

REVIEW

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Medical application of exopolymers produced by marine bacteria

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Abstract

Background: Natural products have been viewed as essential sources that could create potential chemotherapeutic agents. In the look for new bioactive substances, examinations were extended to marine territories.

Results: Humanity has known for the last few thousand years that a marine organism contains substances fit for strong biological activity. However, the main genuine examination of marine living beings began just 50 years prior. Since then, all types of life in the marine condition (e.g., bacteria, algae, and fungi) have been researched for their bioactive content.

Conclusions: Exopolymers can be applied in a wide range of industrial applications in biomedicines.

Keywords: Exopolymers, Marine bacteria, Bioactive substances

Introduction

It was recently found that over a long period of time, plants, animals and microorganisms from the marine condition have uncovered a part of what is obviously a huge source of bioactive metabolites. Among other natural sources, the marine biological system is progressively being recognized as a wellspring of potential natural product (Abad et al. 2011; De Jesus Raposo et al. 2014; Devesh et al. 2017; Wang et al. 2018).

An exopolymer is a biopolymer that is secreted by an organism into the environment (i.e., external to the organism). These exopolymers include the biofilms produced by bacteria to anchor them and protect them from environmental conditions (Flemming et al. 2004; Dupraz and Visscher, 2005). Most exopolymers consist of polysaccharides (exopolysaccharides) and proteins, may also include other molecules such as DNA, lipids, and humic substances (Aguilar et al. 2007; Braissant et al. 2009).

EPS is a sugar polymer mainly produced by bacteria and microalgae, in two forms as capsular polysaccharide (CPS) which is bound to the cell wall or slime EPS which is liberated into the culture medium (Sutherland 1972; Cao et al.

2019). The classification and chemistry of bacterial EPS are scheduled in Table 1. It was known that EPS is the main line of biological defense against different attacks and physical stresses (Whitfield 1988; Roberts 1996; Looijesteijn et al. 2001; Paolucci et al. 2015). Based on structural structure, EPS can be microbial. They are classified into three groups, homo-polysaccharide, hetero-EPS, and polysaccharides with irregular structures (Jin et al. 2010; Delbarre-Ladrat et al. 2014).

Moreover, EPS additionally have appeared with wide scope of different applications, for example, emulsification, thickness, absorption, film development, gel arrangement, and anticancer treatment (Lee et al. 2001; Ohno et al. 2001; Ke et al. 2009; Thomas and Kim, 2013; Yahya et al. 2019). EPS have great biological activity and assume jobs in the control of cell division and differentiation, immune regulation, and additionally have antitumor, antioxidant, and antiviral activities. Due to the antioxidant activity of EPS, it prevents different diseases, inflammation, and atherosclerosis (Lu et al. 2000; Zhang et al. 2003; De Jesus Raposo et al. 2015; Asker et al. 2015).

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Table 1 Some roles of microbial exopolymeric material (EPS) in the marine environment (El-Raheem El-Helw and El-Said, 1988)

Role of Exopolymer	Example
Assists in attachment to surfaces	Exopolymers of marine <i>Vibrio</i> MH3 were involved in reversible attachment. Cross-linking of adjacent polysaccharide chains aided in permanent adhesion.
Facilitates biochemical interactions between cells	Exopolymer mediated bacterial attachment to the polar end of blue-green N ₂ -fixing alga. EPS aided attachment to symbiotic host such as vent tube worm to absorb metals and detoxify microenvironment. Exopolymer buffered against sudden osmotic changes.
Provides protective barrier around the cell	Bacteria in aggregates were less preferred by grazers than freely suspended bacteria. EPS-producing deep-sea hydrothermal vent bacteria showed resistance to heavy metals. Metal binding involves cell wall components as well as polysaccharides. Exopolymer in sea-ice brine channels provided cryoprotection by interacting with water at low temperature to depress freezing point. Nutrient uptake by bacteria in aggregates was higher than for free-living cells in low nutrient systems.
Absorbs dissolved organic material	Porous and hydrated matrix acts like a sponge and sequesters and concentrates dissolved organics.

Marine floras

Marine floras incorporate microflora and blossoming plants. Possessing relatively 71% of the globe, the sea is wealthy in biodiversity, and the microflora and microalgae alone establish over 90% of maritime biomass (DeVugst and Vandamme 1994; Kathiresan and Duraisamy 2005; Kathiresan and Thiruneelakandan 2008; Nadia et al. 2016). This tremendous marine floral resource will offer

an incredible breadth for revelation of new medications. The marine floras are wealthy in therapeutically powerful chemicals having a place with polyphenols and sulfated polysaccharides (Haefner 2003; Mayer and Lehmann 2004; Xu et al. 2011; Cao et al. 2019). Marine condition offers a huge biodiversity, and polysaccharides have been found displaying an incredible synthetic variety that is to a great extent species specific. The investigation of the

natural properties of the polysaccharides from marine eukaryotes and marine prokaryotes revealed that the polysaccharides from the marine condition could be alternative for customary polysaccharides, for example, glycosaminoglycans. Marine EPS present a genuine potential for natural bioactive drugs used in medical applications (Martins et al. 2014; Devesh et al. 2017 and Elsakhawy et al. 2017).

Marine microorganisms are a wellspring of new genes (Table 1), and it is probably going to prompt the revelation of new medications and targets. EPS produced by marine microbes have yielded pharmaceutical items, for example, novel anti-inflammatory agents, such as pseudopterins, topsentins, scytonemin, and manoalide; anticancer agents (e.g., bryostatins, discodermolide, eleutherobin, and sarcodictyin); and anti-microbials (e.g., marinone). The use of probiotic microscopic organisms, i.e., bacteria, for example, *Lactobacilli* and *Bifidobacteria*, is for the most part in the control of pathogenic microorganisms, through generation of antibacterial protein to be specific, bacteriocin (DeVugst and Vandamme 1994; Kathiresan and Thiruneelakandan 2008) and anticancer substances (Wollowski et al. 2001; Meera et al. 2011; Yahya et al. 2019). The dietary enhancements of lactobacilli are purportedly diminishing the induction of colon cancer (Goldin and Gorbach 1992; Wu and Chen 2006; Selim et al. 2018 a). EPS from marine microorganisms are important to new medication revelation (Han et al. 2005; Miranda et al. 2008; Xu et al. 2009; Diao et al. 2014; Selim et al. 2018 b).

Bacterial exopolysaccharides (EPS)

Bacteria have been producing several polysaccharide (Tables 2 and 3). Screenings have been performed basically on mesophilic microorganisms as opposed to on psychrophilic, thermophilic, or hyperthermophilic strains. Up to date, three principle genera of polysaccharide-delivering microorganisms have been distinguished: *Pseudoalteromonas* sp., *Alteromonas* sp. also, *Vibrio* sp. during fermentation, every bacterium can free into the medium (an oxygen-consuming sugar-based medium), one explicit EPS with a unique structure and with an intriguing yield, from 0.5 to 4 g of polysaccharide/liter of culture stock (Guezennec 2002; Raza et al. 2011). The *Vibrio diabolicus* bacterium was secluded from a *Pompeii* worm tube (*polychaete Alvinella pompejana*); the EPS it emitted was portrayed by equivalent measures of glucuronic acid and hexosamine (N-acetyl glucosamine and N-acetyl galactosamine). It is a hyaluronic acid-like polymer (Fig. 1) (Raguene et al. 1997; Rougeaux et al. 1999; Arias et al. 2003) and its name is Hyalurifit.

Pharmacological applications of polysaccharides

During the previous three decades, numerous polysaccharides and polysaccharide protein complexes have

been secluded from mushrooms, parasites, yeasts, green growth, lichens, and plants with therapeutic properties. Bacterial growth is regularly joined by the creation of EPSs (Table 4), which have essential biological and physiological functions. Due to EPS' immunomodulatory and antitumor impacts, they have more consideration in the biochemical and restorative fields. The capacity of bioactive polysaccharides and polysaccharide-bound proteins in immune functions might be because of the basic structural diversity and variability of these macromolecules. A fruitful methodology in malignant growth treatment is to trigger apoptosis yet usually confounded by improvement of multi drug resistance (MDR) mechanisms (Salgaller and Hotel 1998). EPS can down direct P-glycoprotein and reverse MDR (De Vuyst and Degeest 1999; Ooi and Liu 2000; Laws et al. 2001; Wei et al. 2008 and Kambourova et al. 2009). Bioactive compounds have been the pillar of disease chemotherapy for as long as 30 years and are probably going to give a significant number of the lead structures, and these will be utilized as formats for the development of novel compounds with improved biological properties (John 2002; Poli et al. 2010; Donato et al. 2016; Elsakhawy et al., 2017; Yahya et al. 2019).

Characteristics of exopolymers as antioxidant activity

The oxidative stress, characterized as the imbalance among oxidants and antioxidants for the oxidants potentially prompting harm, has been proposed to be what cause aging and different illnesses in people. In present day western prescription, the harmony among antioxidation and oxidation is accepted to be a basic idea of keeping up a healthy biological system (Dreosti 1991; Ahmad 1995; Davies 2000; Tiwari 2001; Katalinic et al. 2006; Hu et al. 2011). Physiologically, antioxidants assume a noteworthy job in keeping the arrangement of free radicals, which are in charge of numerous oxidative procedures; antioxidants might be engineered or of normal source (Hu et al. 2001; Abas et al. 2006; Asker et al. 2010; Chen et al. 2011).

Free radicals can respond with biomolecules, making broad harm to DNA, protein, and lipid, which are viewed as identified with aging (Oliveira et al. 2010), degenerative maladies of maturing (Gey, 1990; Oberley, 2002), and malignant growth (Sangeetha et al. 1990). Free radicals and reactive oxygen species (ROS) assume vital physiological jobs; they are basic for generation of energy, combination of biologically essential compounds, and phagocytosis, a basic procedure of immune system. They additionally assume a fundamental job in signal transduction. There is additionally expanding proof that these ROS may assume a causative job in an assortment of illnesses including coronary illness, atherosclerosis,

Table 2 Some exopolysaccharides producing marine bacteria

Marine bacteria	Sources	1
<i>Planococcus maitriensis</i> Anita I	Coastal sea water of Bhavnagar District, India	
<i>S. degradans</i>	-	
<i>Vibrio furnissii</i> strain VB0S3	Coastal region of Goa	
<i>Enterobacter cloacae</i>	Marine sediments	
<i>Halomonas</i> spp.	-	
<i>Halomonas anticariensis</i>	-	
<i>Halomonas ventosae</i>	-	
<i>Alteromonas haloplanktis</i> KMM 156	-	
<i>Alteromonas infernus</i> (<i>A. infernus</i>)	Deep sea hydrothermal vent	
<i>Alteromonas macleodii</i> 2MM6	Intertidal zone of Halifax, Nova Scotia	
<i>Bacillus licheniformis</i> (<i>B. licheniformis</i>)	Volcano island	
<i>Bacillus marinus</i>	Marine sediment	
<i>Bacillus</i> strain B3-15	Shallow water, marine hot spring	
<i>Bacillus</i> strain B3-72	Shallow vent	
<i>Bacillus thermoantarcticus</i>	Ischia island	
<i>Geobacillus</i> sp.	-	
<i>Desulfovibrio</i> sp. strain Ind1	Indonesian coast	
<i>Flavobacterium uliginosum</i>	-	
<i>Hahella chejuensis</i>	-	
<i>Pantoea</i> sp. BM39	Seafloor sediments	
<i>Pseudoalteromonas atlantica</i>	-	
<i>Pseudoalteromonas</i> sp. strain S9	Marine sediment	
<i>Pseudomonas</i> sp strain NCMB 2021	Madilyn fletche Halifax, Nova	

and cancer (Liu et al. 1997; Mau et al. 2002; Blander et al. 2003; Asker and Shawky 2010).

Free radicals and ROS assault lipids, sugars, proteins, and DNA and initiate their oxidation, which might result

in oxidative harm, for example, membrane dysfunction, protein modification, enzyme inactivation, and breakage of DNA strands and modification of its bases. In spite of the fact that all life forms have antioxidant defense and

Table 3 Sugar and non-sugar components of bacterial exopolysaccharides (El-Raheem El-Helw and El-Said, 1998)

Type	Component	Example	Mode of Linkage
Sugar	Pentoses	D-Arabinose	
		D-Ribose	
		D-Xylose	
	Hexoses	D-Glucose	
		D-Mannose	
		D-Galactose	
		D-Allose	
		L-Ramnose	
		L-Fucose	
		Amino sugars	D-Glucosamine D-Galactosamine
Uronic acids	D-Glucuronic acid D-Galacturonic acid		
Non sugar	Acetic acid		O-acyl, N-acyl
	Succinic acid		O-acyl
	Pyruvic acid		Acetal
	Phosphoric acid		Ester, Diester
	Sulfuric acid		Ester

fix systems to secure against oxidative damage, these systems are regularly lacking to keep the harm totally (Moskovitz et al. 2002).

Antioxidants assume a vital job in the later phases of malignancy improvement. There is expanding proof that oxidative processes advance carcinogenesis, despite the fact that the mechanisms for this are not surely known. The antioxidants might have the capacity to cause the relapse of premalignant lesions and hinder their advancement into

cancer (Langseth 1995; Hobbs 2000; Liu et al. 2009; Hu et al. 2010). Probiotic microorganisms synthesize (EPSs) with commercially noteworthy physiological and medical activities. This essential class of biomolecules is additionally portrayed by their capacity to expel ROS that are framed in the digestive tract by different metabolic responses; henceforth, they display antioxidant activities. The probiotic bacterium, *Bacillus coagulans* RK-02, produces an EPS in the exponential and stationary development stages when grown

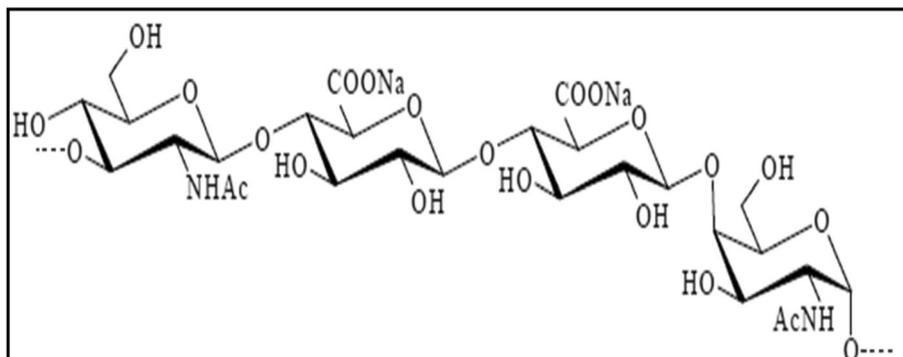
**Fig. 1** Repeating unit of the marine bacterial polysaccharide (HE800 EPS) produced by *Vibrio diabolicus*

Table 4 Some potential biotechnological applications of marine bacterial EPS

Marine bacteria	Biotechnological applications
<i>A. infernus</i> strain GY785	Anticoagulant activity, increased the viability and protein engineering
<i>Alteromonas macleodii</i> subsp. <i>fijiensis</i>	Thickening agent in food industry, detoxification of waterborne diseases, protection of sensitive skin against chemical irritants
<i>B. licheniformis</i> B3-15	Antiviral activity
<i>Bacillus thermodenitrificans</i> strain B3-72	Immunomodulatory and antiviral activity
<i>Geobacillus</i> sp. strain 4004	Pharmaceutical applications
<i>Paracoccus zeaxanthinifaciens</i> subsp. <i>payriae</i>	Bioremediation of toxic metals
<i>Polaribacter</i> sp. SM1127	Food, cosmetic, pharmaceutical, biomedical
<i>Pseudoalteromonas</i> strain 721	Gelling properties
<i>Pseudoalteromonas</i> strain CAM025	Cryoprotection
<i>Pseudoalteromonas</i> strain CAM036	Trace metal binding
<i>Pseudoalteromonas</i> strain SM9913	Flocculation behaviour and biosorption capacity
<i>Vibrio diabolicus</i> strain HE800	Bone regeneration

in a glucose mineral salt medium. The antioxidant and free radical scavenging capability of produced EPS were assayed by different assays. The outcomes demonstrated that the EPS, which is a heteropolymer made out of four monosaccharides, delivered by *B. coagulans* RK-02 had noteworthy antioxidant activity (Kodali and Sen 2008; Ye et al. 2009; Yan et al. 2011; Selim et al. 2015).

Cancer stays as a driving reason for death, all inclusive. IARC (2010) as of late assessed that 7.6 million passing around the world, because of cancer with 12.7 million new cases for each year were being accounted for around the world. A noteworthy extent of this weight is borne by developing countries; 63% of malignant growth passings are accounted for to be from developing countries. Cancer is a multigenic and multicellular malady that can emerge from all cell types and organs with a multi-factorial etiology (Liu et al. 2005; Ferlay et al. 2010; Yan et al. 2010; Jemal et al. 2011). The clinical treatment techniques against cancer include the following: medical procedure, which is neighborhood extraction of

tumor; radiotherapy, which dispense with tumor by presenting to radiation; chemotherapy, which depends on medication focusing on tumor cells; joined methodology treatment, which incorporates each of the three previous medicines together; and immunotherapy, which summons a safe reaction against tumor. Most tumor medications bring about symptoms like complexities and toxicity; along these lines, patients need to experience the ill effects of the agony of medicines (Borchers et al. 1999; Funahashi et al. 2001; Shibata et al. 2002; Allen 2002; Yamasaki et al. 2012).

A definitive explanation behind the suffering underlies in the comparability between tumor cells and normal cells. It is important to discover a treatment that could take out cancer cells while shielding ordinary cells from being slaughtered (Miller et al. 1981; Matsuda et al. 2003; Pang et al. 2007; Pangestuti and Kim 2011; Yahya et al. 2019). The capacity of bioactive EPS and polysaccharide bound proteins to balance such a large number of vital immune functions might be because of the basic

structural diversity and variability of these molecules. An effective methodology in malignant growth treatment is to trigger apoptosis; however, this is usually entangled by advancement of multi-drug resistance (MDR) mechanisms (Salgaller and Cabin 1998). EPS can down direct P-glycoprotein, and invert MDR (De Vuyst and Degeest 1999; Ooi and Liu 2000; Laws et al. 2001; Wei et al. 2008; Kambourova et al. 2009).

Bacterial EPS have great biological activity and assume jobs in the control of cell division and separation, immune regulation, and additionally have antitumor, antioxidant, and antiviral activities (Zhang et al. 2003; Selim et al., 2018a, b).

Umezawa et al. (1983) screened EPS of marine microorganisms for their anticancer activity against sarcoma-180 strong tumor in mice. Lactic acid bacteria (LAB) for example, *Lactobacillus*, are imperative microorganisms in healthy human microbiotic environment (Macfarlane and Cummings 2002). LAB are useful bacteria, which have been related with a few probiotic impacts in both people and animals (Fuller 1989; Yang et al. 2001; Iwai et al. 2004). Various reports have shown that both LAB and milk exert apply anticancer impacts (Biffi et al. 1997; Lee et al. 2004). Information from epidemiological and exploratory examinations have likewise shown that the ingestion of certain LAB strains, or of milk exert, may reduce the danger of particular sort of malignant growths and repress the development of tumors (Kato et al. 1994). Be that as it may, the exact component by which LAB applies anticancer impacts stays obscure. *Enterobacter cloacae* Z0206, a bacterial strain, can create a lot of EPSs. It has been accounted for that glycoproteins from *E. cloacae* demonstrated antitumor consequences for mice with S180 tumors (real), and F3, one of the glycoprotein parts, could particularly restrain QGY7703 (liver malignant growth), A549 (glandular cancer of the lungs), Kato III (gastric carcinoma), and Sw1116 (intestinal cancer) cell strains (Zhang et al. 2002).

Ruiz-Ruiz et al. (2011) demonstrated that the novel halophilic bacterium *Halomonas stenophila* strain B100 emits EPSs with high sulfate substance. This hetero-EPS when over sulfated applied anticancer activity on T cell lines getting from acute lymphoblastic leukemia (ALL). Just tumor cells were vulnerable to apoptosis actuated by the sulfated EPS (B100S), while essential immune system cells were safe. In addition, naturally detached essential cells from the blood of patients with ALL were additionally susceptible to B100S-induced apoptosis. EPS are presently drawing in more prominent consideration inside the field of medicine. This is on the grounds that the EPS have various impacts that incorporate the capacity to animate T-cell formation and potentiate the induction of various sorts of antitumor effector cells, for example, cytotoxic T-cells, NK cells and macrophages

(Wasser and Weis 1999). Numerous immunostimulating PS likewise have antitumor properties (Borchers et al. 1999; Ikewa 2001). PS with antitumor activity have different chemical compositions, configurations, and also in their physical properties. Antitumor activity is shown by a wide scope of glycans reaching out from homopolymers to very unpredictable heteropolymers (Ooi and Liu 1999). The difference of EPS activity can be related with dissolvability in water, size of the particles, branching rate, and form.

Mechanisms announced for the anticarcinogenic effects incorporate (i) hindrance of cancer induction (Reddy et al. 1984), (ii) restraint of hyaluronidase activity (Shibata et al. 2002), (iii) anti-inflammatory, (iv) antiproliferative activities (Berge et al. 2002), (v) control of mammary organ uprightness (Aceves et al. 2005), (vi) antioxidative (Eskin et al. 1995), (vii) apoptosis induction (Kwon and Nam 2006; Yamasaki et al. 2009) through the expression of transforming growth factor (TGF- β), (Funahashi et al. 2001), (viii) concealment of tumor inception VEGF165 (vascular endothelial growth factor 165) binding to its cell surface receptors (Dias et al. 2008; Satoru et al. 2003; Ye et al. 2005; Yumi et al. 2009), (ix) restraint of tumor cells intrusion (Ye et al. 2005), (x) immune response enhancement (Itoh et al. 1995), (xi) SOD activity hindrance (Funahashi et al. 2001), and (xii) estrogen generation concealment. The present understanding of the anticancer and immunomodulating impacts of EPSs are as per the following: (1) coordinate hindrance of development of different sorts of malignant cells; (2) immunostimulating activity against tumors in combination with chemotherapy; (3) preventive impact on spreading or relocation of malignancy cells in the body (Wasser 2002; Moradali et al. 2007; Martins et al. 2014) (Fig. 2a). Figure 2 b illustrates the mechanism of action in the drug activity marine PSs (anti-inflammatory effect and immune modulation effect).

Antiviral activity

Li et al. (1995) showed that sulfated EPS (counting fucoidan) displayed antiviral activities both in vivo and in vitro, with low cytotoxicity contrasted with other antiviral medications right now utilized in clinical medicine. Fucoidan of *Laminaria japonica* has anti RNA and DNA virus functions. The antiviral impacts of fucoidan because of poliovirus III, adenovirus III, ECHO6 infection, coxsackie B3 infection, and coxsackie A16 are surprising. Fucoidan can restrain the improvement of cytopathic impact (CPE) and shield social cells from contamination caused by above infections. The sulfated EPS are known to interfere with the absorption and penetration of infections into host cell and to restrain different retroviral reverse transcriptases (Masuda et al. 1999; De Clercq

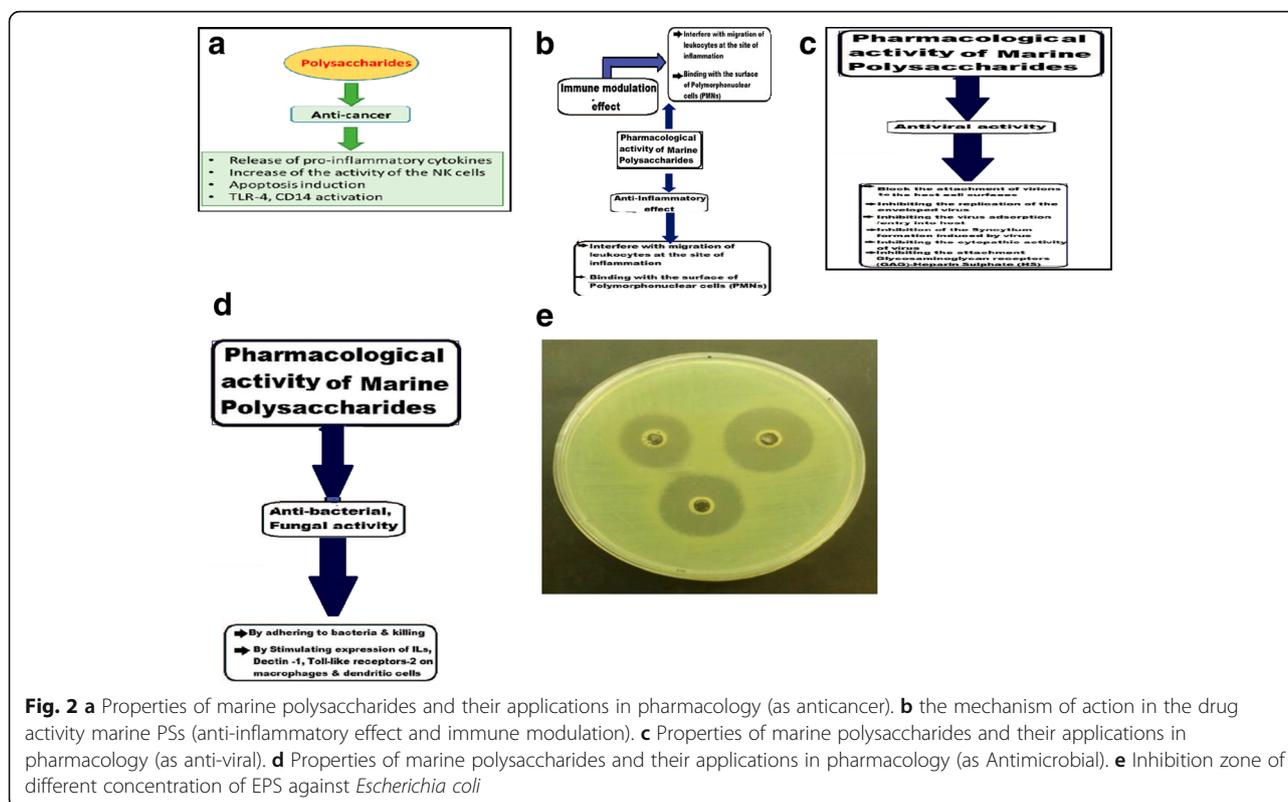


Fig. 2 **a** Properties of marine polysaccharides and their applications in pharmacology (as anticancer). **b** the mechanism of action in the drug activity marine PSs (anti-inflammatory effect and immune modulation). **c** Properties of marine polysaccharides and their applications in pharmacology (as anti-viral). **d** Properties of marine polysaccharides and their applications in pharmacology (as Antimicrobial). **e** Inhibition zone of different concentration of EPS against *Escherichia coli*

2004; Senel and McClure 2004; Seng et al. 2008; Hayashi et al. 2008).

Research on bioactive compound having antiviral activity is essentially centered around low-molecular-weight compounds disengaged from plants since they can be chosen based on their ethno-therapeutic use (Kinghorn 2001). The primary report of the antiviral activity of molecular-weight PS showed up very nearly 60 years prior by Ginsberg et al. (1947). After 17 years, Nahmias and Kibrick (1964) exhibited that heparin can go about as inhibitors of herpes simplex infection (HSV). Various sulfated EPS from marine bacteria, cyanobacteria, and green algae were depicted appearing inhibitory impacts against a few human and animal viruses (Luescher-Mattli 2003; Damonte et al. 2004; Arad et al. 2006). Sulfated PS of synthetic origin has antiviral activity (Witvrouw and De Clercq 1997). A portion of these macromolecules are now experiencing clinical assessment (Kleymann 2005; McReynolds and Garvey-Hague 2007). They have a promising point of view to be developed into a novel kind of antiviral medications. The antiviral activities are depending on the degree of sulfation, furthermore molecular weight (Hemmingson et al. 2006). Sulfated PS may hinder the connection of viruses with target particles on the cell surface (Ponce et al. 2003; Pilar et al. 2005).

The viral connection peptides are very saved areas inside rather than factor platforms of viral surface glycoproteins. These peptides are just inadequately subject to adjustments by the common antigenic drift of viruses. Moreover, they are not expected to visit locales of medication-incited resistance mutation. Sulfated PS that is coordinated toward these objective peptides are in this manner favored possibility for antiviral medication improvement. Also, sulfated polymers appeared in vitro antiviral action against mutants resistant to nucleoside analogs (Adhikaria et al. 2006; Mandal et al. 2007).

Arena et al. (2009) revealed the antiviral and the immunoregulatory impact of another EPS (EPS-2) from a thermotolerant *Bacillus licheniformis* secluded from a shallow vent of Vulcano Island (Italy). EPS seemed to enhance immune surveillance of human peripheral blood mononuclear cells (PBMC) toward HSV-2 (herpes simplex infection) disease by setting off the generation of Th1-type cytokines. The treatment of PBMC with EPS-2 at higher doses (300 and 200 µg/ml) incites the arrival of a more prominent measure of Th1 cytokines. As an outcome, the advancement of a cytokine coordinate with a net genius provocative impact, identified with expanded protection from viral replication, can be theorized. The treatment of PBMC with 100 µg/ml of EPS-2 did not block HSV-2 replication but rather was as yet

ready to trigger infected PBMC to discharge some type 1 cytokine, for example, TNF- α and IL-18, and also obvious measures of IL-4 and IL-10 (Fig. 2c).

Antimicrobial activity

Nguyen et al. (2008) built up a bacterially produced EPS (cellulose), containing nisin so as to control *Listeria monocytogenes* in foodstuff. Bacterial EPS was created by *Gluconacetobacter xylinus* K3. Nisin (2500 IU/mL) was joined into the polymer matrix. EPS decreased *L. monocytogenes* populaces on foodstuff of around 2 log CFU/g following 14 days of storage.

Orsod et al. (2012) isolated two EPS from marine bacteria and screened their activities against *Lysinibacillus* and *Paenibacillus* sp. which represent Gram-positive bacteria and (*Pseudomonas* sp., *Escherichia coli*) as Gram-negative bacteria. The produced EPSs showed antimicrobial activities against all the tested organisms.

Some studies exhibited the adequacy of lentinan administrated intraperitoneally before infection of *Mycobacterium tuberculosis*. The outcomes proposed that lentinan could assemble, have protection potential, and diminish *Mycobacterium* disease (Markova et al. 2003). Another exploration exhibited that lentinan prompted abnormal state of alveolar macrophage enactment showed through improved bactericidal impact against *M. tuberculosis*, which corresponded with the induction of responsive nitrogen intermediates, expanded movement of lysosomal enzymes (acid phosphates), and with powerful phagolysosomal combination pursued by decimation of *Mycobacterium* (Markova et al. 2005; Shanmugam et al. 2008; He et al. 2010) (Fig. 2d and e).

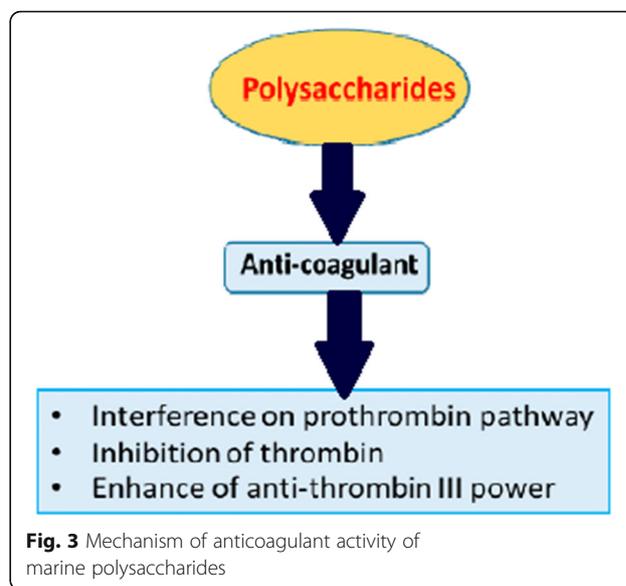
Anticoagulant activity

Some carbohydrates have anticoagulant impacts by repressing thrombin or by initiating against thrombin III or by expanding the coagulating time. Additionally, these molecules can likewise have an antithrombotic action by blocking thrombin movement, interceded through the heparin cofactor II (Li et al. 2012; De Jesus Raposo et al. 2015).

Yet, different researchers prove that they likewise interfere in the prothrombin (PT) pathway, and hence, are not ready to influence the outward coagulation pathway (Nishino et al. 1989; Silva et al. 2010; Wijesekara et al. 2011; Cao et al. 2019). Besides, a critical job of the substance in sulfate has been assigned in the anticoagulant activities, as the nearness of sulfate and its circulation design assume a vital job in the procedures of coagulation (Fig. 3).

Multifunctional pharmaceutical excipients for marine polysaccharides

A medication-infused intravascularly specifically enters the blood and creates its pharmacological impacts. The



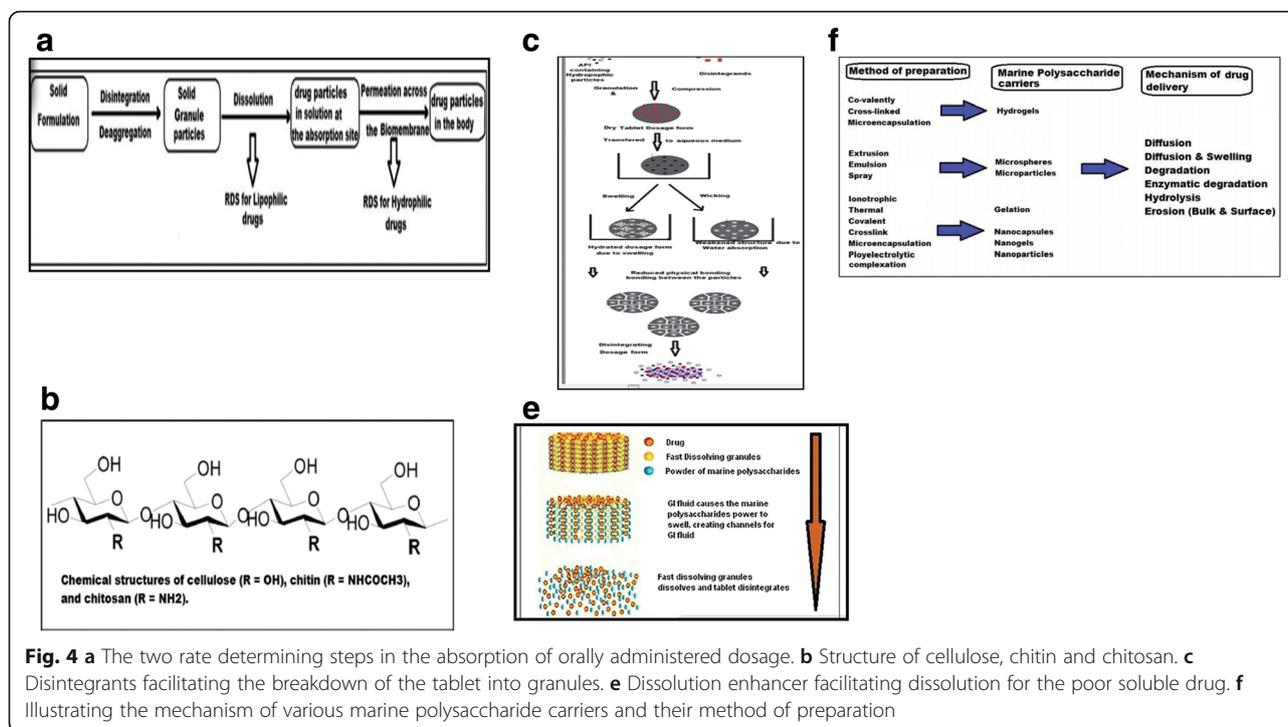
larger parts of medications are controlled extravascularly, more often than not through oral course. Such medications can create their pharmacological activities just when they come into the blood circulation from their site of application. So as to achieve the blood circulation, orally-managed plan must break down, deaggregate, and disintegration of the medication in the watery liquid at the ingestion site must happen. If the medications are not hydrophilic in nature, the retention procedure of medications like these is normally disintegration rate constrained. Better absorption can be accomplished by adjusting the attributes of the measurement shape utilizing pharmaceutical excipients. Additionally, pharmaceutical excipients help in the assembling procedure by serving as binder, diluents, wetting agent, filling agent, disintegrating agents, dissolution enhancers, etc. (Fig. 4a) (Saravanan et al. 2003; Laurienzo 2010; Dhanaraju et al. 2011).

As binder

EPS from marine bacteria can fill in as decent binders in the creation of tablets by the wet granulation technique for fabricate. In this job, binders are either included as a solution or as a solid into the powder mix (following which the granulating liquid, commonly water, is included). Because of the high centralization of hydroxyl bunches in the polysaccharide, for the most part have a high water-restricting limit that makes wet granulation less demanding (Paolucci et al. 2015).

As diluents

Bacterial marine EPS can be utilized as diluents/fillers in the form of tablets (by all strategies) to build the mass of the strong measurement frames that hold a low centralization of therapeutic agent and thereby render



the assembling procedure increasingly solid and reproducible (De Jesus Raposo et al. 2015). For instance, chitin and chitosan are utilized as a diluent or filler and as a binder in direct pressure of tablet preparing, as a disintegrant, etc. Chitin and chitosan have a least mass and tapped thickness that reason great stream and compaction during filling and tablet pressure handling. Figure 4 b demonstrates the structure of cellulose chitin and chitosan.

As disintegrants

Disintegrants are materials added to the dose shapes that improve the separation or deterioration of tablet plans into littler particles that break up quicker than without disintegrants. These materials have the fundamental job to restrict the productivity of tablet binder and physical powers that act under pressure to shape the tablets. Tablet disintegrant of 132 biological activities and utilization of marine EPS are typically considered as the rate determining advance (RDS) in a quicker medication release. Marine bacterial EPS may act as a decent deteriorating operator by expanding the porosity, wettability, and wicking or slender activity and work by swelling within the sight of watery liquids in tablet definitions to encourage the breakdown of the tablet into granules upon section into the stomach (Thomas and Kim 2013) (Fig. 4c).

As dissolution enhancers

Bacterial EPSs from marine may fill in as a disintegration enhancer for the poor dissolvable medication (Hoare and Kohane 2008). These powders can decrease firm

powers holding a tablet measurement shape together and incite the separation into littler granules, consequently expanding the viable surface region for disintegration (Fig. 4d).

As drug delivery carriers

Marine EPS have been generally used to synthesize drug delivery carriers. They are bio-perfect, non-dangerous, and bio-degradable and upgrades response that makes marine EPS fitting hotspots for the building of complex loading devices with a discharge that can be viably controlled (Dhanaraju et al. 2011). Drug delivery devices can be developed utilizing different techniques and can be orchestrated in an assortment of shapes, for example, hydro gels, smaller scale or nanoparticles, and capsules, fit for ensuring an assortment of bioactive operators, for example, proteins and nucleic acids (Fig. 4e).

Conclusion

Microorganisms play an important role in the recycling of elements and ecological balance, especially in the marine environment (oceans and seas) that occupies the largest area of land. EPS produced by these microorganisms are one of the most important secretions responsible for survival in the marine environment through different strategies such as storing food, forming bio-films, and acting as a dispersion agent during hunger. Polysaccharide is also a major player in carbon sequestration and the stability of metal ions through the so-called biological pump responsible for assembling small

particles of the surface, which causes them to sink to the bottom. The secretions of microorganisms (especially external polysaccharides) are the masterminds of this pump. On the other hand, these secretions provide a renewable range of materials used in industrial and pharmaceutical applications. Therefore, EPS can be applied in a wide range of industrial applications in biomedicines as antibacterial, antifungal, antioxidant, antitumor, anti-inflammatory, and antiviral.

Recommendations and future works

1. The fed-batch and continuous of marine bacteria which produced exopolymers using pilot-scale fermentor should be carried out in future.
2. Using molecular biology study to increase the exopolymers
3. Search for other new medical application of exopolymers produced by marine bacteria

Abbreviations

EPS: Exopolysaccharides; CPS: Capsular polysaccharide; MDR: Multi-drug resistance; ROS: Reactive oxygen species; LAB: Lactic acid bacteria; ALL: Acute lymphoblastic leukemia; TGF: Transforming growth factor; CPE: Cytopathic impact; HSV: Herpes simplex infection; PBMC: Peripheral blood mononuclear cells; PT: Prothrombin

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