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Ashok Kumar Nadda
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Microbial Exopolysaccharides as Novel and Significant Biomaterials

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Preface

In the last few decades, the demand of eco-friendly and bio-based products has been increased substantially. The issues of environmental sustainability and climate change can be resolved by replacing the majority of chemical and synthetic compounds with bio-based products. The present book is motivated by the current state of affairs of exopolysaccharides (EPSs) and their composites in wide range of applications. This book had been written to provide a framework of synthesis and production of EPSs using microbes and algae. This book mainly emphasizes on the range of applications of EPSs in various sectors. A variety of EPSs were reported to produce from microorganisms having remarkable properties to use for industrial purposes. These are heterogeneous polymeric substances which have immense applications in pharmaceuticals, medical, food and fabric industry. This polymeric nature also makes these as an alternative of synthetic plastic- and petroleum-based chemicals. Microbes present in marine or terrestrial ecosystem are efficient producers of EPSs. The biofilm forming bacteria are also a major source of the EPSs.

Their function in the aquatic microorganisms is attachment of cells to solid surface and also to defend the microbes from the predatory organisms. Researchers have explored the production of EPSs from microbes by media engineering, genetic engineering and recombinant DNA technologies. These are secreted by the cells in extracellular environment. So, their purification and large-scale production have some advantage over enzyme purification which is a tedious process. These are carbohydrate-rich compounds and produced in the excess of sugar-rich substrate. Now, microbes are quite efficient to utilize a variety of sugar-rich substrates available in the nature due to the presence of wide variety of enzymes encoding genes present in their genome. When these are secreted outside the cells, these may acquire the form of slimy layer or stable cohesive layer. These can be collected and produced at large scale from a number of algae, archea, thermophilic bacteria and microbes of extreme environment. Due to the superior performance and functional properties, microbial polysaccharides are the excellent choice over the plant and micro-algal-derived gums. Microbial polysaccharides are rheology-modifying agents, which can be thickening, stabilizing, emulsifying, flocculating, chelating and encapsulating agents as well. Microorganisms such as bacteria, yeast and fungi produce polysaccharide with various physiological roles. The immense functional properties of microbial polysaccharides undoubtedly rely on their structural conformation and physicochemical properties. Xanthan gum, gellan, dextran and pullulan are the most commercially used microbial polysaccharides. Xanthan gum is an omnipresent food ingredient, serving as thickener, leavener, stabilizer and texture enhancer. Gellan is a remarkable gelling agent that helps to rapidly set the food preparation at low concentration. Dextran is the most medically important polysaccharide used as an antithrombotic agent. Yeast-derived pullulan or its derivative have various biomedical applications such as drug delivery, plasma substitution, tissue engineering and so forth. β-glucan derived from baker's yeast *Saccharomyces cerevisiae* is a commercially available immunostimulatory agent.

The non-toxic nature and inherent biocompatibility have encouraged their applications in the tissue engineering, scaffolds or matrices, bone repair, drug delivery, wound healing and bio-plastic synthesis. These EPSs are also quite useful for in vivo applications as these have inherent capability to undergo auto-degradation in the body cells and tissue. The researchers from various countries have contributed their knowledge and recent progress in the synthesis, production and applications of these exopolysaccharides from various sources. We compiled the chapters written by various experienced researchers working in the microbiology and relevant areas. The rationale of this book is to provide a toolbox from which researchers, students, and industry professionals, can collect the information to utilize and EPSs in various fields. Another major reason for editing the book was the topic of the research area of our interest. Generally, we spend many hours to collect the information on a wide range of topic and were able to get little information or puzzling results. Thus, in the book, we complied the chapters on all the important issues which need to be solved urgently. Chapters "Microbial Exopolysaccharides: An Introduction" and "Techniques Used for Characterization of Microbial Exopolysaccharides" will introduce the various origin historical prospects of EPSs in nature and analytical techniques to study these bio-based compounds. Chapters "Molecular Basis and Genetic Regulation of EPS" and "Molecular Engineering of Bacterial Exopolysaccharide for Improved Properties" describe the molecular basis and modification of microbial EPSs. Chapters "Extremophiles: A Versatile Source of Exopolysaccharide" and "Pullulan: Biosynthesis, Production and Applications" focused on the sources and applications of microbial EPSs. Various pharmacological and industrial applications of the EPSs were described in the chapter "Exopolysaccharides in Drug Delivery Systems "–"Microbial EPS as Immunomodulatory Agents". Chapter "Novel Insights of Microbial Exopolysaccharides as Bio-adsorbents for the Removal of Heavy Metals from Soil and Wastewater" and "Applications of EPS in Environmental Bioremediations" emphasized on the environmental applications of microbial

EPSs. The last chapter summarizes the "Cost-Benefit Analysis and Industrial Potential of Exopolysaccharides". We firmly hope that the present book will be beneficial for all the early stage researchers and industrialists.

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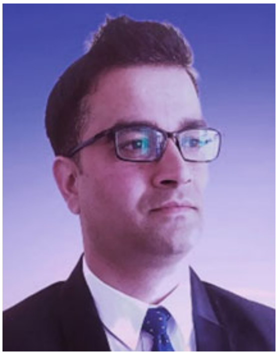

Dr. Ashok Kumar Nadda is working as Assistant Professor in the Department of Biotechnology and Bioinformatics, Jaypee University of Information Technology, Waknaghat, Solan, Himachal Pradesh, India. He holds an extensive research and teaching experience of more than 8 years in the field of microbial biotechnology, with research expertise focusing on various issues pertaining to 'nano-biocatalysis, microbial enzymes, biomass, bioenergy' and 'climate change'. He is teaching enzymology and enzyme technology, microbiology, environmental biotechnology, bioresources and industrial products to the bachelor, master and Ph.D. students. He also trains the students for enzyme purification expression, gene cloning and immobilization onto nanomaterials experiments in his laboratory. He holds international work experiences in South Korea, India, Malaysia and People's Republic of China. He worked as a postdoctoral fellow in the State Key Laboratory of Agricultural Microbiology, Huazhong Agricultural University, Wuhan, China. He also worked as a Brain Pool Researcher/Assistant Professor at Konkuk University, Seoul, South Korea. He has a keen interest in microbial enzymes, biocatalysis, CO_2 conversion, biomass degradation, biofuel synthesis and bioremediation. His work has been published in various internationally reputed journals, namely *Chemical Engineering Journal, Bioresource Technology, Scientific Reports, Energy,* *International Journal of Biological Macromolecules, Science of Total Environment and Journal of Cleaner Production*. He has published more than 100 scientific contributions in the form of research, review, books, chapters and others at several platforms in various journals of international repute. The research output includes 74 research articles, 25 chapters and 16 books. He is the main series editor of *Microbial Biotechnology for Environment, Energy and Health* that publishing the books under Taylor and Francis, CRC Press, USA. He is also a member of the editorial board and reviewer committee of the various journals of international repute. He has presented his research findings in more than 40 national/international conferences. He has attended more than 50 conferences/workshops/colloquia/seminars, etc., in India and abroad. He is also an active reviewer for many high-impact journals published by Elsevier, Springer Nature, ASC, RSC and Nature Publishers. His research works have gained broad interest through his highly cited research publications, book chapters, conference presentations and invited lectures.

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Dr. Swati Sharma is working as assistant professor in University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, India. She is working extensively on the waste biomass, biopolymers and their applications in various fields. She has completed her Ph.D. from Universiti Malaysia Pahang, Malaysia. She worked as a visiting researcher in the college of life and environmental sciences at Konkuk University, Seoul, South Korea. She has completed her master's (M.Sc.) from Dr. Yashwant Singh Parmar University of Horticulture and Forestry, Nauni, Solan HP, India. She has also worked as a program co-coordinator at the Himalayan Action Research Center, Dehradun, and senior research fellow at India Agricultural Research Institute in 2013–2014. She has published her research papers in reputed international journals. Presently, her research is in the field of bioplastics, hydrogels, keratin nano-fibers and nano-particles, biodegradable polymers and polymers with antioxidant and anticancer activities and sponges. She has published 22 research papers in various internationally reputed journals, 5 books and a couple of book chapters.

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Microbial Exopolysaccharides: An Introduction

Kuttuvan Valappil Sajna, Swati Sharma, and Ashok Kumar Nadda

Abstract Microbes secrete high molecular-weight polysaccharides of diverse structures into the surrounding environment termed exopolysaccharides (EPSs). EPSs serve multifarious roles which aid the microbes to thrive at different ecosystems. Many EPSs are industrially/clinically relevant polymers owing to their biocompatibility, biodegradability, non-toxic nature and distinct physicochemical properties. Considering their past success for various applications ranging from hydrocolloids to biomedical applications, microbial EPSs still hold considerable attention of biotechnologists. They are high-value products, and their market value will grow in the coming years due to their potential nutraceutical, therapeutic and industrial potential. The objective of the chapter is to update the readers with recent findings on microbial EPSs. This chapter also gives interesting insights into physiological roles and biosynthesis of microbial EPS. The chapter also discusses the recent advances in applications of microbial EPSs and their commercial prospects.

Keywords Microorganisms · Polysaccharides · Hydrocolloids · Polymers · Biomedical application

1 Introduction

Microbes are the source of many biotechnological products due to their metabolic diversity and ease of cultivation. One such product-exopolysaccharides (EPSs) are widely used as the polymers in various industries owing to distinct physicochemical

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properties, non-toxic nature, biocompatibility, biodegradability and the ease of production. Microbial polysaccharides are of two types—intracellular polysaccharides and extracellular polysaccharides. Extracellular polysaccharides are further classified into capsular polysaccharides that encapsulate the microbes (exocellular polysaccharide) and exopolysaccharide (EPS) which secreted into the surrounding environment [1]. Intracellular polysaccharides are the storage polysaccharides serving as a rapid carbon source under nutrient deprivation [2]. Capsular polysaccharides play a significant role in microbial pathogenesis. The immunogenic property of capsular polysaccharide makes them a good target for vaccine development [3]. EPSs play diverse roles from biofilm formation to pathogenesis.

The first EPS discovered was dextran by Louie Pasteur in the nineteenth century as a microbial product in the wine industry [4]. The contribution by Allene Jeanes in the mass level production of dextran and discovery of xanthan revolutionized the industrialization of microbial EPS. EPSs are high molecular weight compounds with the molecular weight ranging from 0.5×106 to 2×106 daltons. EPSs may be of homopolymeric or heteropolymeric in sugar composition and can be linear or branched, structurally [5]. Apart from the monosaccharide composition and structural complexity of EPSs, EPSs may contain functional groups such as acetyl, carboxyl, sulfate, phosphate, pyruvate and uronic acid groups, which all determine the physicochemical and biological properties of EPSs.

Microbial EPSs are inevitable for modern human lifestyle as the ingredient in food and personal care formulations. They have immense clinical applications including emergency medicine or an ingredient in pharmaceutical formulations. They are also used extensively in the petroleum industry, household product formulations and construction applications. Considering the current R&D scenario in microbial EPS, their clinical, lifestyle and other implications will be accentuated in the near future. Table 1 summarizes commercially available microbial EPS with potential industrial/clinical applications.

2 Novel Exopolysaccharides with Therapeutic/Industrial Significance

Considering the past success of EPSs for various applications ranging from hydrocolloids to biomedical applications, exopolysaccharide still holds considerable attention of biotechnologists. Many novel EPSs with significant clinical/industrial applications have been reported in the last decade (Table 2). Some of these microbial sources are already known for EPS production. Novel variation in EPS can be pinpointed by investigating the monosaccharide composition of EPS. Strain-specific EPS is encoded by unique EPS biosynthetic genes. Diversity of epsE gene in *Lactococcus lactis* strains result in strain-specific EPS production [25]. Some of the most common sources for the isolation of EPS producing microbes are dairy products, fermented products and plant parts. Identification of lactic acid bacteria

Table 1 Summarizes commercially available microbial EPS with potential industrial/clinical applications

EPS	Microbial strain	Structure	Industrial/ clinical uses	References
Dextran	*Leuconostocmesenteroids*	α-1,6-Glucan with branching of α-1,3-glycosidic linkage	Clinical applications—plasma volume extender, antithrombotic agent, blood substitute, vascular surgery, drug delivery agent, clinical management of iron deficiency anaemia, preservation solution for organs, and wound healing agent. Other uses—food packaging, photographic uses, separation technology, cell culture techniques and cryoprotectant agent	De Belder [6], Bhavani and Nisha [7], Abir et al. [8], Debele et al. [9], Rutherford et al. [10], Aman et al. [11], Candinas et al. [12], Zhu et al. [13]
Xanthan	*Xanthomonas campestris*	A polymer of D-glucose, D-mannose and D-glucuronic acid	Additive in food, medical and personal care formulations; used as drilling fluid in oil field drilling and building materials for construction applications	BeMiller [14], Akpan et al. [15, Plank [16]
Pullulan	*Aureobasidium pullulans*	Glucan of α-(1-6) and α-(1-4) glycosidic linkage	Food and pharmaceutical additive; oral care ingredient	Singh et al. [17]

(continued)

Table 1 (continued)

EPS	Microbial strain	Structure	Industrial/ clinical uses	References
Gellan	*Sphingomonas elodea*	A polymer of tetrasaccharide units comprised of D-glucose, D-glucuronic acid, D-glucose L-rhamnose	Food, pharmaceutical and personal care formulation; an additive in household products; also used in tissue culture media preparations	Iurciuc et al. [18]
Curdlan	*Agrobacterium* sp.	(1-3)-β-glucan	Food additive; used in pharmaceutical formulation and drug delivery system	Zhang and Edgar [19]
Scleroglucan	*Sclerotium rolfsii*	β-1,3-β-1,6-glucan	Petroleum recovery; used in nutraceutical and pharmaceutical industry; in food and personal care formulations; construction applications	Castillo et al. [20]
Schizophyllan	*Schizophyllum commune*	β-1,3-β-1,6-glucan	Therapeutic application, cosmetic application	Leathers et al. [21]
Bacterial cellulose	*Acetobacter xylinum*	β-1-4 glucan	Hydrocolloid dressing; cosmetic and textile industrial application	Wang et al. [22–24]

secreting a novel EPS composed of unusual monomer like *N*-acetylglucosamine from a fig leaf highlight the importance of bioprospecting of environmental source such as these for EPS producers [26]. Exploring the ecological hotspots and extreme environments can lead to the discovery of the microbes producing novel EPS with significant biotechnological implications. Delbarre-Ladrat et al. [27] that the majority of bacterial species inhabiting deep-sea hydrothermal vents has the potential of producing structurally diverse high-value EPS, which emphasized the bioprospecting of marine environment for EPS producing microbes.

Table 2 Novel EPS of therapeutic/industrial significance

EPS	Source organism	Monomeric composition	Potential application	Reference
EPS-NA3	*Lactobacillus coryniformis*	α-rhamnose, α-mannose, α-galactose, and α-glucose	Antioxidant and antibiofilm agents	Xu et al. [28]
α-mannan	*Pseudoalteromonas* SM20310	2-α- and 6-α-mannose	Cryoprotection	Liu et al. [29]
EPS-1 and EPS-2	*Bacillus amyliliquefaciens C-1*	Glucose, mannose, galactose and arabinose (EPS-1); Glucose and mannose (EPS-2)	EPS-1 as an antioxidant agent	Yang et al. [30]
Neutral EPS	*Lactobacillus paracasei* IJH-SONE68	*N*-acetylglucosamine	Anti-inflammatory agent	Noda et al. [26]
Acidic EPS	*Lactobacillus plantarum* SN35N	Glucose, galactose, and mannose	Anti-inflammatory agent	Noda et al. [31]
Pseudozyma EPS	*Pseudozyma* sp. NII 08165	Glucose, galactose, and mannose	Emulsifying and suspending agent	Sajna et al. [32, 33]
DM-1 EPS	*Bacillus licheniformis* strain DM-1	Proteoglycan	In situ microbial enhanced oil recovery	Fan et al. [34]
EPS	*Lactobacillus fermentum* R-49757	D-glucose and D-mannose	Not investigated	Do et al. [35]
EPS-S3	*Pantoea* sp. YU16-S3	Glucose, galactose, *N*-acetyl galactosamine and glucosamine	Wound healing applications	Sahana and Rekha [36]
EPS	*Lactobacillus paraplantarum*	Glucose, galactose and mannose	Emulsifying and texturing agent	Sharma et al. [37]
EPS-SN-1	*Bacillus velezensis SN-1*	Glucose, mannose and fructose	Antioxidant agent	Cao et al. [38]
EPS	*Bifidobacterium breve* lw01	Rhamnose, arabinose, galactose, glucose, and mannose	Anticancer activity	Wang et al. [22–24]
Nat-103	*Natronotaleasambharensis* AK103^T	Mannose, glucose and glucuronic acid	Antioxidant activity	Singh et al. [39]
EPS	*Lactobacillus mucosae* VG2	D galactan	Not investigated	Fagunwa et al. [40]

3 Physiological Roles and Ecological Aspects of EPS

EPS serve multifarious roles which aid the microbes to thrive in different ecosystems. EPS plays a varying role from biofilm formation, quorum sensing to pathogenesis and the functions depend on ecological niche of host organisms. Physiological roles of EPS are unravelled using the approach of knocking out EPS biosynthetic genes to create mutant deficiencies in EPS production. Pullulan produced by a desert isolate *Aureobasidium melanogenum* confers adaptation for living in the harsh desert environment by protecting from various abiotic stresses [41]. EPS produced by an arctic sea isolate *Pseudoalteromonas* strain SM20310, plays a significant role in environmental adaptation of strain in sea ice by providing high salinity tolerance and cryoprotection [29]. EPS has implication in the protection of plant growth-promoting *Rhodotorula* sp. from adverse environmental conditions [42]. Similarly, pH buffering property of cyanobacterial EPS matrix protects the dryland cyanobacteria from acid damage [43].

On solid surfaces, EPS facilitates the growth of bacterial communities as biofilm by leading bacterial cell adhesion and bacterial cell aggregation. Caro-Astorga et al. [44] revealed that each EPS produced by *Bacillus cereus* serve distinct roles. EPS1 contributes to bacterial motility, while EPS2 is involved in biofilm formation and gut colonization, thus playing a role in host-pathogen interaction. Being an integral part of biofilm, EPS makes the bacterial colonies recalcitrant to a wide range of antimicrobial agents. During the biofilm formation by *Pseudomonas aeruginosa*, production of matrix EPS 'psl' and the intracellular signalling molecule 'c-di-GMP' that stimulates the synthesis of biofilm matrix EPS is in the feedforward control loop. Hence, targeting the biofilm signalling mechanism can be an effective strategy to tackle chronic *P. aeruginosa* infections [45]. Another EPS, pel is cationic and hold the extracellular DNA in the biofilm matrix, apart from being the structural element of biofilm [46].

Studies on EPS produced by *Lactobacillus* species revealed the role of EPS in bacterial surface properties and host interaction. EPS affected the surface properties such as colony phenotypes and bacterial surface charge. Gene deletion studies revealed that EPS plays a significant role in bacterial cell aggregation. Concealing the surface structure with EPS might be one of the tactics to reduce the cell-cell interaction and the role of EPS in host cell interaction is strained specific [47–49]. EPS 1, a major virulence factor of a phytopathogenic bacteria *Ralstonia solanacearum* regulate the feedback loop of quorum sensing [50].

In the case of lactic acid bacteria, EPS protect the bacteria from bacteriophage, nisin and lysozyme [51]. EPS is the major arsenal for microbes to compete with each other for food and space. Toska et al. [52] suggested that EPS is involved in the antagonistic interaction between bacterial species and lead to the successful establishment of bacterial communities. In Gram negative bacteria such as *Vibrio cholerae*, EPS protect bacteria from other bacterial attacks by inhibiting the type 6-secretion system (T6SS). Type 6 secretion system by gram-negative bacteria is used to deliver the toxic protein into adjacent eukaryotic and bacterial cells. Deletion of EPS biosynthetic genes makes the *V. cholerae* more susceptible to T6SS attack by heterologous bacteria. On other hand, the same EPS of *V. cholerae* will not affect its T6SS attack on other bacteria [52].

EPS plays an important role in the establishment of plant microbial symbiosis. Plant root attachment of nitrogen-fixing bacteria *Paraburkholderia phymatum* is determined by the production of an EPS, cepacian [53]. Plant-growth promoting soil-borne *P. aeruginosa*, *P. syringae*, *P. putida*, and *P. fluorescens* produce EPS 'alginate'. Alginate play an important role in Zn^{2+} biosorption and phenazine biosynthesis, a biocontrol agent produced by fluorescent *Pseudomonas* strain. Increased alginate production affects the rhizosphere compatibility with improved biofilm formation and enhanced root colonization [54]. EPS helps to maintain the spore physiology and improve spore survival. *pzX* is an eps exclusively produced during sporulation of *Bacillus* species. Composition of amino sugar provides unique properties to *pzX* like lowering the surface tension and inhibiting cell-spore aggregates formation [55]. Metagenomic analysis of biological soil crust showed the presence of EPS and lipopolysaccharide (LPS) producing bacterial species. Here, EPS and LPS act as soil glue for soil aggregate formation that aid the formation of biological soil crust [56].

EPS plays a crucial role in etiology of dental caries. Demineralization of teeth by cariogenic biofilms leads to the formation of the oral cavity. In the presence of carbohydrates, cariogenic microbes produce organic acids that leach calcium from the teeth. A study showed that cariogenic microbes such as *Streptococcus mutans*, *Lactobacillus rhamnosus*, and *Candida albicans* produce EPS that have a high calcium-binding affinity, which attributes to the calcium tolerance of the microbes. Apart from structural anchorage to the biofilm, EPS also serve as a survival tool of cariogenic microbes to defuse high calcium concentration [57]. Targeting EPS can be an effective strategy to control cariogenic microbes [58]. However, in the case of catheter-associated urinary tack infection, EPS secreting *P. aeruginosa* adopt exopolysaccharide independent biofilm formation [59]. Hence, understanding the role of microbial EPS is crucial for developing therapeutic interventions against pathogenic microbes in which EPS production can be targeted. Furthermore, ecological functions of microbial EPSs promote their huge agronomical implications.

4 Biosynthesis and Metabolic Regulations of EPSs

Functional genomics analysis provides valuable information on EPS biosynthesis, export, and regulation. Identifying the gene targets can pave the ways to engineer high EPS producing strains or strains that produce tailor-made EPS [60]. Genomic analysis of microbes can reveal microbial potential to produce unknown exopolysaccharides. Borlee et al. [61] identified a novel EPS biosynthetic gene cluster involved in biofilm formation of *Burkholderia pseudomallei*. Genome annotation of EPS producing thermophilic bacteria *Geobacillus* may improve its prospects as a microbial cell factory for EPS production [22–24]. Padmanabhan et al. [62] studied differential gene expression during EPS biosynthesis by *Streptococcus thermophilus* ASCC 1275 in different sugar-containing media at stationery and log phases. They observed a correlation between high EPS production and upregulation of genes involved in sugar metabolism. A similar observation of increased UDP-glucose and UDP-galactose synthesis associated with a high yield of EPS, by *S. thermophilus* S-3 was reported by Xiong et al. [63]. Proteomic analysis revealed that upregulation of proteins involved in sugar transport, EPS assembly and amino acid metabolism was also associated with high EPS production [62, 64].

Availability of whole genome sequence of EPS producing microbes facilitates the metabolic engineering strategies for EPS production [65]. Evaluation of EPS production by gene knockout mutants, gene overexpression mutants and gene complementation mutants of EPS biosynthetic genes can shed light on the role of each EPS biosynthetic genes in EPS production [66]. CRISPR-Cas9 genome editing had enabled researchers to produce EPS variants with different monomeric composition from *Paenibacillus polymxa.* These EPS variants can give insights into the structure-function relationship of polysaccharides and aid to create customized EPS with desirable properties [67]. *Xanthomonas campestris* strains were engineered to produce xanthan gum variants with distinct secondary structure and rheological properties, which may be suitable for application in various industries. Structure-activity relationship of these tailor made-xanthan gums revealed that terminal mannose is one of the major determinants of rheological properties of xanthan gum, while the terminal mannose and internal acetyl group are integral to its double-helical conformation [68]. Genome editing and metabolic engineering could yield tailor-made EPS with improved stability and higher performance, which can have huge commercial potential when compared to native EPS.

5 Applications and Commercial Prospects of EPS

Due to the presence of a large number of hydroxyl groups, microbial EPS have been long used as hydrocolloids, which modify the rheology of the system by altering the flow behaviour and texture. In food and personal care industry, they serve as a thickening, gelling, stabilizing, emulsifying and water-binding agents [69, 70]. Xanthan gum is a widely used thickener in food formulation. In food and confectionary, xanthan gum has become more prominent in recent years due to its status as vegan-friendly. In gluten-free baking, xanthan gum provides structure and elasticity to dough or batter, and as an egg substitute, it emulsifies and thickens the food preparations. Xanthan gum based thickened fluid appears promising for treatment of patients with oropharyngeal dysphagia. Apart from safety and efficacy, it is resistant to α-amylase and preferred by patients, when compared to starch-based thickener [71, 72]. The concentration, type and setting time of xanthan gum-based food thickeners are the main factors in designing the infant food formulation used for paediatric dysphagia [73]. Gellan gum exhibit excellent gelling properties. To overcome the limitation of the gellan gum such as low mechanical strength and high gelation temperature, blending with natural or synthetic polymer has been employed [74]. Synergistic hydrogels of xanthan gum and gellan gum with other natural polymers are promising for the preparation of food packaging materials [75].

Antioxidant property and water-absorbing/retention properties are some of the features of EPS attractive for cosmetic applications [76]. ‘Lubcan’ an EPS with remarkable skin lubricating property produced by *Paenibacillus* sp. ZX1905 could be a low-priced replacement of hyaluronic acid in cosmetic formulations [77]. Extremophilic microbes may provide EPS with excellent keratinocyte protective ability from temperature or radiation-induced damage. An EPS of momomers-*N*-acetyl glucosamine, mannose and glucuronic acid produced by an artic marine bacterium *Polaribacter* sp. SM1127 could be an excellent cosmetic ingredient as it is dermatologically safe, possess better moisture retention properties than hyaluronic acid and good antioxidant activity, and protect human dermal fibroblast from low temperature-induced damage [78]. Radiation-resistant *Deinococcous radiodurans* derived EPS (deinopol) protect keratinocytes from radiation-induced ROS damage [79].

Potential bioactivities reported for EPS include antitumor, antioxidant, immunomodulatory, antiviral, antibacterial, anti-inflammatory, and cholesterol-lowering properties. Consumption of bioactive EPS can have potential health benefits [80]. Antitumor property of EPS stems from its ability to modulate oncogenic pathways. EPS produced by many lactic acid bacteria can induce apoptosis and cell cycle arrest in tumour cells, without any toxicity to normal cells [81]. EPS secreted by probiotic yeasts-*Kluyveromyces marxianus* and *Pichia kudriavzevii* were reported to induce apoptosis in colorectal cancer cells by inhibiting AKT-1, mTOR, and JAK-1 pathways [82]. Though many studies demonstrated the antitumor potential of EPS, the viability of EPS as a coadjuvant for cancer therapy needs to be addressed by in-depth in vivo studies. Some researchers observed that the sugar composition of EPS primarily determines its antitumor property. For instance, Tukunmez et al. [83] observed that the apoptotic induction by *Lactobacilli* EPS was related to the mannose content of EPS. The mode of action of *Lactobacilli* EPS is by upregulation of Bax, Caspase 2 and 9 and downregulation of Bcl-2 and Survivin leading to caspase-mediated apoptosis [83].

EPSs have been commonly used in pharmaceutical formulations for controlled and sustained release of drugs, coating of pills or as suspension stabilizers. Presence of hydroxyl groups and free carboxyl groups in EPS enables the structural modification of EPSs, improving the biostability and mechanical properties or impart novel functionality to EPSs, thus broadening their applications [84]. Adding hydrophobic moiety to xanthan gum reduces its solubility and porosity, and modified its rheology. The resulting amphiphilic xanthan gum reduced the surface tension/interfacial tension and stabilized the emulsion, which improves its prospects for pharmaceutical applications, in comparison to native xanthan gum [85]. Du et al. [86] reported an antibacterial hydrogel made of hydrophobically modified chitosan and oxidized dextran with improved wound healing properties than that of traditional gauze. Similarly, a thermoreversible hydrogel made with xanthan and konjac glucomannan appear promising for in situ would healing [87].

Non-immunogenicity, biocompatibility and biodegradability determine the applicability of EPS in biomedical application. Dextran is the most clinically used bioabsorbable EPS. Dextran has been used as a plasma extender and an antithrombotic agent. Dextran is neutral in charge, exhibit excellent pharmacokinetics and is easily degraded by dextranase enzyme in our body [88]. Acetalated dextran (Ac-Dex) is modified dextran with hydrophobic nature. It can be easily formulated to micro/nanoparticle, which can encapsulate a diverse payload. Its pH-sensitive nature makes it an effective drug delivery system for protein, miRNAs and chemotherapeutic drugs [89–91]. Studies with natural compound ganothalamine revealed promising application of Ac-Dex as an encapsulating agent for the sustained release of the anticancer drug [92]. Wannasarit et al., [93] synthesized a conjugated dextran-based polymeric nanoparticle which can mimic viral entry to the cell. Adapting a viral mode of delivery of therapeutics to the cytoplasm is a good approach to bypass the lysosomal degradation that happens after the internalization of the drug. The prepared poly(lauryl methacrylate-comethacrylic acid)-grafted acetalated dextran carrying the payload of asiatic acid showed improved therapeutic efficacy than treatment with asiatic acid alone. Pinho et al. [94] prepared a dextran-based photocrosslinked membrane which shows potential as implantable devices for biomedical application. In vivo studies using rat models indicated that the developed dextran-based membrane is biocompatible.

With the aim to restore or regenerate the damaged tissue, tissue engineering comprises of cells and growth factors in a biomaterial that acts as the scaffold for cell growth. Biocompatibility, gelation and mechanical properties are the attractive properties of EPSs for their use as biomaterials in tissue engineering [95]. Microbial EPS containing hexosamine and uronic acid as monomers and acetyl/sulfate groups as functional groups hold great therapeutic potential due to their structural resemblance with mammalian glycosaminoglycans (GAG). Using bacterial GAG-like polymers over mammalian GAG have the following advantages. Bacterial EPSs are produced by fermentation that is more feasible when compared to strenuous extraction of GAG from animal tissue. Bacterial EPSs are free of prions and viruses as in the case of mammalian GAGs. EPS produced by marine isolated *Vibrio diabolicus* and *Alteromonas infernus* are promising candidates for tissue repair and remodelling. Chemical modifications of these depolymerized polysaccharides using *N*-deacetylation and sulfation can yield heparin-like polymers [96–98]. Cross-linked dextran is an effective injectable hydrogel for cartilage regeneration [99]. Capsular alginate extracted from *Azotobacter agile* exhibit lower cytotoxicity on mesenchymal stem cells than algal alginate. Moreover, tailor-made alginate with attractive properties to serve as a biomaterial can be produced by metabolic engineering of host bacterium [100].

The petroleum industry has been using EPS as a viscosifier for the drilling purpose. In situ EPS production by *Pseudomonas stutzeri* XP1 isolated from oil reservoir could enhance the oil recovery that demonstrated the potential of EPS for enhanced oil recovery [101]. EPS can be a potential bioadsorbent for heavy metal removal. They are environmentally friendly, cost-effective, and require milder conditions to operate. Metal adsorption by EPS depends on ionic nature of metal, its size and charge density. Positively charged heavy metals can be sequestered using anionic charged EPS [102]. When arsenic degrading bacteria was cultivated in arsenic-containing media, they produced EPS that can effectively sequester arsenic. These EPS are rich in polyanionic functional groups, which result in electrostatic to covalent binding with arsenic [103]. Similarly, studies also demonstrated the excellent flocculating activity of microbial EPS [33, 104].

EPS can be effective and sustainable soil strength improver. Using EPS as the soil stabilizer can alleviate the negative environmental impact associated with traditional soil stabilizers such as lime and cement. Improvement in soil shear strength and soil fabric was noted on addition of xanthan gum to the organic peat matrix, due to the hydrogen and electrostatic binding between xanthan gum and clay particle [105, 106]. Xanthan gum and sodium alginate could alleviate soil erosion and reduce the collapsible potential of soil material [107, 108]. Water adsorption and moisture-retention abilities of soil can be greatly improved by the addition of xanthan gum [109].

Exopolysaccharide-derived oligosaccharides can be considered for sustainable agricultural practices. Plant growth-promoting biostimulants can greatly benefit agriculture by stimulating the nutrient uptake, enhancing the photosynthetic activity of plants and protect the plants by mitigating abiotic stress [110]. Low molecular weight oligo-gellan prepared by depolymerization of gellan gum is promising as a biostimulant, which improved the plant growth and survival of Red Perilla plants under normal and stress conditions. Biostimulatory activity may be due to elicitation of plant polyphenol content and other secondary metabolites, leading to high antioxidant activity [111]. Though gellan gum also confers some biostimulatory effects on plants, the oligo-gellan exhibited better performance [112].

6 Conclusions

Microbial EPSs are one of the industrially significant microbial products, which are used as the functional ingredient in the food, pharmaceutical, personal care and other industries. Functional application of EPS is correlated to their structural complexity, which determines their physicochemical properties and bioactivities. Besides, the structural modification of EPS and synergistic manipulation with natural or synthetic polymers to broaden the applications of EPS, researchers are actively searching for novel EPS with versatile physicochemical properties or unique bioactivities which can have industrial/therapeutic applications. For that, they pursue the bioprospecting of EPS producing microbes from different environmental samples, specifically extreme environment. The ability of microbes to produce unknown exopolysaccharide is also being studied by genomic analysis.

Some latest studies shed light on the role of EPS in host-microbial symbiosis and pathogenesis. Understanding the physiological roles of EPS secreted by pathogenic or opportunistic microbes is quite crucial for developing novel therapeutic strategies against these microbes. Employing multiple omics techniques and metabolic engineering strategies in the field of microbial EPS can greatly expand the knowledge in EPS biosynthetic pathways and also, leads to the generation of tailor-made EPS with superior properties.

Microbial EPS possess excellent rheological, emulsifying, and water-retention properties, which makes them highly sought-after industrial polymers in food, personal care, pharmaceutical and oil-drilling industry. In addition to this, they possess stability in a wide range of temperature and pH that heighten their commercial prospects. Furthermore, EPS may possess biological activities such as antioxidant, antitumor, immunomodulatory and antimicrobial properties and are promising for therapeutic and nutraceutical applications. Structural modified EPS with natural or synthetic polymers make an effective hydrogel with implications in clinical and biomedical field as wound dressing and tissue engineering applications. Growing researches demonstrate the potential use of EPS for bioremediation, soil conservation and sustainable agricultural practices.

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