 2019
Others		

Weissman & Müller 2010). According to various research reports, actinomycetes are capable of producing new bioactive agents with antiviral activity against numerous pathogenic viruses which comprise Zika virus, HIV-1, Western equine encephalitis virus, influenza A and acyclovir-resistant herpes simplex virus (Uyeda, 2004; Jakubiec-Krześniak et al 2018).

Recently, with the advent of microbial engineering technology several natural products ranging from piperidine alkaloids, aromatics, polyketides, terpenoids and nucleotide analogs were synthesized in diverse microbial hosts having great potential against viral infections (Table 2). Among all, most abundantly aromatic compounds have been genetically engineered inside microorganisms due to its lipophilic nature that predominantly act on different stages of viral multiplication viz. starting from the adsorption, entry, translation of RNA of virus and repackaging. **2**

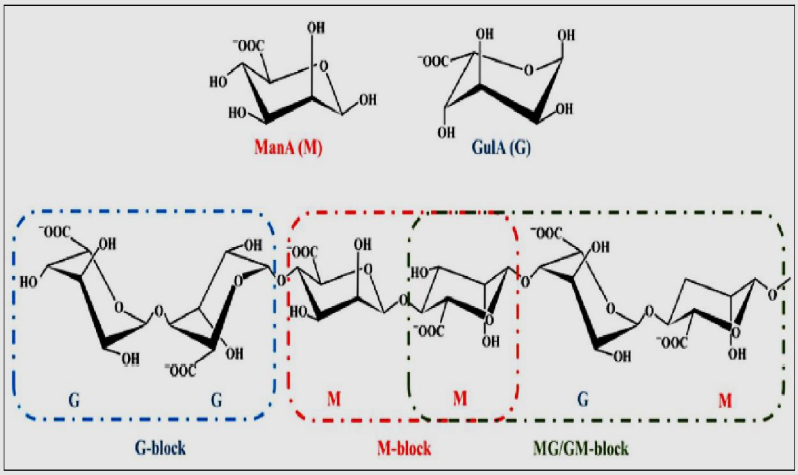


Fig. 3 Structure of alginate. Monomeric units of alginate are ManA (M) i.e. β-D-mannuronic acid and GulA (G) i.e. α-L-guluronic acid

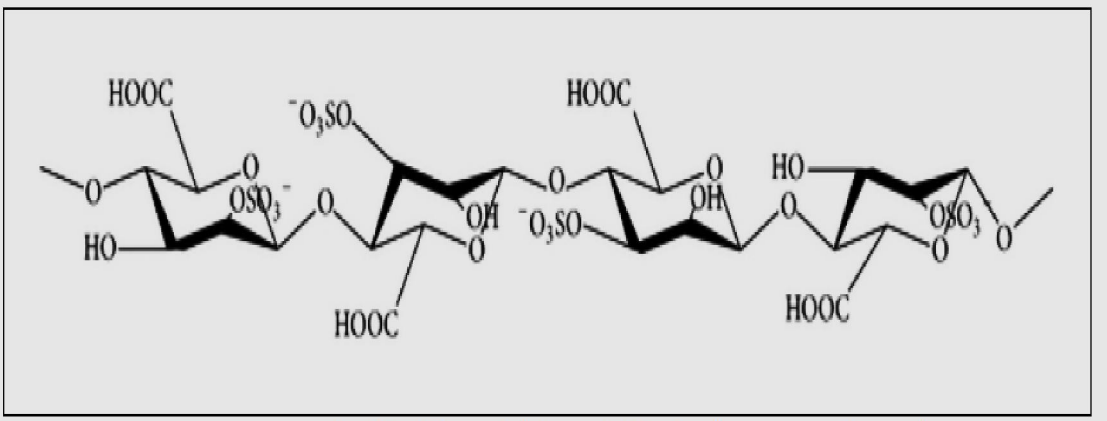


Fig. 4 Structure of sulfated form of alginate (sulfated polymannuroguluronate)

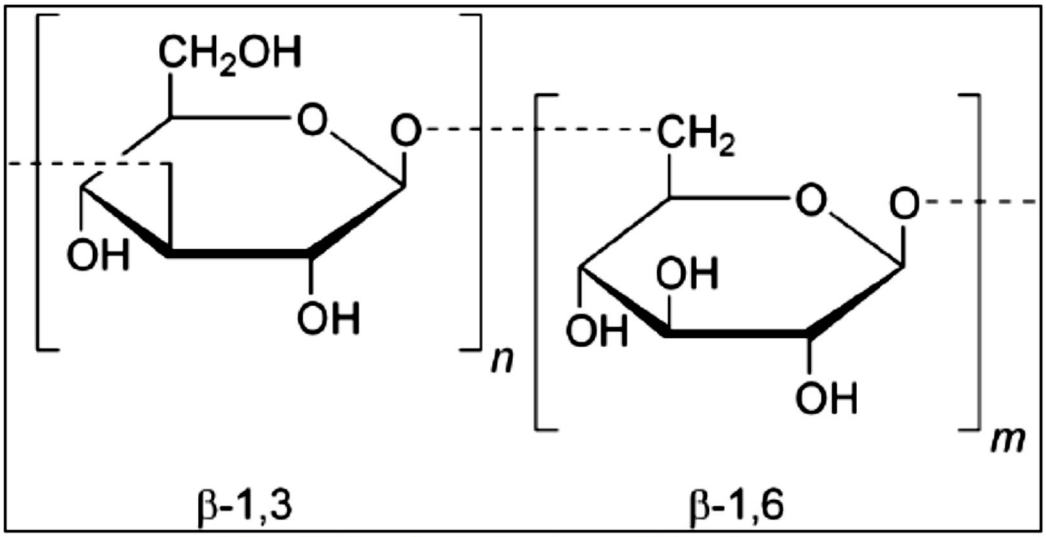


Fig. 6 Chemical structure of Laminaran

Fungal sources of antiviral agents

Secondary metabolites (small organic molecules) extracted from fungi are an auspicious origin of several drugs which can be used against viral infections. High molecular weight compounds for example lignin-derivatives, proteins and polysaccharides are another category of bioactive compounds can be exploited against specific viruses (Table 3).

2.1 ***Secondary Metabolites***

Secondary metabolites of fungi are not essential for the growth. It has been postulated that these compounds mimic defense compounds of plants and thus offer communication and competition against pathogens (Khaldi et al 2010; Kusari et al 2012).

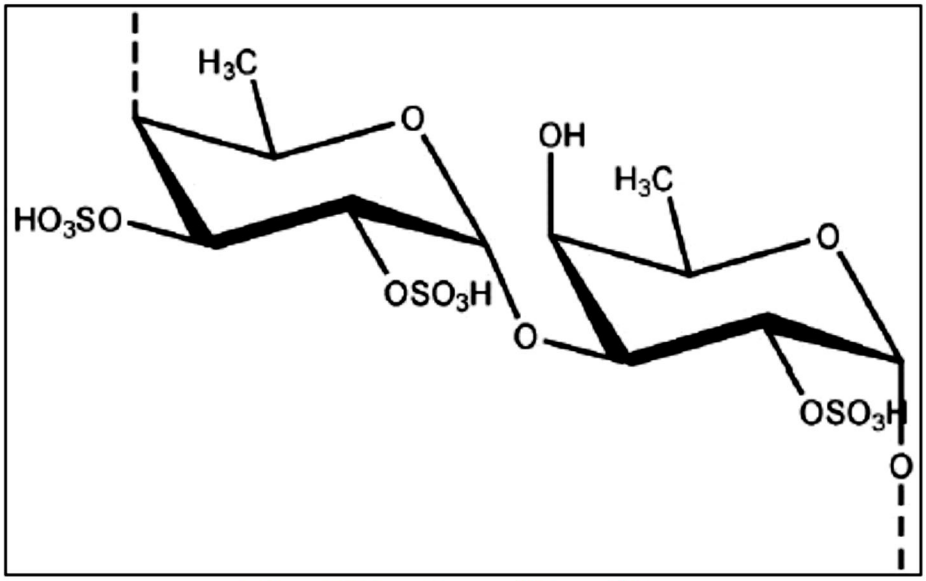


Fig. 5 Structure of Fucoidan

2.1 *High molecular weight compounds*

The cell wall of fungus is mainly composed of polysaccharides and proteins although huge variation can be observed among fungal species as well as in the same species (Bowman and Free, 2006). Polysaccharides (lentinan, mannan, glucan and chitin) extracted from mycelium and fungal fruiting bodies have potential activities against viruses (Cardozo et al 2011; Rincão et al 2012). Cell wall proteins take part in the regulation, interaction along with formation of metabolites (Bok and Keller, 2016). There are a number of mechanisms to inhibit infection of viruses at diverse stages (Table 4). The foremost mechanism is direct attack on virus particle prior to their attachment on host cell's receptors. Another probability to inhibit viral life cycle is inhibition of receptor binding (Cagno et al 2018). In addition, several targets are being exploited for combating viral infection such as lipids, cholesterol, viral proteases or polymerases.

These studies have determined numerous extracted bioactive compounds and extract which exhibited inhibitory effect on the adsorption or else directly upon the virus particles. There are several other fungal sources for antiviral compounds (Table 5). Bioactive molecules for example phomasetin in addition to equisetin are derived among marine fungus *Phoma* sp. and *F. heterosporum*, respectively, as well as have displayed HIV-1 integrase inhibition. Furthermore, *Fusarium* sp. are a major source of Sansalvamide A (a cyclic depsipeptide) and this compound exhibited inhibition of the topoisomerase activity of the poxvirus by stopping relaxation of DNA bring out by topoisomerase, binding of DNA and formation of covalent complex (Hwang et al 1999). Stachyflins, with a pentacyclic moiety, shows its anti-viral capacity contrary to influenza A virus and is occurred via the avoidance of fusion amongst the cell membrane of host and virus envelope (Minagawa et al 2002). Another antiviral compound is Halovirs A-E (novel peptides), derived from *Scytidium* sp. (fungus), ensure strong antiviral action contrary to HSV (type 1 & 2) (Rowley et al 2003). The halovirs reduce HSV non-infectious via probable destabilization of membrane.

3 *Algal sources of antiviral agents*

Algal derived polysaccharides are naturally occurring polymers that are harmless, non-hazardous, inexpensive, biocompatible and biodegradable (Guo et al 1998). Researchers took keen interest in algal derived polysaccharides because of noticeable natural activities of diverse algal polysaccharides for instance carrageenan, galactan, agar, fucoidan, alginate, proteoglycans, laminaran, rhamnan sulfate and galactosyl glycerol (Li et al 2008; Rioux et al 2010). Major marine sources of algal polysaccharides with their antiviral activities have been summarized in Table 6.

Table 3 Bioactive compounds from Fungi possessing activities against viruses.

Category of chemical	Source (Order)	Reference
Low molecular weight (Secondary metabolites) compounds from Ascomycota		
Terpenoids	Xylariales, Amphisphaeriales, Hypocreales, Eurotiales and Pleosporales.	Sawadjoon et al 2004; Zhang et al 2014
Indole alkaloids	Capnodiales, Pleosporales Eurotiales and Hypocreales	Zhang et al 2011; Peng et al 2013; Zhao et al 2017
Polyketides (PKS)	Amphisphaeriales, Eurotiales, Diaporthales, Pezizales, Hypocreales, Sordaliales and Pleosporales.	Peng et al 2014; Sacramento et al 2015; Pang et al 2018
High molecular weight compounds from Basidiomycota		
Polysaccharide-amino acid/protein complex	Polyporales	Kim et al 2000
Polysaccharides	Polyporales and Agaricales	Cardozo et al 2011; Yamamoto et al 2013
Lignin-derivatives	Polyporales	Sarkar et al 1993
Proteins	Polyporales and Agaricales	Ngai and Ng, 2003; Gu et al 2007

3.1 *Algal Sea Extract*

Algal sea extracts are high molecular weight polysaccharide (sulfated) extracted from Rhodophyta '*Schizymenia pacifica'*. It belongs to carrageenan, that is made up of 3, 6-anhydrogalactose, sulfonate and galactose with a percentage of 0.65, 20 and 73, respectively. It has great potential towards reverse transcriptase inhibition and replication under in vitro conditions in case of HIV (Nakashima et al 1987).

3.2 *Carrageenans*

These inhibit various enveloped or non-enveloped viruses selectively simply by preventing the virus binding with the respective host cell. Carrageenan is potential inhibitor of Human papillomavirus (sexually transmitted disease) that result in genital warts and cervical carcinoma (Gonzalez et al 1987). The low molecular weight (3 to 10 kDa) carrageenan along with its derivatives such as sulfated or acetylated, showed antiviral potential against influenza under in vivo case studies using mice as an experimental organism. Antiviral action of carrageenans (Fig. 1) in case of Herpes simplex virus 2 and human rhinovirus propagation through inhibiting the replication of virus is also reported (Tischer et al 2006). In addition to this, effectiveness in case of dengue virus is also depicted

3.3 *Nostoflan*

Nostoflan is a polysaccharide present in Cynaobacteria, *Nostoc flagelliforme.* It is predominantly composed of sugar sequences of (→4)--D-Glcp-(1→4)-D-Xylp-(1 and→4)-[-D-GlcAp-(1 → 6)-]--D-Glcp-(1→4)-D-Galp-(1→). Nostoflan has an inhibitory action on enveloped viruses comprising HSV (1 & 2), type A influenza and human cytomegalovirus (HCMV). Nostoflon induces antiherpetic effect simply by preventing the binding of viral particle with its respective host cell (Kanekiyo et al 2007).

3.4 *Galactan*

Sulfated galactans are the foremost polysaccharides (extracellular) isolated from red algae. They are consist of galactose molecules arranged in linear manner with some exemptions; an alternating G-units (3--D-galactopyranose) as well as 4--D-galactopyranose or 4-3,6-anhydro galactopyranose form backbone with presence of L unit in agarans and D units (D-series) in carrageenan (Fig. 2) (Delattre et al 2011). The DL hybrids are another exceptional galactans. These unique polysaccharides of algae possess strong antiviral potential against various enveloped viruses, for example HIV (type 1 & 2), HSV (type 1 & 2), hepatitis A and DENV virus. Galactan sulfate extracted from *Agardhiella tenera* shows an operational control in case of HIV. It obstructed the attachment of viruses to host, besides the adherence of gp120 on $CD4^+$ T cell receptor (TCR) to gp120 of HIV (Witvrouw et al 1994). Sulfated galactans' antiviral activity extracted from the *S. binderi* against HSV (type 1 & 2) with lowest cytotoxicity was observed by Matsuhiro (2005) and his Colleagues.

Table 4 Different mechanisms used to inhibit infection of viruses

Bioactive compound	Source	Mechanism	Target viruses	Reference
GFAHP (Protein)	*Grifola frondosa*	Direct action on virus particle	Herpes simplex virus	Bruggermann et al 2006
Aurenitol	*C. coarctatum*		Influenza A virus subtype H3N2	Sacramento et al 2015
β-glucan protein	*Agaricus subrufescens*	Adsorption	HSV-1	Yamamoto et al 2013
Polysaccharopeptide	*Trametes versicolor*		HIV	Collins and Ng 1997
Polysaccharide	*A. brasiliensis*	Replication	Polio virus	Faccin et al 2007
Triterpenoids	*Ganoderma sinense*	Viral proteins	HIV Protease	Sato et al 2009
Ganoderic acid	*Ganoderma lucidum*		HIV Protease	Min et al 1998
Velutin	*Flammulina velutipes*		HIV reverse transcriptase	Wang and Ng 2001

Table 5 Marine fungal sources of antiviral compounds

Fungal source	Bioactive Compound	Associated activities	References
Phoma sp.	Phomasetin	Inhibition of integrase enzyme of HIV type 1	Singh et al (1998)
F. heterosporum	Equisetin		
Fusarium sp.	Sansalvamide A	Stopping DNA relaxation bring out by topoisomerase, binding with DNA also formation of covalent complex	Hwang et al (1999)
Stachybotrys sp. RF-7260	Stachyflin	Fusion of Influenza virus (H1N1)	Minagawa et al (2002)
Scytidium sp.	Halovir A-E	HSV(type 1 & 2) destabilization of membrane	Rowley et al (2003)

3.5 *Calcium Spirulan*

It is a sulphated polysaccharide was extracted from *Arthrospira* platensis. The polysaccharide consists of glucose, galactose, xylose, mannose, glucuronic acid, fructose, rhamnose, ribose, galacturonic acid, calcium and sulfate. Calcium spirulan was the selective inhibitor of numerous viruses, comprising HCMV (in HEL cells), HIV-1 (in MT-4 cell), Human simplex virus 1 (in HeLa cell), type A influenza (in MDCK cell), polio, Coxsackie virus, measles and mumps in Vero cells. The antiviral activities are credited to virus inhibition entry inside host cell (Hayashi et al 1996).

3.6 *Alginate*

These are linear polysaccharides and anionic in nature, made up of a foremost back of G blocks and M blocks, in conjunction with alternating GM blocks (Fig. 3) (Wang et al 2012). These are commonly exist in cell wall of Phaeophyceae family comprising *L. digitata, L. hyperborea, L. japonica, M. pyrifera* and *A. nodosum.*

These are predominantly attractive for their antiviral potential. One of the promising drug titled 911 obtained from alginate inhibited HIV replication through preventing viral adsorption, enhancing host's defense mechanism and decrementing the reverse transcriptase activity (Xianliang et al 2000). Furthermore, this drug has a potential against hepatitis B virus via suppressing the DNA polymerase action. The sulfated poly-mannuroguluronate (Fig. 4) affected the inhibition of HIV primarily via vigorous adhesion of viral protein (gp120) with $CD4^+$ TCR (Meiyu et al 2003).

Table 6 Marine source of algal polysaccharides with their antiviral activities (Reproduced from Ahmadi et al 2015)

Polysaccharide (Antiviral)	Associated organism	Virus involved
Sea Algae Extract (SAE)	Rhodophyta, *Schizymenia pacifica*	RMLV RT, AMV RT and HIV RT
Carrageenan (Anionic sulfated polysaccharides)	Rhodophyta, *Gigartina skottsbergii*	HIV, HRV, HPV, HSV-1 & 2, DENV and virus Influenza
Nostaflan	*Nostoc flagelliforme,* Blue green alga	Human cytomegalovirus, influenza A, HSV (Type 1 and 2)
Galactan Sulfate	Rhodophyta, *Cryptonemia crenulata, Callophyllis variegate, Schizymenia binderi* and *Agardhiella tenera,*	HAV, DENV, HIV, HSV-1 & 2, and enveloped viruses (arenavirus, togavirus and herpes virus)
Calcium spirulan	*Arthrospira platensis* and Blue green alga	HCMV, HIV, HSV, polio, influenza, coxsackie, mumps and measles
Alginate	Brown algae, *Macrocystis pyrifera, Laminaria hyperborea, Ascophyllum nodosum, Laminaria japonica* and *Laminaria digitata*	HBV, IAV, HIV
A1 & A2	Microalga and *Cochlodinium polykrikoides*	Parainfluenza type 2, Influenza A and B, RSV (Type A and B)
Fucan & Fucoidan	Brown algae, *Fucus vesiculosus, Adenocystis utricularis, Cladosiphon okamuranus, Undaria pinnatifida, Cystoseira indica* and *Stoechospermum marginatum*	HIV-1, Sinbis virus, VSV, HCMV, HSV-1 and HSV-2
Naviculan	Diatoms and *Navicula directa*	HSV (Type 1 & 2)
p-KG03	Microalgae and *G. impudicum*	Influenza virus plus EMCV
Laminaran	Phaeophyceae, *A. nodosum, F. vesiculosus* and *S. longicruris*	HIV

3.7 *A1 and A2*

Marine microalgae, *C. polykrikoides* are the main supply of sulphated polysaccharides A1 and A2. The chief components of polysaccharides are mannose, uronic acid, galactose and aldohexose with distribution of sulphate groups. These have great potential to prevent the cytopathogenic effects of respiratory illness virus sorts A & B in MDCK cells and HIV- one in MT 4 cells. A1 and A2 polysaccharides also are effective against herpes

simplex and adenovirus sort two, each in HMV 2 cell lines, respectively (Hasui et al 1995).

3.8 *Fucan and Fucoidan*

These are sulfated polysaccharides with high mass. They are categorized into 3 groups: xylofucoglycuronans, fucoidans and glycuronogalactofucans. These polymeric compounds are usually present in the mucilaginous matrix and cell wall of family Phaeophyceae. They're thought of as a supply of L-fucose with various percentages of sugars as an example aldohexose, brain sugar, uronic acid and mannose (Vo and Kim, 2010). The algal fucans structure differs amongst species that's why they're distinctive compounds and thus they have a potential as a unique drug. Fucans have an extensive variety of natural bio-activities as an example anti-proliferative and anti-adhesive effects might specifically defend the cells from viral infections (Rocha et al 2005). The sulphated fucans from *Fucus vesiculosus*, *Spatoglossum schroederi*, *Dictyota mertensii* and *Lobophora variegate* could prevent HIV infection through obstruction the reverse transcriptase activity and these outcomes showed the requisite of carboxyl and sulfate groups in the repressing activity of these polysaccharides (Queiroz et al 2008). From *Cladosiphon okamuranus* and *Sargassum bacciferum piluliferum* isolated fucan polysaccharides with sulfated fucose units and glucuronic acid suppressed DENV 2 infections in BHK 21 cell lines and influenza virus, respectively (Hidari et al 2008). Additionally, activity in case of herpes simplex virus was determined with sulphated fucans isolated from *Cystoseira indica*.

Fucoidan (Fig. 5) features a higher percentage of sulfated fucose within the matrix of diverse algae as an example komby, mozuku, limumoui, wakame and hijiki. Fucoidans includes α 1,3-linked sulphated L fucose, a repetition sequence of alternating α(1-3) with the potential α(1-4)-glycosidic bonds (Pomin and Mour˜ao, 2008). Fucoidan conjointly holds many biological activities as an example activity against many deoxyribonucleic acid and RNA viruses comprising main pathogens of human such as dengue fever virus, cytomegalovirus, HIV and HSV (Hidari et al 2008) via blocking the viral interaction to host in an attempt to prevent viral evoked cytoplasm formation (Damonte et al 2004). Fucoidans from *Undaria pinnatifida, Adenocytis utricularis, Cystoseira indica* and *Stoechospermum marginatum* showed antiviral activities in case of type 1 & 2 herpes simplex virus. Moreover, fucoidan might enhance system health by stimulation of immunoreactions of the body substance and cellular varieties (Leite et al 1998).

3.9 *Naviculan*

Naviculan may be a sulfated polyose isolated from a phytoplankton known as *Navicula directa*. It's product of various sugars for instance mannose, fucose, xylose, rhamnose and galactose. Naviculan includes a robust antiviral action in case of HSV-1 & 2 and influenza virus by inhibiting the preliminary phases of replication of virus, perhaps blocking viral internalization in respective host cell. Furthermore, it revealed a repressing action on fusion amongst CD4 receptors with HIV gp160 showing Hela cell lines (Lee et al 2006).

3.10 *p-KG03*

p-KG03 may be a sulfated exopolysaccharide made by microalgae *Gyrodinium impudicum* strain KG03. It's a homopolysaccharide of brain sugar associated with sulfate groups and uronic acid. It was the primary reportable marine metabolite to subdue tumour growth and infections by encephalomyocarditis virus (Yim et al 2004). It additionally shows repressing activity against influenza A by targeting adsorption and acquisition of virus into respective host. Consequently, it was concluded that the sulphated compounds from aquatic bodies can be a probable candidate for the progress of drug development (Kim et al 2012).

3.11 *Laminaran*

Laminaran is a variety of linear polyoses widely distributed in alga like *Ascophyllum nodosum*, *S. longicruris* and *F. vesiculosus*. It's created from (1, 3) connected aldohexose within the main chain, with (1, 6) linked side chain branching (Fig. 6) (Vera et al 2011). There are two types of laminaran: initial sort is G-series (glucose residues), whereas the second sort is M-series (D-mannitol residues). Laminaran polyoses isolated from brown algae are ready to inhibit the HIV via blocking the attachment on T cells and activities of reverse transcriptases, which is crucial for microorganism proliferation (Muto et al 1988).

4 *Eucalyptus essential oil components as a source of antiviral agents*

Aromatic plants are most widely used as source of traditional medicine (Chiang et al 2003). Literature survey revealed that, despite great development in the field of synthetic chemistry and western medicine, plant life is still backbone of crucial healthcare. Worldwide underutilized plants are widely used as herbal medicine in villages (Newman and Cragg, 2016). So detailed investigation of these underutilized plants is need of the hour particularly in developed and under developed counties, wherever primary healthcare strongly relay on traditional drugs. Due to antioxidant properties the utilization of these plants is growing gradually for development of novel and biodegradable effective drugs as alternative to

contemporary medicine. Medicinal plants contribution to phytomedicine to the well-being of world population has attracted significant amount of interest from all disciplines. Plant based herbal formulations are better, harmless and more consistent as compare to synthetic medicines (Tlili et al 2010). Medicinal plants were utilized as an important basis of therapeutic drugs molecules as they possess secondary metabolites. The major bio-active components are secondary metabolites produced by these plants such as alkaloids, flavonoids, phenols, saponins, generally produced by plants as defense mechanism have been implicated as therapeutics drug molecules in medicinal plants (Gao et al 2012). Herbal agents are mixture plant parts in addition to their preparations are essential with reference to antioxidant, nutrient and medicinal values.

Plant essential oils are secondary metabolites being derived from aromatic plants. Essential oil is complex mixture of various bioactive chemical molecules such as aromatic derivatives, hydrocarbons, terpenes and their oxygenated derivatives like mono and sesqui-terpenoids, esters and alcohols other aromatic compounds (Raho and Benali, 2012). Due to these diverse complex bio-structures that act synergistically, essential oil poses various biological activities like antimicrobial, antiviral, fungicidal, insecticidal and herbicidal (Batish et al 2008). It was reported that yield and constitution of essential oils greatly depends upon plant organs (leaves, flowers, stems) as well as the ecosystem in which plant grows (Michalak, 2006). Essential oils are so named because they represent the very essence of odor and flavor the plant. This essence of odor of oils comes from volatile substances like aliphatic and aromatic hydrocarbons, aldehydes, alcohols, esters, and other constituents being emanated from flowers, sees, bark of tress. At present about 3000 essential oil from different aromatic plants are known, which due to their fragrance and odor are commercially important in cosmetic and perfume industry. Various potent biological activities comprising antioxidant, antibacterial and anticancer are attributed to essential oils, hence playing a significant role as therapeutics in the scientific community (Silva et al 2003). Due to their herbal nature, safer alternative to chemical drugs, interest in these kind of secondary metabolites in plants increasing day by day. Consequently, over the time a great interest has been given to essential oils that could be used as therapeutic agents (Su et al 2006).

Eucalyptus, member of Myrtaceae family, is a fast growing tree which reaches height up to 25-50 meters. This tree can grow in wide climatic conditions, and flourishes best in humid to moderate conditions. It can tolerate drought stress henceforth can be cultivated in waste lands and drought areas with temperature range from 0-47°C (Silva et al 2003). The *Eucalyptus* consists of approximately 900 species and dispersed worldwide because of its easily cultivable quality, ease of adaptability, rapid growth and acceptance towards a broad range of ecological conditions. Many reports show that above 300 species of *Eucalyptus* have more content of essential oil inside their leaves. Hence variability of oils in plant species is often reticulated by increased chemical complexity, seasonal, geographical and climatic conditions, harvest time and extraction techniques (Ahmad et al 2005). *Eucalyptus globules,* inherent to South East Australia and Tasmanian, member of Myrtaceae family are one of extensively spread genera. The leaves of this plant are utilized to extract *Oleum Eucalypti* (eucalyptus oil) worldwide. Essential oil from this aromatic plant has long history to be used as customary medication in earliest times. Because of enriched occurrence of 1,8 cineole in its essential oil, leaf extracts from this plant is widely used in cosmetic, pulp, food beverages, pharmaceutical, phototherapy and aromatherapy (Goodger et al 2016). In this respect, alcohol monoterpenoid component of the volatile compound of the *Eucalyptus globulus* essential oil are economically available for managing respiratory tract infections. Essential oil from Eucalyptus plants are great demand in market due to broad spectrum of applications like : flu, colds, muscular pain, expectorant in case of bronchitis (cough syryps), treatment of gum disease like “pyorrhea” , mosquito repellent products, anodyne, deodorant, hemostat, fumigant, sedative, vermifuge, burns, boils, cancer, dysentery, diarrhea, inflammation, leprosy, malaria, soar throat, sores, spasm, wounds etc (Cimanga et al 2002; Siramon and Ohtani, 2007; Raho and Benali 2012). Patient from asthma are advised to inhale vapors of this oil as aromatherapy. It shows a significant antiseptic role in the preparation of menthol and thymol used in toothpastes. Worldwide it is also used in the preparation of aerosol which is used in chemical as well as in varnishing industries (Su et al 2006). Although EOs from this plant has been empirically used as antimicrobial agent but its mechanism of action is still in infancy.

Conclusion

Inadequate information about the detailed considerations for the growth and cultivation of microorganisms has discouraged therapeutic industries for commercialization of bioactive compounds with special reference to marine compounds. Conversely, with advancement in biotechnological tools, an effective and organized exploration of extreme environments is possible (Tziveleka et al 2003). Main challenge in coming days will be the production of

these bioactive agents at larger scale level so as to satisfy the demand for development of drug and clinical trials. In future for commercial production of these molecules, metabolic and genetic engineering would be an important solution. Combinatorial biosynthesis including cloning of new genes (biosynthesis) into microbes would consequence in the production of the unique metabolites (Bhadury et al 2006). For sustainable production, amalgamation between computer based molecular modeling designs and combinatorial biochemistry accompanied by post genomic technologies can be used. Fermentation processes have attained substantial impact for commercial production of these molecules in the last few years. Solid State Fermentation was used extensively for the making secondary metabolites from fungus.

Another imperative challenge with antiviral drugs would be the resistance development. Though, with the isolation of unique bioactive agents from undiscovered or novel microbes, it is possible to tackle with this issue of resistance too. It is significant to observe that numerous microbes of diverse species are able to produce identical group of metabolites. Those viruses have established resistance towards specific drugs possibly would not develop resistance to more agents of comparable group. Furthermore, chemical derivatives can be produced via manipulating natural compounds through biochemical technologies which are of superior quality (Bhadury et al 2006). Consequently, it seems encouraging to isolate new microorganisms that signify unique genera plus species from undiscovered environments for the invention of exclusive agents with antiviral potential. Currently, quite less information is available regarding mechanisms of diverse antiviral products on viruses. Consequently, advanced comprehensive understanding on the definite targets at molecular levels is essential so as to improve these metabolites with the intention of competently fight viruses in the forthcoming.

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