Review

Pharmacological, pharmaceutical, cosmetic and diagnostic applications of sulfated polysaccharides from marine algae and bacteria

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Marine environment with rich biodiversity offer unlimited choice for novel biopolymers. Sulfated polysaccharides isolated from marine algae and bacteria constitute an important group in the marine-derived biomolecules and biopolymers. They possess unique structural features which can be exploited to their fullest potential in the development of new therapeutic molecules, design of nanocarriers and stimuli-responsive drug delivery systems, development of anti-aging and moisturizing creams and as molecular probes in diagnosis of cancers and cardiovascular diseases. The aim of the present review is to highlight the sources, characteristics and applications of sulfated polysaccharides and exopolysaccharides isolated from marine algae, cyanobacteria, extremophilic and halophilic bacteria. Detailed description of physicochemical properties and versatile applications of ulvan, fucoidan, galactofucan sulfate, laminarin, mauran, cyanobacterial exopolysaccharides and other lesser known exopolysaccharides of marine bacterial origin has been provided. In a nutshell, it can be concluded that sustainable exploitation of the renewable, diverse library of these unique and novel sulfated polysaccharides will unravel newer possibilities in future and will enrich the existing arsenal of biopolymers.

Key words: Exopolysaccharide, marine biopolymer, molecular probe, nanocarriers, stimuli-responsive drug delivery systems, sulfated polysaccharide.

INTRODUCTION

Around the world, demand for novel biopolymers and bioactive molecules with unique characteristics and improved functionalities has increased. Occupying almost ¾-ths of the Earth’s surface, the oceans represent underexploited but sustainable source of biologically significant and relevant natural products which can also be used for various other industrial processes. Marine environment is a highly diverse environment which is a...
home to different species of bacteria, algae or seaweeds, invertebrates and vertebrate animals. Some particular marine environments offer wide biodiversity and hence chemi-diversity. It is often said that the marine microbial world can be regarded as the largest world of chemical diversity. Many of the natural products obtained from the marine ecosystem have been investigated for their potential applications and benefits in the field of medicine, pharmacy and diagnosis (Borresen et al., 2010). Compounds obtained from taxonomically diverse marine flora have exhibited antioxidant, anti-inflammatory, immune-stimulatory and antimicrobial properties. Moreover, they can control carcinogenesis by preventing oxidative damage of DNA, inducing apoptosis in cancer cells and therefore, can serve as lead compounds for anticancer agents (Boopathy and Kathiresan, 2010). Some of the most commonly exploited marine biomaterials in pharmaceutical field include agar, agarose, alginates, carrageenan, chitosan, chitin, collagen, hyaluronan etc. Advancements in biotechnological approaches and isolation techniques have created opportunities for exploring the vast world of marine flora for chemically diverse, novel bioactive molecules and biopolymers (Ige et al., 2012; Fink, 2015).

Seaweeds or marine algae are being used from time immemorial in China and Japan either as dietary components or as remedies because of their immense therapeutic benefits. They are rich sources of carotenoid pigments, omega-3-fatty acids, phycocyanin, fucoestersols, iodine organic products, mannitol, macro- and micro-elements, vitamins A, B, C and E, unsaturated fatty acids, polyphenols, sulfated polysaccharides, essential amino acids, peptides and proteins (Boopathy and Kathiresan, 2010; Lee et al., 2013; Moghadamtousi et al., 2014; Menshova et al., 2016). Marine algae have been classified as Rhodophyta, Phaeophyta, Chlorophyta and Cyanophyta which are known as red, brown, green seaweeds and blue-green algae, respectively and till date, almost 680 species have been identified (Boopathy and Kathiresan, 2010; Silva and Alves et al., 2012). This classification has been done by botanists on the basis of the photosynthetic pigments present (Cunha and Grenha, 2016). Some of the compounds isolated from seaweeds that have been widely exploited in the pharmaceutical industry for commercial purposes include carrageenan (from red seaweed) and algicin (from brown seaweed). Crude extracts or seaweed as a whole have been traditionally used for amelioration of joint pain, inflammation and also for treatment of burns (Fittion et al., 2016). There are reports of anticancer effects of different species of brown algae, Sargassaceae sp., Dictyota dichotoma, and Desmarestia ligulata against various cancer cell lines (human leukaemic T cell lymphoblast [Jurkat], human Burkitt's lymphoma [Daudi], human chronic myelogenous leukaemia [K562] cells, human breast adenocarcinoma [MCF-7], human prostate cancer cells [DU 145, PC-3, and LNCa], murine colon cancer cell line [CT-26], human leukemia [THP-1], mouse melanoma [B-16], and human leukemia [U-937] cells (Moghadamtousi et al., 2014).

Bioactive metabolites of varying chemistry have been reported to be present in marine algae. They are brominated phenols, brominated oxygen heterocyclics, nitrogen heterocyclics, kainic acids, guanidine derivatives, phenazine derivatives, amino acids and amines, sterols, sulfated polysaccharides and prostaglandins. Most of the sulfated polysaccharides have been found to possess health-promoting effects (Lee et al., 2013). Polysaccharides are ubiquitous natural macromolecules consisting of osidic monomers. They can be classified as homopolysaccharides or heteropolysaccharides depending on the occurrence of single type of monosaccharide or different osidic residues. They are characterized by a regular back-bone structure with a repeating unit, which may be linear or branched, comprising up to 10 monomers and organic or inorganic substituents such as phosphate, sulfate, and lactyl, succinic, acetic and pyruvic acids. Monosaccharide composition, linkages between the monosaccharide, sequence of the repeating units and non-carbohydrate substituents in the polysaccharide vary with the algal species, fermentation and harvesting conditions as well as the physiological state of the microbe. Types of glycosidic linkages between the monomeric units such as β-1,4 or β-1,3 provide a rigid backbone and α-1,2 or α-1,6 glycosidic linkages yield molecule with flexible regions (Ladrat et al., 2014). Polysaccharides have been reported to display an array of biological activities like antioxidant, anticoagulant, anticancer, antiviral, anti-inflammatory activities (Posocco et al., 2015; Cardoso et al., 2016). Biocompatibility, biodegradability, non-toxicity and stimuli-responsiveness of marine polysaccharides support their utilization in the fabrication of stimuli-responsive “smart” or “intelligent” drug delivery systems. Marine polysaccharides have found wide applications in the field of nanotechnology, in design of controlled release drug delivery systems for encapsulation of bioactive agents, in formulation of hydrogels, in gene delivery and also in regenerative medicine.

Sulfated polysaccharides obtained from marine algae and bacteria are unique in the sense that they possess different innovative and complex chemical structures and functionalities, with no parallels or equivalents being found in terrestrial organisms (Cunha and Grenha, 2016). Exopolysaccharides (EPS) are glycopolymers obtained from marine mesophilic, heterotrophic as well as extremophilic (psychrophilic, thermophilic and halophilic) bacteria and all of them are capsular polymers. These are attached to the cell membrane through lipopolysaccharides or proteins present in cell membrane, facilitate growth by promoting adhesion to solid surfaces,
protect the microorganisms against extreme environmental conditions of high or low temperature and/or salinity and lastly, against predators. Potential applications of marine bacterial exopolysaccharides include therapeutic applications as immunomodulator, antitumor, antiviral agents as well as adjuvants in vaccine delivery systems and diagnostic imaging agents. Extracellular polysaccharides of commercial importance have been produced from unicellular red algae, Porphyridium cruentum and P. aeruginae and also from Chlamydomonas mexicana and certain species of green and blue-green algae. Porphyridium polysaccharide has the potential to replace the carrageenan in biomedical field (Laurienzo, 2010; Poli et al., 2010; Ladrat et al., 2014; Cardoso et al., 2016).

Numerous studies indicate pharmacological effects from chemically diverse compounds such as polyphenols, phlorotannins, alkaloids, polysaccharides, extracted from different species of marine alga and exopolysaccharides from marine bacteria. Overexploitation of petroleum resource for synthesis of additives and excipients used in pharmaceutical and cosmetic industry not only depletes the reserve but also adds to environmental risks and occupational hazards. Therefore, alternative and renewable source for less toxic and environment-friendly excipients is the need of hour. Among the different sulfated polysaccharides of marine algal origin investigated till date, number of studies has been carried out on various aspects of carrageenan (from red algae). Although, therapeutic potential of fucoidan (from brown algae) has been studied extensively, other applications of fucoidan in the design of drug delivery systems and as diagnostic tools have not been reported in a systematic manner. The situation is more or less similar with ulvan (from green algae) and other sulfated polysaccharides such as galactofucan, laminarin, mauran, species-specific sulfated polysaccharides and exopolysaccharides from different bacterial population. Thus, there is lack of comprehensive review on pharmacological, pharmaceutical, cosmetic and diagnostic applications of sulfated polysaccharides isolated from various species of marine algae and bacteria. The present review attempts to fill up this lacunae and focuses on the source, physicochemical characteristics and biofunctional activities of sulfated polysaccharides obtained from marine algae and bacteria, namely ulvan, fucoidan, galactofucan sulfate, laminarin, mauran, cyanobacterial exopolysaccharide and sulfated polysaccharides of not-so-frequent occurrence in different algae and bacteria.

PHYSICOCHEMICAL CHARACTERISTICS OF SULFATED POLYSACCHARIDES

Sulfated polysaccharides obtained from marine algae include sulfated fucans or fucoidans, sulfated galactans which include carrageenans and agarans, sulfated glucans and sulfated arabinogalactans. They may be classified as linear or branched polymers and classification can be on the basis of charge of the functional groups attached to the central sugar backbone (Raveendran et al., 2013a). Depending on the marine algal source and type of sugars present, commonly occurring sulfated polysaccharides can be divided into a. water-soluble fucan or fucoidan, obtained from brown algae, containing fucose, xylose, uronic acid, galactose with varying degrees of sulfation, b. linear galactans and carrageenans, obtained from red algae, composed of sulfated galactose and 3,6-anhydro galactose and lastly, c. water-soluble, ulvan which consists of sulfated rhamnose and sulfated aldobouronic acid and obtained from green algae (Patel, 2012).

Chemical composition of the sulfated polysaccharides obtained from various families of marine algae is species-specific, depends on their ecophysiological origin and differs in the degree and distribution of the sulfate groups (Chiellini and Morelli, 2011). The soluble fibers found in abundance in brown seaweeds are alginates, fucans and laminarins. Similarly, the soluble fibers in red algae include amorphous polymers, sulfated galactans (agars and carrageenans), xylans and floridean starch. Starch, xylans, mannans and ionic sulfated polysaccharides are present in green algae. They also contain uronic acids, rhamnose, xylose, galactose, and arabinose (Raveendran et al., 2013a; Hamed et al., 2015).

Physical properties of sulfated polysaccharides such as aqueous solubility or ionic interactions and biological activity depend on their chemical structure, sequence of the monomeric units, and nature of linkages between the monomers. Nature of the substituents also governs the geometry and conformation of the polysaccharide molecules. Structural modification through depolymerisation or over-sulfation results in development of new properties and improvement in polymer functionality (Chopin et al., 2014; Ladrat et al., 2014).

Ulvan is a branched sulfated anionic polysaccharide isolated from the green algae, Ulva and Enteromorpha, and consists of sugar residues-glucose, rhamnose, xylose, glucuronic acid, iduronic acid and sulfated rhamnose. Presence of iduronic acid and sulfated rhamnose makes ulvan unique from that of other marine polysaccharides and accounts for its similarity with mammalian glycosaminoglycans. It shows variations in molecular weight (1.14-2 × 10^5), electronic density and charge distribution (Silva et al., 2012a; Cardoso et al., 2016). Composition of Ulva-derived sulfated heteropolysaccharide depends on taxonomic origin, growth conditions, period of collection and post-collection treatment (Chiellini and Morelli, 2011). Compounds such as 4-O-(β-D-glucuronosyl uronic acid)-L-rhamnose and small quantities of aldobouronic acids, 3-O- and 4-O-(D-glucurononosyluronic acid)-D-xylose could be detected in
high percentages in ethanolic extracts of *Ulva lactuca*. An acidic tetrasaccharide, D-glucuronic acid-(1→4)-L-rhamnosyl (1→3/4)-D-glucuronosyluronicacid-(1→3) D-glucose, was obtained on partial acid hydrolysis of desulfated and carboxy-reduced ulvan (Umaporani et al., 2016). Net charge of the polysaccharide solution is governed by the pH and ionic strength of the medium in which it is dissolved. The pH of the aqueous solution has been found to be 7.5. Conformation change from ordered state to disordered structure occurs only at a critical charge density. Aqueous solution of ulvan displays low intrinsic viscosity (18-100 cps) attributed to the formation of necklace-type ultrastructure (Chiellini and Morelli, 2011; Cunha and Grenha, 2016).

Another sulfated polysaccharide of interest is fucoidan which is obtained from brown algae, namely mozuku, komby, limu moui and from edible species such as *Fucus vesiculosus*, *Laminaria japonica*, *Analipus* sp., *Chordus* sp. and *Undaria pinnatifida*. Different types of fucoids could be isolated from tropical brown sea weeds such as *Turbinaria turbinata*, *Sargassum filipendula*, *Dictyota caribaea* and *Padina perennisata* and were found to be homofucan, heterofucan and galactofucan (Garcia-Rios et al., 2012). The molecular weight of fucoidan varies between 10-950 kDa. It usually exists in two forms: F-fucoidan comprising of I-fucose units and U-fucoidan consisting primarily of glucuronic acid units. The α-L-fucose units (also known as α-L-fucopyranose) may be sulfated at C-2, C-4 and sometimes at C-3 positions. Occurrence of fucoidan results in structural roughness and flexibility of the brown algae and also provides protection to the algal cell against UV rays and harsh environmental conditions. Other sugar components, including mannose, galactose, glucose, xylose, uronic acids and non-sugar acetyl groups are also present. Fucoidan isolated from *F. vesiculosus* consists primarily of fucose with low degree of acetylation (Moghadamtousi et al., 2014; Fitton et al., 2016). The aqueous solubility of the sulfated polysaccharide has been reported as 10 mg/ml. Although fucoidan is hygroscopic, its aqueous solution displays low viscosity. Rheological studies on fucoidan isolated from *F. vesiculosus* exhibited Newtonian behavior and highest viscosity compared to polysaccharides isolated from other species. Viscoelasticity of fucoidan is affected by the presence of electrolytes like sodium chloride and calcium chloride and also non-electrolytes like sugar. Stability of the polysaccharide is pH-independent (Silva et al., 2012; Kim and Venkatesan, 2015; Cunha and Grenha, 2016). It has an excellent oral safety profile in animals and humans and is GRAS according to FDA specifications (Dithmer et al., 2014; FDA GRAS Notice, 2014; Lean et al., 2015).

A water-soluble sulfated polysaccharide has been extracted from Korean green alga *Maesaengi* (*Capsosiphon fulvescens*). It is a glucuronogalactomannan, whose backbone consists of alternating sequence of 4-linked L-rhamnose-3-sulphate and D-xylose residues (ulvobiose U3s) having monomeric D-glucuronic acid or D-glucuronic acid-3-sulphate as the side chains on O-2 of some of the L-rhamnose-3-sulphate units (Synytsya et al., 2015). Sulfated polysaccharide is also present in another species of brown algae, *Eclonia cava*, which consists of high percentage of fucose and smaller percentages of galactose, xylose and mannose (Boopathy and Kathiresan, 2010). An acidic polysaccharide isolated from brown seaweed *Lobophora variegata* was found to possess a high level of sulfated fucose and galactose and is named as galactofucan sulfate (Castro et al., 2016).

Laminarin, which is a linear storage glucan has been isolated from some species of brown algae, *Ascophyllum nodosum*, *Laminaria hyperborea*, *Laminaria digitata*, *Ecklonia kurome*, *Saccharina sp.* etc. Laminarin consists of (1,3)-β-D-glucan having (1,3)-β-D-glucopyranose residues with some 6-O-branching in the main chain and some β-(1,6)-intrachain links. The molecular weight of the polysaccharide is approximately 5 kDa. It has a cloud-like and spongy appearance in the solid state. The aqueous solubility depends on the degree of branching (Silva and Alves et al., 2012; Burgess et al., 2015; Ji et al., 2015; Kadam et al., 2015). Its high solubility in both organic and aqueous solvents but low viscosity of the aqueous solution favor its easy handling for industrial applications (Custodio et al., 2016).

Exopolysaccharides (EPSs) are high molecular weight anionic or neutral heteropolysaccharides, abundant in marine microbes, as extracellular component. They contain three or four different monosaccharides arranged in groups of 10 or less to form the repeating unit and are usually linear with molecular weight in the range of 1-3kDa. Uronic acids (D-glucuronic acids, D-galacturonic acids) or ketal-linked pyruvate, succinate, acetate or inorganic residues such as phosphate or sulfate occur in the structure. Monosaccharide such as pentoses (as D-arabinose, D-ribose, D-xylose), hexoses (D-glucose, D-galactose, D-mannose, D-allose, L-rhamnose, L-fucose), amino sugars (D-glucosamine and D-galactosamine) are present in EPS (Polli et al., 2010).

Mauran is an anionic sulfated exopolysaccharide, isolated from a moderately halophilic bacterium, *Halomonas maura*. The polysaccharide has exhibited characteristic viscoelastic, pseudoplastic and thixotropic behavior (Raveendran et al., 2013b; Srivastava and Kowshik, 2015).

Exopolysaccharides produced from Cyanobacteria are released as soluble polysaccharides (RPS) in the culture medium and exhibit protective function by providing sheaths, capsules or slimes over the bacteria. They are unique in the sense that they are heteropolymers composed of 6-10 different monosaccharides, the most abundant being glucose. Variation in structure results in different architectures. Rheological properties of aqueous
solutions of RPS are unaffected by alterations in pH, temperature or ionic strength. Presence of uronic acid and sulfate groups imparts affinity for metal cations (Laurienzo, 2010).

The average molar mass of extracellular sulfated polysaccharide occurring in marine red microalgae, Porphyridium sp. has been found to be $2.3 \times 10^6$ g/mol. Increased sonication of aqueous solution of the polysaccharide resulted in significantly lower viscosity, indicated by transition from weak gel-state to liquid-like state (Geresh et al., 2002).

Two different EPS have been extracted from Bacillus licheniformis strain B3-15 and Geobacillus sp. 4004 EPS. The former is a tetrasaccharide repeating unit with sugars having a manno-pyranosidic configuration. In the latter, in the repeating saccharidic unit, two residues have a gluco/galacto configuration and three possess a manno configuration (Poli et al., 2010). The exopolysaccharide, HE 800, secreted by deep vent marine bacterium, Vibrio diabolicus, is structurally analogous to hyaluronic acid, possesses a linear backbone with a molecular weight of about 8 kDa and is regarded as glycosaminoglycan (Courtois et al., 2014).

THERAPEUTIC ACTIVITIES OF SULFATED POLYSACCHARIDES AND EXOPOLYSACCHARIDES FROM MARINE ALGAE AND BACTERIA

The unique structures and sulfation patterns of marine sulfated polysaccharides are responsible for their vast array of therapeutic activities including immunomodulatory and cytotoxic effects. Some of the molecules are already marketed as nutraceuticals and few others are in various stages of preclinical trials. They are known to possess low immunogenicity (Boopathy and Kathiresan, 2010; Glycomer, 2012). Molecular weight, sulfate content and distribution, introduction of other functional groups, monosaccharide composition and structure of the backbone of ulvan and fucoidan determine the anti-oxidant, anti-coagulant and anti-tumor efficacy of the sulfated polysaccharides. Higher molecular weight accounts for improved anti-coagulant action (Silva et al., 2012; Kim et al., 2015; Cardoso et al., 2016; Cunha and Grenha, 2016).

Ulvan shows diverse pharmacological actions such as antitumor, anti-hyperlipidemic, immune modulation, antibacterial, antiviral, laxative, antifungal, hepatoprotective, antiprotozoal, leishmanicidal, anti-inflammatory, anti-nociceptive, antioxidant and anticoagulant actions. It can be used as a chelating agent owing to its ability to form complexes with metal ions and can prove beneficial in treatment of metal poisoning. Ulvan, isolated from U. lactuca, exhibited antimitotic activity during investigation on Allium cepa meristematic root tip whereas that from Ulvan rigida has demonstrated immunomodulatory activity on murine macrophages (Chiellini and Morelli, 2011; Silva et al., 2012; Cardoso et al., 2016; Umapoorani et al., 2016).

Fucoidan is known for its multifarious biological activities like anti-inflammatory, anti-coagulant, anticancer, anti-metastasis, antiviral (against herpes simplex virus type 1 [HSV-1], HSV-2 and human cytomegalovirus), anti-lymphangiogenesis and immunomodulatory actions (Silva et al., 2012; Kim and Venkatesan, 2015; Cunha and Grenha, 2016; Menshova et al., 2016). Various mechanisms have been postulated to explain the chemotherapeutic and chemopreventive action of fucoidan and also its anti-inflammatory activity (Moghadamousi et al., 2014; Atashrzam et al., 2015; Lowenthal and Fittin, 2015; Choo et al., 2016). Role of fucoidans in inhibiting the attachment of H. pylori to gastric epithelial cells has been investigated which can be exploited in prevention of gastric cancer (Chua et al., 2015). Fucoidan is safe for use in age-related macular degeneration AMD (Dithmer et al., 2014). Intestinal inflammation and inflammatory bowel disease can be successfully controlled by oral administration of fucoidan preparation as nutraceutical (Lean et al., 2015). Use of fucoidan and its chemically modified derivatives in management of osteoarthritis is in various stages of development (Glycomer, 2012). Fucoidan is already available as a liquid nutritional supplement, FuCoyDon® and claimed to rejuvenate health (FuCoyDon® Factsheet). It also shows promise in treatment of fibrosis (Fittin, 2011). It can be exploited as an adjuvant in vaccine therapy (Fittin et al., 2015).

Galactofucan sulfate isolated from brown seaweed exhibited hepatoprotective effect in mice through lowering of serum levels of marker enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (γ-GT). It also affected sodium pentobarbital-induced sleep and demonstrated anti-oxidant and anti-inflammatory effects (Castro et al., 2016). It is being tested for its ability to control herpes virus infections (Fittin, 2011; Glycomer, 2012). Although the sulfated galactofucan demonstrated strong antithrombotic effect without causing any hemorrhage yet it did not exhibit anticoagulant activity. This might occur due to synthesis of highly sulfated heparin sulfate by the endothelial cells of the vascular wall as a result of the effect of the polysaccharide (Rocha et al., 2005). The polysaccharide isolated from Capsosiphon fulvescens was capable of stimulating the macrophage cells, RAW264.7 cell line, as evident from production of nitric oxide and prostaglandins and thus can be regarded as immunomodulators (Karnjanapratum et al., 2015). It could also stimulate rat intestinal epithelial cells (IEC-6) in a dose-dependent manner via increase in the expression of cyclinD1 and c-myc and induction of ERK1/2 phosphorylation (Hwang et al., 2011). It is reported to inhibit melanogenesis in B16 cells, induce apoptosis in
AGS gastric cancer cells, and lower cholesterol levels in hypercholesterolemic rats (Sun et al., 2016).

Laminarin is reported to possess anti-oxidant, anti-microbial, anti-apoptotic, anti-inflammatory, anticoagulant and immunostimulatory activities (Burgess et al., 2015; Kadam et al., 2015). Since, it is non-hydrolysable and non-digestible, it can reach the intestinal lumen in intact form and can regulate gene expression of pro- and anti-inflammatory cytokines in situation of ulcerative colitis and inhibit colonic Enterobacteriaceae. Moreover, colonic IL-6 mRNA level is also lowered (Shea et al., 2016). Laminarin was found to increase the release of hydrogen peroxide, calcium, nitric oxide, monocyte chemotactic protein-1, vascular endothelial growth factor, leukemia inhibitory factor, and granulocyte-colony stimulating factor in RAW 264.7 cells (Lee et al., 2012). It is known to induce apoptosis in human colon cancer cells by multiple pathways (Ji and Ji, 2014). It demonstrated protective effect against cisplatin-induced ototoxicity (Han et al., 2016). Oversulfated laminarin leads to improvement in antitumor activity (Ji et al., 2013).

Mauran has been reported to show immunomodulatory and anticancer effects owing to its high sulfate content (Srivastava and Kowshik, 2015). It also possesses antioxidant, antihemolytic and antithrombogenic activities (Sun et al., 2015).

Sulfated polysaccharide present in the cell walls of red microalgae, Porphyridium sp. have demonstrated hypcholesterolemic effect in Sprague-Dawley rats, through enhanced excretion of cholesterol and bile acid in the feces. Lower serum cholesterol levels, increase in the HDL/LDL ratio and enhanced levels of the hepatic enzyme hydroxymethyl glutaryl CoA reductase (HMG - CoA reductase) were also observed in the experimental animals (Dvir et al., 2009). Sulfated polysaccharide isolated from brown algae, Eclonia cava, was found to exhibit in vitro anti-proliferative activity on various cancer cells in a selective and dose-dependent manner. Results from Western blot analysis revealed marked effect on caspase 7 and 8, known to cleave protein substrates like PARP, thereby inducing apoptosis and subsequently DNA damage (Boopathty and Kathiresan, 2010). Non-digestible polysaccharide isolated from the brown alga Saccharina latisima has demonstrated antioxidant activity (Jimeenez-Escrig et al., 2015).

Alteromonas macleodi subsp. fijienisis is an exopolysaccharide-producing aerobic, mesophilic bacterium isolated from a hydrothermal vent. The repeating unit is an hexasaccharide consisting of three uronosyl residues with branching at a galacturonosyl residue and a side chain. It can be used in bone healing and even in management of cardiovascular diseases. An EPS extracted from B. licheniformis strain (B3-15) exhibited immuno-modulating properties (Poli et al., 2010). SM1127 EPS demonstrated significant antioxidant activity (Sun et al., 2015). High molecular weight exopolysaccharide secreted from Vibrio diabolicus, resulted in bone and skin regeneration. It also exhibited antitumor, antiviral, and immunostimulant activities. “Heparin-like” or “heparin-mimetic” anticoagulant compound was obtained by sulfation of low-mass derivatives of depolymerised native exopolysaccharide, GY785 isolated from Alteromonas infernos, residing in deep hydrothermal vent of Guaymas region. It can promote wound healing and proliferation of human umbilical vein endothelial cells. Soluble exopolysaccharides isolated from blue-green algae, Spirulina platensis (RPS) have been reported to show antiviral actions owing to presence of high percentage of sulfate groups (Laurienzo, 2010; Sun et al., 2015).

PHARMACEUTICAL USES OF POLYSACCHARIDES

Two factors contribute to utilization of sulfated polysaccharides in the development of drug delivery systems. Glycosidic bonds, present in the molecule can facilitate enzyme-catalysed hydrolysis and thus biodegradation. Presence of negatively charged sulfate groups and hydroxyl groups render easy chemical modifications through introduction of several functionalities in addition to potentiation of interaction with negatively charged mucus membrane and thereby favoring muco-adhesion. Introduction of different moieties leads to modified sulfated polysaccharides of marine origin with customized properties.

Ulvan find applications in the fabrication of nanofibers and membranes and in the design of nanocarriers for drugs. Two-dimensional and three-dimensional platforms of ulvan have been developed by cross-linking, incorporating dexamethasone as model drug and have been investigated for use in wound healing and bone tissue regeneration with success. Modified ulvan has been tested for cytotherapy applications (Cardoso et al., 2016). Ulvan hydrogel formation requires the presence of boric acid and calcium ions at slightly alkaline pH. Ionic strength of the solution and alterations in pH can affect the stability of the thermo-reversible hydrogel. Mechanical strength of ulvan hydrogel has been improved by carrying out photopolymersiation using large excess of methacrylic anhydride in presence of cytocompatible photoinitiator and exposing to UV radiation for short duration thereby yielding ulvan methacrylate macromer. The hydrogel demonstrated good degree of swelling in phosphate buffered saline, good stability and excellent mechanical properties (Chiellini and Morelli, 2011).

Fucoidan alone has failed to produce gels even at 25% concentration. However, electrostatic interactions resulting from mixing polymers of opposite charges such as chitosan and poly(2-hydroxyethyl methacrylate) led to the formation of gels and films (Cunha and Grenha,
Fucoidan-chitosan nanoparticles prepared by ionotropic-gelation method could protect the encapsulated curcumin from the acidic environment of the stomach and delayed the drug release till pH 7.0. Therefore, the polysaccharide-based nanoparticles could act as pH-sensitive carriers for oral delivery of curcumin (Huang and Lam, 2011). Self-assembly of sulfonated fucoidan, fucoidan-lauran with berberine and chitosan resulted in the formation of nanoparticles with high loading efficiency and fast release in simulated intestinal fluid. Thus they can be used in the local delivery of berberine for treatment of defective intestinal tight junction barrier (Wu et al., 2014).

Novel laminarin-based non-viral gene transfer vector has been designed to transfer B-cell-specific Moloney leukemia virus inset site 1 gene (BMI-1) targeting siRNA in breast cancer cells. Surface modification of laminarin nanoparticles by polyethyleneimine(PEI) reduced the toxicity and improved therapeutic efficacy (Ren et al., 2016). Biocompatible photo-cross-linkable methacrylate hydrogel has been synthesized for encapsulation of human-adipose-derived stem cells (Custodio et al., 2016).

Extremophilic bacterial polysaccharide, mauran has been complexed with cationic chitosan to form stable, biocompatible nanoparticles which have been used for encapsulation of 5-fluorouracil. Drug-loaded nanoparticles could kill the breast adenocarcinoma cells and glioma cells in a sustained and controlled manner (Raveendran et al., 2013; Raveendran et al., 2015). Magnetic nanoparticles coated with mauran have demonstrated biocompatibility and low cytotoxicity towards normal cells. Application of magnetic hyperthermia along with administration of drug-loaded mauran nanoparticles resulted in killing of 80% of cancer cells within a very short time (Balasubramanian et al., 2014). Mauran has been reported to stabilize ZnS:Mn2+ quantum dots(QDs) thereby improving biocompatibility and lowering the cytotoxicity potential (Srivastava and Kowshik, 2015).

Although hydrophilic in nature, deoxysugars such as fucose and rhamnose present in cyanobacterial exopolysaccharides (EPS) are responsible for their hydrophobicity and their usefulness as emulsifying agents (Laurienzo, 2010).

A polysaccharide bioflocculant, MBSF17, extracted from halophilic bacterium, Bacillus subtilis, MSBN17, could yield spherical silver nanoparticles in reverse micelles through reduction of silver nitrate. Presence of carboxyl, hydroxyl and methoxyl groups in MBSF17 stabilised silver nanoparticles by forming a coating. Nanoparticles thus produced demonstrated broad spectrum antimicrobial effect (Srivastava and Kowshik, 2015).

Exopolysaccharides obtained from various marine extremophilic bacteria (Geobacillus sp. 400, Halomonas species, Hahella chejuensis, Polaribacter sp. SM1127) have been found to possess high viscosity and thus can be used as thickening agents. Most of them have been found to be highly active at the surface and thus can be employed as biosurfactants or emulsifiers. They are also reported to exhibit good pH stability and salt tolerance (Poli et al., 2010; Sun et al., 2015).

**COSMETIC USES**

Highly concentrated fucoidan extract (89% fucoidan) from Undaria pinnatifida is available commercially as Maritech Reverse™. It is known to protect skin against UV irradiation, prevent wrinkles and also act as soothing agent. The extract has been found to be non-sensitizing and non-allergenic to skin. Moreover, it is Halal Kosher certified (Fitton et al., 2016).

Oligosaccharides present in laminarin have been found to stimulate, regenerate and rejuvenate human fibroblasts and human epidermis keratinocytes (Yvin et al., 1999).

High molecular weight exopolysaccharide, HYD657, obtained from marine bacteria, Alteromonas macleodii subsp. filijens biovar deepsane, has been used for cosmetic purposes (Poli et al., 2010). Water-binding capability of cyanobacterial EPS can be exploited in the development of cosmetic formulations (Laurienzo, 2010).

Owing to the presence of fucose in addition to large amounts of glucuronic acid and N-acetyl glucosamine in the molecule, the exopolysaccharide, SM1127 EPS demonstrated superior water-retention and hence, humectant property compared to hyaluronic acid. Therefore, it can act as a moisturising agent in cosmetics and free radical scavenging activity makes it a good candidate for anti-aging preparations. It is safe to use and non-irritant to skin (Sun et al., 2015).

In a previous study on sulfated polysaccharide obtained from red alga, Porphyridium cruentum, it has been found to improve the amount of cornified envelope maturation in stratum corneum and reinforcement of the Dermal-Epidermal Junction (DEJ). Therefore, it seems to be a good choice for improving the skin characteristics of dry or aged facial skin and can prolong the effect of moisturizers when applied topically (Ghibaudo et al., 2014).

**DIAGNOSTIC APPLICATIONS**

Injectable, cross-linked dextran-pullulan microparticles functionalized with fucoidan and radiolabelled with Technetium 99m were developed as innovative SPECT diagnostic tool for abdominal aortic aneurysm, owing to the ability of fucoidan to target cell adhesion molecule, P-selectin (Bonnard et al., 2014). Reports of fucoidan as a molecular imaging probe for myocardial infarctions, it is
possible application in detection of thrombosis, myocardial ischemic memory, detection of inflammation in experimental autoimmune myocarditis exist in the literature (Cognet et al., 2014; Saboural et al., 2014; Chollet et al., 2016; Mikail et al., 2016). Doxorubicin-loaded fucoidan-capped gold nanoparticles can be exploited as a contrast agent in imaging of breast cancer using photoacoustic imaging technique (Manivasagan et al., 2016). Mauran-chitosan nanoparticles labeled with fluorescein isothiocyanate (FITC) could act as safe and non-toxic vehicles for imaging of cancer cells by employing confocal microscopic imaging and flow cytometry (Raveendran et al., 2013; Balasubramanian et al., 2014; Raveendran et al., 2015).

A sulfated polysaccharide, isolated from the red marine algae, Solieria filiformis has been studied for its nociceptive and inflammatory effects in experimental animal models. Anti-nociceptive effects of the polysaccharide are mediated through a peripheral mechanism whereas, prostaglandins, nitric oxide and cytokines are responsible for edematogenic effects of the polymer. The results indicate that the tested sulfated polysaccharide can find use as a tool for studying the inflammatory processes associated with nociception (Araújo et al., 2011).

**CHALLENGES IN COMMERCIALISATION OF NEWER SULFATED POLYSACCHARIDES**

Marine algae and bacteria seem to produce a vast array of safe, biodegradable and biocompatible novel polysaccharides and exopolysaccharides with unique physicochemical properties, potential therapeutic benefits and diagnostic applications. Possibilities of being exploited in the pharmaceutical and cosmetic industry remain unlimited. However, only few have been marketed till date which include guar gum, alginate, pectin and carrageenan. Technical challenges in identification, ensuring product quality with high reproducibility, screening and isolation of active principles, high production cost, need for expensive chemicals for fermentation medium and poor handling properties of the newer polymers render them unsuitable for commercial scale utilization. Another important factor that hinders uninhibited research is secured access to the marine resources guided by intellectual property rights in order to protect the vast marine ecosystem biodiversity (Borresen et al., 2010).

**FUTURE PROSPECTS**

Numerous studies have been done on the applications of sulfated polysaccharides in their native, chemically modified forms or in combination with other natural polymers, primarily in the field of nanotechnology. Scope of their use in the field of targeted controlled drug delivery system, stimuli-responsive systems and in the fabrication of drug reservoir matrices is high. Theranostic applications are still unexploited. Design and synthesis of functional polymers for each of the new sulfated polysaccharide, with specific customized properties and uses is an unexplored area, which will also lower material usage. Till date, very few investigations have been done on the pharmacokinetic characterization of the novel sulfated polysaccharides obtained from marine algae and bacteria. Moreover, it has been observed that physicochemical characteristics and applications depend highly on the species from which the polymer has been extracted. Therefore, a detailed database needs to be constructed with information on every aspect of a marine polymer, obtained from different species of the same microorganism. Future studies in this regard and deep understanding of chemistry, fate and species-specific structural variability of the marine polymers will unravel a lot of possibilities for them (Fitton et al., 2015).

**CONCLUSION**

Marine-derived polysaccharides and their products possess immense potential to be alternative, renewable resource in synthesis of novel drug molecules with wide applications, in the design of patient-compliant novel controlled release site-specific drug delivery systems, in the field of cosmetic science and ultimately in diagnosis of cardiovascular diseases and cancers. Marine algae and bacteria possess a vast and valuable chemical library of unique polysaccharides. Sustainable exploration of this marine ecosystem will ensure both environmental and economic benefits and will ultimately enrich the medical, pharmaceutical, cosmetic and diagnostic field with availability of a range of non-toxic biopolymers of marine origin.

**Conflict of Interests**

The authors have not declared any conflict of interests.

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