Diversity of Polysaccharides in Cyanobacteria

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Abstract

Polysaccharides show immense structural variability by virtue of their monomer composition, linkages, oligomer units, branching, size, and interactions with non-saccharide components. In cyanobacteria, polysaccharides are found as storage molecules, in cell envelopes, and as extracellular polysaccharides (EPS). Storage molecules exist as glycogen and cyanobacterial starch and exhibit lowest diversity. As part of the cell envelope, lipopolysaccharides (LPS) in the outer membrane contribute 70–75% to the cyanobacterial cell surface. O-antigen polysaccharide imparts structural heterogeneity and thus strains specificity even in the cyanobacterial species sharing the same habitat. LPS is responsible for a diverse range of health effects in man. EPS that interfaces with the surrounding environment shows maximal structural diversity and functional versatility. Functions of the EPS vary with the species and provide as the primary mechanism for survival in extremes, defence against toxins, heavy metals, predators, and other antagonists. They modify fluidity of the external milieu and are involved in cellular communication important in structuring the biofilm community. In fact, both survival and growth of the organism are dependent on the organisms' EPS arsenal. Thus, the cyanobacteria spend up to 70% of the total energy reserve in the production of EPS. Such diversity of polysaccharides is not easy to be replicated through synthetic processes. This chapter provides glimpses of the diversity of polysaccharides found in cyanobacteria and their industrial potential to encourage prospective work in this area.

Keywords

Cyanobacteria · Extracellular polysaccharides · Glycogen · Lipopolysaccharides · Starch · Semiamylopectin

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15.1 Introduction

Cyanobacteria are efficient at solar energy capture investing as much as 9% of the solar energy into biomass as compared to only 0.5–3% for higher plants (Dismukes et al. 2008; Branco dos Santos et al. 2014). They can fix an estimated 25 gigatons of carbon from CO_2 per year into energy dense biomass (Paumann et al. 2005) constituting 0.05% of global carbon in biomass (Garcia-Pichel et al. 2003). Cyanobacteria have existed since the Proterozoic era (2500–570 Ma) where they were the principal primary producers and the ultimate source of atmospheric oxygen (Schopf and Walter 1982). The transition from a reductive to an oxidative environment triggered diversification of cyanobacterial lineages and appearance of new traits (Schirrmeister et al. 2016). The group has acquired remarkable adaptations in the evolutionary journey establishing them in the most diverse aquatic and terrestrial environments across the latitudes, from the polar to the tropical, along all altitudes and extremes and in a variety of ecological associations. Polysaccharides have played a critical role in establishing these communities in the process.

Diverse structures can be created by simply linking different monosaccharides through glycosidic bonds, different conformations, configurations, branching, and interactions with other non-saccharidic components that further generate macromolecular, structural, and functional versatility to the roles that they perform. Polysaccharides by nature are designed to perform various specific functions in a living organism. They usually act as carbon sinks that provide energy reserve; maintain structural integrity; alleviate stress; defend against toxins, parasites, and preys; and act as information systems (Lohman 1990). Minor modifications in the structure can cause major changes in the properties and attributes of the polysaccharide. Remarkably, these modifications may be brought about in response to as little changes in the abiotic and biotic factors. Cyanobacteria produce polysaccharides either endogenously serving as storage polysaccharides as part of the cell wall or exogenously, and discussion on these components is the primary focus of this review.

15.2 Cell Wall Polysaccharides

Cyanobacterial cell walls resemble the Gram-negative bacterial architecture comprising of cytoplasmic membrane, peptidoglycan layer, and an outer membrane. Though the overall structure of cyanobacterial cell wall is that of a Gram-negative wall, the peptidoglycan layer is considerably thicker resembling a Gram-positive wall. In unicellular strains like *Synechococcus* sp., the layer is about 10 nm thick, and the filamentous forms like *Phormidium uncinatum* have a 15–35-nm-thick peptidoglycan, while larger forms like *Oscillatoria princeps* have a 700-nm-thick layer. The extent of crosslinking is also high: 55–63% in cyanobacteria as against 20–33% in Gram-negative bacteria (reviewed by Hoiczyk and Hansel 2000). The outer membrane is composed of lipopolysaccharides that are amphiphilic heteropolymers comprising 10–15% of the outer membrane and covering nearly

75% of the total cell surface (Lerouge and Vanderleyden 2002). They are heat-stable endotoxins and have been recognized as a key factor in septic shock in humans. LPS contributes to the structural properties of the cell envelope and acts as a physical barrier to protect the cell. More external layers like the capsule, S layer, sheath, and slime that occur above the outer membrane along with the cell wall are annotated as the cell envelope. Additionally, cell type-specific structures also exist like glycolipid layer and polysaccharide layer around the heterocysts of filamentous cyanobacteria (Herrero et al. 2016).

15.3 Lipopolysaccharides

Lipopolysaccharides (LPS) are highly acylated saccharolipids with a molecular mass of about 10–20 kDa (Lerouge and Vanderleyden 2002). This complex amphiphilic macromolecule is composed of a glucosamine disaccharide backbone with hexa- or hepta-acyl chains, linked to a hydrophilic polysaccharidic core that extends out to the environment (Raetz and Whitfield 2002). The O-antigen consists of repetitive subunits that extend out from the bacteria and can include from 1 to 25 chemically identical repeating oligosaccharide units, which, in turn, contain 2 to 7 monosaccharide residues, generally hexoses (Wilkinson 1996). The polysaccharide chains show heterogeneity in terms of monosaccharide composition, their alternative configurations, and the innumerable types of glycosidic linkage, length, branching degrees, and noncarbohydrate substituents. It exhibits interstrain as well as intrastrain heterogeneity and is the basis of serological and antigenic specificity of the organism (Lerouge and Vanderleyden 2002). Presence of O-antigen modifies the appearance of a bacterial colony from rough to smooth. Another morphological variant is called "semi-rough" and contains short-chain-type LPS having only one O-chain repeating unit (Nazarenko et al. 2011).

15.3.1 Core

The core region is less varied than that of O-antigens comprising up to 15 sugar residues and responsible for antigenicity in the rough-type LPS (Caroff and Karibian 2003; Steimle et al. 2016). It is divided into a proximal and a distal region. The proximal region, called "inner core," contains 3-deoxy D-manno-oct-2-ulosonic acid (Kdo), heptoses, and negative charges usually derived from phosphate groups, and it is important for maintaining the integrity of the outer membrane. The distal region, called "outer core," provides attachment to the O-antigen, if present, and is usually composed of hexoses and shows more structural variability (Caroff et al. 2002; Caroff and Karibian 2003; Gemma et al. 2016). The core region is further linked to lipid A via a Kdo residue. Usually, the core region contains L-glycero-D-manno-heptose (L,D-Hep) and an L-α-D-Hep(1,3)L-α-D-Hep(1,5) [α Kdo (2,4)] α-Kdo tetrasaccharide (Hep II, Hep I, Kdo II, and Kdo I, respectively), which may be further substituted by other sugars or phosphate residues or sometimes by acetyl

groups or amino acids. In addition to L, D-Hep, several LPS contain its biosynthetic precursor, D-glycerol-D-manno-heptose (D, D-Hep). There are other LPS that contain only D, D-Hep or even lack any heptose. Kdo may be replaced by the stereochemically similar sugar acid D-glycero-D-talo-oct-2-ulosonic acid (Ko) (reviewed by Holst 2011).

15.3.2 Backbone

Lipid A (endotoxin), a glycophospholipid that provides anchorage to the molecule in the outer membrane, is composed of a glucosamine disaccharide backbone in 1,6 linkage and is a highly conserved segment. At 1′ and 4′ positions, the disaccharide contains α-glycosidic and nonglycosidic anionic phosphoryl groups, and at positions O 2, O 3, O 2′, and O 3′ are (R) 3-hydroxy fatty acids in ester and amide linkages. Two of these fatty acids are usually further acylated at their 3-hydroxyl group. Most of the bacteria show acylation with 4–6 chains ranging from 10 to 16 carbon atoms in length. The type of hexosamine present, degree of phosphorylation, the presence of phosphate substituents, chain length, number, and position of the acyl groups impart individuality to the cells (Kabanov and Prokheronko 2010; Steimle et al. 2016).

15.3.3 Cyanobacterial Lipopolysaccharides

Cyanobacterial lipopolysaccharides are structurally and functionally different from the proteobacteria (Hoiczyk and Hansel 2000; Snyder et al. 2009). Most cyanobacteria possess a simplified LPS structure containing 31–80% carbohydrates, 8–18% fatty acids, and 0.1–8% proteins (Durai et al. 2015). There are none or trace amounts of 3-deoxy-D-manno-oct-2-ulosonic acid (KDO), which is ubiquitously present in enteric Gram-negative bacteria. But some strains of cyanobacteria, viz., *Spirulina platensis* (Tornabene et al. 1985), *Microcystis aeruginosa* NRC1 (Raziuddin et al. 1983), *Phormidium* sp. (Mikheyskaya et al. 1977), *Anacystis nidulans* (*Synechococcus* PCC 6301) (Katz et al. 1977), and *Agmenellum quadruplicatum* (*Synechococcus* PCC73109) (Buttke and Ingram 1975), possess KDO.

Heptoses are absent in most cyanobacteria. Some cyanobacteria do not have phosphates, while others show its presence in variable amounts (Weckesser et al. 1974, 1979; Schmidt et al. 1980a, b; Keleti and Sykora 1982; Carillo et al. 2014; Simkovsky et al. 2016). Unlike Gram-negative LPS, the presence of galactose and glucosamine is also variable. Studies have indicated that neutral sugars like rhamnose, fucose, xylose, mannose, galactose, and glucose are conserved among most of the cyanobacterial species. Immense variability exists down to the chemotype (Schmidt et al. 1980a, b). The LPS molecules also contain relatively large quantities of oleic, palmitoleic, linoleic, and linolenic acids that are typically absent in Gram-negative LPS molecules. They lack phosphate residues and instead have a single galacturonic acid attached to glucosamine.

The carbohydrate region in *Anacystis nidulans* is comprised of fucose, galactose, glucose, mannose, rhamnose, KDO (2-keto-3-deoxy-octonic acid), glucosamine, and 2-amino-2-deoxy-heptose (Weise et al. 1970). Katz et al. (1977) reported the presence of KDO and β-hydroxymyristic acid in *A. nidulans* (*Synechococcus* PCC 6301), which are also seen in LPS of Gram-negative bacteria. However, it lacked heptose and had phosphate and glucosamine in small amounts in its lipid moiety. Besides the common core sugars and xylose, there is L-acofriose in *Anabaena variabilis*, fucose in *Anabaena flos-aquae*, and 3,6-dideoxyhexose in *Anabaena cylindrica* (Keleti and Sykora 1982), and galacturonic acid as the main component in the core oligosaccharide of *Oscillatoria planktothrix* FP1 (Durai et al. 2015). LPS in *Schizothrix calcicola* contained neutral sugars, viz., galactose, glucose, mannose, rhamnose, xylose, and glucosamine as the only amino sugar without any KDO and heptose (Keleti et al. 1979).

Snyder et al. (2009) working on *Synechococcus* sp. observed that the core region was primarily composed of a 1,4-linked glucose chain with low levels of glucosamine and galacturonic acid. Its strain WH8102 also had a single rhamnose. Raziuddin et al. (1983) reported substantial amounts of KDO, glucose and other hexoses, 3-deoxy sugars, glucosamine, fatty acids and their esters, and phosphates in the LPS of *Microcystis aeruginosa* NRC1, while Martin et al. (1989) reported absence of KDO and heptoses in two strains of *M. aeruginosa*, PCC 7806 and UV-017. A study by Fujii et al. (2012) on the O-chain of *Microcystis aeruginosa* reported glucose (66%), rhamnose, xylose, mannose, and galactose and that of *M. aeruginosa* NIES-87 was found to be composed of glucose alone. It suggested that glucose (and its derivative) being the sole monosaccharide component in the O-chain of *M. aeruginosa* may imply that the functional roles of the O-chain might differ from its role in proteobacteria.

The O-antigen of *Synechococcus elongatus* PCC 6301 is reminiscent of the polymannose O-antigen of *Escherichia coli* O8 and O9 (Katz et al. 1977). LPS of *Agmenellum quadruplicatum* was found to be unique due to the presence of xylose in the polar heads and unusual pentoses in the O-antigen, while galactose was absent. Presence of rhamnose and mannose along with absence of heptoses conformed with common cyanobacterial LPS structures (Durai et al. 2015). Sugar analysis of the LPS of *Spirulina platensis* showed presence of common core sugars as glucose, KDO, rhamnose, mannose, galactose, fucose, ribose, and xylose, along with a variety of unique sugars such as inositol, D-glycero-D-manno-heptose, D-glycero-L-mannoheptose, and 3- or 4-O methylhexoses and glucosamine as the lone amino sugar. Minor quantities of 3-hydroxy palmitic acid were also detected (Tornabene et al. 1985). Sugar composition of some of the cyanobacterial polysaccharides is presented in Table 15.1.

Lipid A is an acylated glycolipid that anchors the LPS molecule in the outer membrane of the Gram-negative bacteria and is the most conserved biochemical structure of this group of organisms (Stewart et al. 2006). Its fatty acid composition is reported to be highly heterogeneous both in terms of length and degree of saturation, ranging from lauric acid (C12) to stearic acid (C18) along with other polyunsaturated fatty acids like linoleic and linolenic acid. Such long- chain fatty

Table 15.1 Sugar composition of cyanobacterial lipopolysaccharides

Organism	Glu	Gal	Man	Xyl	Rha	Fuc	GluA	maA	KDO	Others	References
Anabaena cylindrica	+	+	+	+	+		+			3,6-Dideoxyhexose	Keleti and Sykora (1982)
Oscillatoria brevis	+	+	+	+	+						
O. tenuis	+		+	+	+				L	Heptose present	
Anabaena variabilis (*Anabaena* PCC7118)	+	+	+		+		+			Acofriose, phosphate present	
Anabaena flosaquae UTEX 1444	+	+	+	+	+	+	+		L		
Schizothrix calcicola	+	+	+	+	+		+				Keleti et al. (1979)
Spirulina platensis	+	+	+	+	+	+	+		+	Inositol, ribose, D-glycerol D-mannoheptose, glyceromannoheptose, 3- or 4-O-methylhexose	Tornabene et al. (1985)
Synechococcus sp. strains C9311	+		+	+	L		+			Galacturonic acid	Snyder et al. (2009)
WH8102	+		L		+					Galacturonic acid	Schmidt et al. (1980a, b)
6907	+	+	+		+	+	+				
6307	+	+	+		+	+	+				
6911	+	+	+		+	+	+				
6603	+	+	+			+	+				
6908	+	+	+			+	+				
6311	+	+	+			+	+				
6312	+	+	+			+	+				
6910	+	+	+			+	+				
Synechocystis PCC 6714	+	+	+			+	+				
6803	+	+	+			+	+				

6807	+	+	+		+	+	+				
6308	+	+	+		+	+	+				
Anacystis nidulans (*Synechococcus* PCC 6301)	+	+	+			+	+	+	+	Methyl-D-mannose	
Microcystis aeruginosa NRC1	+						+		+	3-Deoxy sugar, glyceromannoheptose, phosphate present	Raziuddin et al. (1983)
Microcystis aeruginosa NIES 87	+	+	+	+	+						Fujii et al. (2012)
M. aeruginosa PCC 7806	+	+	+	+	+	+	+				Martin et al. (1989)
PCC 7820	+	+	+	+	+	+	+				
UV 017	+	+	+	+	+	+	+				
UV006	+						+				
(*Synechococcus* PCC73109) *Agmanellum quadruplicatum*	+	+	+	+	+		+		+		Buttke and Ingram (1975)
Anacystis nidulans KM	+	+	+			+	+	+	+		Katz et al. (1977)
Phormidium	+	+	+	+	+		+		+	Galactosamine, arabinose, acofriose, phosphate present	Mikheskaya et al. (1977)
Oscillatoria planktothrix			+		+		+			Galacturonic acid	Carillo et al. (2014)

Glu glucose, *Gal* galactose, *Man* mannose, *Xyl* xylose, *Rha* rhamnose, *Fuc* fucose, *GluA* glucosamine, *GalA* galactosamine, *maA* mannosamine, *KDO* 3-deoxy-D-manno-octulosonic acid

acids and polyunsaturated fatty acids are mostly not known in the LPS of Gram-negative bacteria (Weise et al. 1970; Buttke and Ingram 1975; Keleti et al. 1979; Keleti and Sykora 1982; Tornabene et al. 1985; Martin et al. 1989). Only a few studies are covered here to let the reader form a picture of the entire LPS in cyanobacteria as lipid A requires a separate review.

Cyanobacterial lipopolysaccharides contain large amounts of oleic, palmitoleic, linoleic, and sometimes linolenic acids also (Keleti and Sykora 1982). Snyder et al. (2009) found that the lipid moieties in *Synechococcus* sp. had tri- and tetra-acylated structures with odd-chain hydroxy and nonhydroxy fatty acids connected to the diglucosamine backbone. In line with other cyanobacteria, LPS of *Oscillatoria planktothrix* FP1 also had no KDO, heptose and phosphate; however, hydroxylated and nonhydroxylated fatty acids have been reported in the glucosamine disaccharidic backbone (Carillo et al. 2014). Digalactosyl diacylglycerol and phosphatidyl diacylglycerol along with unsaturated fatty acids and 3-hydroxy myristate were observed by Tornabene et al. (1985) in *Spirulina platensis*. The lipid A portion of *Schizothrix calcicola* is composed of β-hydroxylauric, β-hydroxypalmitic, linoleic, myristic, oleic, palmitic, pentadecanoic, and stearic acids (Keleti et al. 1979). LPS of *Agmenellum quadruplicatum* and *Anacystis nidulans* contain behenic acid along with β-hydroxy fatty acids analogous to other Gram-negative bacteria (Buttke and Ingram 1975). The lipid portion of LPS from another strain of *Anacystis nidulans* was composed of a series of long fatty acyl chains including β-hydroxymyristic acid (Weise et al. 1970).

15.4 Storage Polysaccharides

15.4.1 Glycogen

Glycogen is a dynamic form of glucose storage that combines low osmotic activity and accessibility to hydrosoluble enzymes. Typically, 5–15% of carbon fixed by cyanobacteria is stored as glycogen, and under certain conditions, it can contribute to up to 70% of dry biomass (Depraetere et al. 2015; Song et al. 2016). It is a highly branched, homogeneous, amorphous, water-soluble polyglucan composed of 9–13, (1,4)-linked α-D-glucose residue interlinked via (1,6)-α-D-glucosidic linkages. It forms a rigid granular structure of about 10^7–10^8 Da (Ball et al. 2011; Damrow et al. 2016) and serves as the main carbon sink and energy storage molecule in cyanobacteria. Each α-1,4-linked chain supports on an average two branched chains reaching 8–10% that are randomly arranged but densely packed and get progressively more crowded toward the periphery (Welkie et al. 2016). The size of the particle increases to a maximum possible diameter of 42 nm (Shearer and Graham 2002) containing up to 55,000 glucose residues with over 36% resting in the outer particle chains (Meléndez et al. 1999). These are readily accessible to cell metabolism without the need for polysaccharide debranching. There is abundance

of short chains with a degree of polymerization (DP) $\leq$8 (32–75%), and < 1% consisted of long chains with a DP $\geq$37 as observed by Meléndez et al. (1999) in *Synechococcus elongatus* PCC 7942.

Despite sharing the same chemical linkages, starch and glycogen differ widely in physicochemical properties. Starch granules are semicrystalline and insoluble in cytosol. They are usually made up of two α-glucan polymers, namely amylopectin and amylose. The minor fraction, amylose, is composed of linear weakly branched glucan chains (less than 1% of α-1,6 branches), while amylopectin, which is the major component, has the same basic structure but has considerably shorter chains and a lot of α-(1,6) branches. This results in a very complex, three-dimensional structure (Hizukuri 1986; Bertoft et al. 2010; Laohaphatanaleart et al. 2010). In amylopectin, α-1,6 glucosidic linkages are densely localized along the glucan chains with 9–10-nm intervals forming unit clusters. Double-helical structures are formed when the degree of polymerization (DP) approaches 10–20 glucosyl units within the cluster (Kainuma and French 1972; Gidley and Bulpin 1987), which are further closely packed with a radial orientation in a starch granule. The number of branches increases with an increase in radius, and consequently, concentric lamellae of alternating amorphous and crystalline regions are formed. The branching rate is nearly half (5%) of that observed in glycogen. Average DP reaches 10^4–10^8 glucose units per molecule corresponding to a molecular mass of 10^6–10^8 g mol^{-1} (Hizukuri et al. 1983; Takeda et al. 1988).

According to Konopka (1984), the formation of polysaccharide is a function of the relationship between energy generation and growth. It is induced when the energy generated is more than that needed for growth. Thus, polysaccharide formation results from overflow metabolism. The biosynthetic pathway of bacterial glycogen is very similar to that of starch biosynthesis in plants, using ADP-glucose as a major substrate for starch biosynthesis with different elongation properties for glucose extensions (Manners 1991; Sivak and Preiss 1998). The enzymes of glycogen metabolism are conserved in all cyanobacteria (Beck et al. 2012). Glycogen is synthesized by the sequential action of three enzymes: ADP-glucose pyrophosphorylase (AGPase) that activates the glucose to form ADP-glucose which is then polymerized to the nonreducing end of an α-1,4-linked glucan chain by glycogen synthase (GS) and the branching enzyme (BE) that introduces symmetrically distributed α-(1,6) glucosidic linkages according to a binary branching principle via a hydrolytic cleavage reaction. The tandem cluster structure of amylopectin is considered to be synthesized by concerted reactions catalyzed by three classes of enzymes, i.e. starch synthase (SS), starch branching enzyme, and starch debranching enzyme, each of which is composed of multiple isozymes making a different contribution to the cluster structure (Nakamura 2002; Ball and Morell 2003). In contrast, it was accepted that glycogen can be synthesized by a single form of glycogen synthase and glycogen branching enzyme in animals and bacteria. However, two types of glycogen synthases (GSI and GSII) have been reported in *Synechocystis* sp. PCC6803 with different elongation capacities. While GSI preferentially extends chains progressively by adding more glucose units to the same

chain, thereby generating longer branch chains in the glycogen structure, GSII adds single glucose units distributively one at a time to many chains adding intermediate-length chains instead (Yoo et al. 2014). Breakdown of the glycogen granule occurs through the actions of two enzymes, a debranching enzyme (DBE; GlgX) and the glycogen phosphorylase (GPase and GlgP) [Reviewed by Shearer and Graham 2002; Welkie et al. 2016].

Glycogen metabolism is under the control of circadian oscillator in *Synechococcus elongatus* PCC7942 (Suzuki et al. 2007), a phenomenon originally considered to be restricted to eukaryotic organisms (Diamond et al. 2015). When cyanobacteria are grown in a 24-h light:dark (LD) cycle, cells perform photosynthesis and accumulate glycogen during the day which provides for cell integrity, function, and viability during the dark period via the oxidative pentose phosphate cycle (Osanai et al. 2007). LD transitions involve changes in cytoplasmic pH and redox state, as well as changes in the intracellular concentration of specific metabolites and metal ions. These factors mainly regulate the switch between assimilatory (photosynthetic) and catabolic pathways in the cyanobacterial cell (Smith 1982). In fact, enzymes in glycogen metabolism are sensitive to the cellular redox state, and LD transitions alone may trigger changes in the glycogen content (Díaz-Troya et al. 2014).

Glycogen metabolism enables efficient energy homeostasis (Cano et al. 2018) acting as buffers and cellular tools for the compensation of stressful energetic transitions, mainly to ameliorate and avoid futile cycles during the process of changing photosynthetic activity and metabolic switching, as has been observed in metabolic networks of *Synechocystis* sp. where glycogen provides for all the precursors for biomass formation, metabolites, and cofactors in the dark (Puszynska and O'Shea 2017). Pattanayak et al. (2014) showed that glycogen in *S. elongatus* oscillates in continuous light conditions and that this oscillation depends on a functional clock that segregates pathways for storage and degradation of carbon temporally. Besides its role in maintenance metabolism under dark, glycogen is also involved in creating homeostasis in periods of starvation, nutrient deficiency, and salt and oxidative stress where again metabolic switching takes place (Suzuki et al. 2010; Zilliges 2014). Glycogen metabolism has also been associated with symbiotic performance, colonization, and virulence in bacteria, but such a role has not been reported in cyanobacteria (Wilson et al. 2010).

Though *Synechocystis* sp. and other forms in the order Chroococcales do not form a resting cell under stress, like species of the orders Nostocales and Stigonematales, these cells also switch stringently from an active photosynthetic protein status to a dormant glycogen status (Kaprelyants et al. 1993). Glycogen is known to accumulate under nitrogen deficiency. In *Arthrospira platensis*, its content increases from 13.7 to 63.2%, while the protein content decreases from 42.7 to 15.4%. *Synechocystis* PCC 6803 is capable of mixotrophic growth on glucose and stores the excess carbon as glycogen increasing intracellularly from 1 to 19 mg g wet cell^{-1} in a nitrogen-deficient medium (Yoo et al. 2007), while nitrogen deprivation with high light intensity (200 μmol photons m^{-2} s^{-1}) further enhances its concentration to 41.35 mg g wet cell^{-1} (Monshupanee and Inchroesakdi 2014). Growth conditions

also affect the structure of glycogen as observed in *Synechocystis* sp. PCC6803 (Yoo et al. 2007). Glycogen production under nitrogen limitation (0.084 g $NaNO_3$ L^{-1}) with 5 mM glucose yielded glycogen with a DP of 10.4, which increased to 10.7 two days after the cultures were transferred from a medium containing normal N concentration (1.5 g L^{-1}) and glucose to a nitrogen-limited glucose-supplemented medium. Glycogen synthesis mutants in another study were found to lose their viability on agar plates containing glucose (Gründel et al. 2012).

Enhanced glycogen production in response to nitrogen limitation has also been reported in *Spirulina maxima*, *Synechococcus* sp. strain PCC 7002, *Synechocystis* sp. strain PCC 6803, *Arthrospira platensis*, *Arthrospira maxima*, *Anabaena variabilis*, and *Anacystis nidulans* (Lehmann and Wöber 1976; Earnst and Boger 1985; De Philippis et al. 1992; Aoyama et al. 1997; Aikawa et al. 2012; Guerra et al. 2013; Hasunuma et al. 2013; Xu et al. 2013). Under nitrogen deficiency, other than photosynthesis, carbon skeleton of glycogen is probably derived from the amino acids released from proteins by gluconeogenesis. Along with accumulation of glycogen, cells undergo bleaching with concomitant breakdown of phycobilisomes and chlorosis (Hasunuma et al. 2013). The cells maintain residual photosynthesis (0.1% of the initial activity) (Sauer et al. 2001) allowing them to preserve full viability for over 6 months (Klotz et al. 2016). Similar long-term survival time has been reported for *Synechocystis* sp. also (Gründel et al. 2012). Mutants of *Synechocystis* sp. incapable of glycogen synthesis cannot perform metabolic switching, and thus, there is absence of chlorotic response while cells spill energy in the form of pyruvate and 2-oxoglutarate with 30–60% loss of carbon. Viability of cells on prolonged nitrogen starvation is lost in absence of glycogen. In the stenohaline cyanobacterium *Synechocystis* sp. PCC6803, a shift in osmotic response is observed in absence of glycogen synthesis with 29 times increase in sucrose synthesis under salt stress as glucosylglycerol, its primary osmolyte, could not be synthesized (Miao et al. 2003).

15.4.2 Semi-Amylopectin/Cyanobacterial Starch

Though soluble glycogen is the primary storage molecule in cyanobacteria, certain unicellular diazotrophs such as *Cyanothece* sp. ATCC 51142 and *Cyanobacterium* sp. CLg1 (Reddy et al. 1993; Falcón et al. 2004), *Synechococcus* sp. BG043511 (Ikemoto and Mitsui 1994), *Cyanobacterium* sp. MBIC10216 (formerly *Synechocystis aquatilis* SI-2), and *Cyanobacterium* sp. NBRC 102756 (Nakamura et al. 2005) contain within their cells numerous carbohydrate storage granules of distinct polysaccharidic nature that resemble amylopectin and thus were called semi-amylopectin. Contrary to the glycogen and phytoglycogen (rice endosperm), the cyanobacterial semiamylopectins were found to be slightly smaller in size (Nakamura et al. 2005) (Table 15.2). Semiamylopectins are composed of 2–6% long chains with a degree of polymerization of $\geq$37. Glycogen of *Synechococcus elongatus* PCC 7942 is composed of only 0.4% long chains in contrast to the rice endosperm that contains 6.2% long chains. The very short chains with a degree of

Table 15.2 Differences in glycogen and starch

S. No.	Property	Glycogen	Starch	Cyanobacterial starch
1	Basic unit	Glucose	2-α-Glucan polymers amylopectin (75%–88%) Amylose (20–25%)	Semiamylopectin, some also contain 5% amylose
2	Crystallinity	Amorphous	Semicrystalline	Semicrystalline
3	Branching	α-1,4-Glucan with 8–10% α-1,6 branching	Amylopectin : α-1,4-glucan with 5% α 1,6 branching Amylose: α-1,4-glucan, linear	α-1,4-Glucan, α-1,6 branching at intervals of 9–10 nm
4	Structure	Random arrangement Dense packing Crowded toward periphery	Tandem cluster arrangement: Branches densely localized along the chain forms. Unit clusters arranged in double helix, oriented radially in concentric rings	Tandem cluster amylose may or may not be present
5	Degree of polymerization (DP)	Most abundant average $(DP)_n$: 6–8 Short chain DP ≤8: 32–75% Long chain DP ≥37: <1% with 2 branches/ chain in 12 tiers. Up to 55,000 residues	$(DP)_n$ amylose: 11–12 $(DP)_n$ amylopectin: 20–30 DP ≥37: 6–7% (rice endosperm) DP ≤8: 7–8% up to ~two million residual molecules	$(DP)_n$ semiamylopectin: 11–12 DP ≥37: 2–6% DP ≤8: 7.5–25%
6	Particle diameter (nm)	Max 42 nm (Shearer & Graham 2002)	0.5–100 μm	0.2–0.7, Spherical or discoid granules
7	Solubility	Soluble in cytosol	Insoluble	Insoluble
8	Synthesis	ADPase, glycogen synthase (GSI GSII), BE	Multiple isozymes of starch synthase, starch branching and starch debranching enzymes	Isozymes reported AGPase, GS/SS, BE
9	Molecular mass	10^7–10^8 Da	Amylopectin: 10^8–10^{10} Da Amylose: 10^6–10^8 Da	Similar to amylopectin
10	Branching enzyme gene copies	1 or 2	1	3

Reference: Welkie et al. (2013, 2016), Meléndez et al. (1998, 1999), Suzuki and Suzuki (2013), Suzuki et al. (2013), Yoo (2001)

polymerization $\leq$8 were in a range between 7.5% and 25%. The proportion of the long to short chains in different species is intermediate between cyanobacterial glycogen and rice endosperm (Nakamura et al. 2005; Shimonaga et al. 2008; Hirabaru et al. 2010; Suzuki et al. 2013). A relative proportion of as low as 2% long glucan chains with a DP of $\geq$37 is enough for the macromolecule to achieve a cluster-like structure. The insoluble semiamylopectins form 0.2 to 0.7 μm spherical or disk-shaped granules with a tandem cluster structure. While *Cyanobacterium* sp. MBIC10216 polyglucan did not show the presence of amylase (Nakamura et al. 2005), starch-like granules in *Cyanobacterium* sp. CLg1 were found to be composed of both an amylopectin-like high mass fraction and a smaller amylose fraction (linear or scarcely branched (Suzuki et al. 2013)). The chain length distribution of the high-mass polysaccharide complies with the definition given for semiamylopectin, as it contains fewer of those chains exceeding a DP of 40 (Nakamura et al. 2005). Because the granules also contain a significant amount of amylose (5%), this material has been called cyanobacterial starch (Cenci et al. 2013). The average DP of amylose ranges from 11 to 12 which has also been reported for semi-amylopectin formed in cyanobacteria.

Analysis of storage polysaccharides from *Cyanothece* sp. ATCC 51142, *Cyanobacterium* strain Clg1, and *Cyanobacterium* strain NBRC 102756 revealed that their storage granules have a molecular mass virtually indistinguishable from that of amylopectin (Suzuki et al. 2013, 2015). Moreover, the thermal properties, crystallinity, and branching structure are similar to those of amylopectin, and the semi-amylopectin material synthesized by these strains is organized in tandem cluster structures. Isoforms have been reported for enzymes involved in the synthesis of cyanobacterial starch. The *Cyanothece* sp. ATCC 51142 has two genes each encoding ADP-glucose pyrophosphorylase (AGPase) and glycogen synthetase (GS)/starch synthase (SS) and three genes for the branching enzyme (BE). The presence of two GS/SS genes is observed in various species of cyanobacteria (Suzuki et al. 2010). Two genes for AGPase are found only in a few strains of *Cyanothece* and *Acaryochloris marina* and may not occur commonly among unicellular diazotrophic cyanobacteria (Suzuki et al. 2013).

15.5 Exopolysaccharides

Cyanobacteria express high molecular weight glycans [extracellular polysaccharides (EPS)] with varying gelling abilities. The gelatinous form that occurs as a thin, firm fibrillar structure surrounding the cell wall, defining the shape of the cell, is called sheath, while the organized, densely packed nonuniform thick layer around the sheath that may/may not be tightly or covalently bound to the cell is called the capsule. Phospholipids covalently bound to the cell wall function as anchors. Attachment is through hydrogen bonds and hydrophobic and electrostatic interactions (Mayer et al. 1999; Wingender et al. 1999). Another fraction may exist loosely attached to the cell surface lacking definite margins or secreted in the environment, which is called slime or mucilage (De Philippis and Vincenzini 1998).

A particulate fraction corresponding to the transparent exopolymer particles (TEPs) has also been found to be associated with cyanobacteria (Thornton 2004).

Nearly 60% of the dry biomass may be composed of exopolysaccharides (Hill et al. 1997) that may be produced as a primary or secondary metabolite. In *Anabaena halophytica* (Sudo et al. 1995), *Spirulina platensis* (Filali Mouhim et al. 1993), and *Cyanospira capsulata* (Vincenzini et al. 1990), polysaccharide production parallels biomass production, while in *Cyanothece* BH68K (Fattom and Shilo 1984), *Nostoc calcicola* (Flaibani et al. 1989), *Phormidium* J-1 (Fattom and Shilo 1984, 1985), *A. flos-aquae* A37 (Moore and Tischer 1964; Tischer and Davis 1971), and *A. cylindrica* 10C (Lama et al. 1996), highest production rates were observed in the late phase. Conversely, in the case of a *Nostoc* strain, the highest rates of polysaccharide synthesis and release were achieved by young cultures (Mehta and Vaidya 1978). While most cyanobacteria produce heteroglycans, homopolysaccharide composed of α-D-1,6 glucose has been reported in a marine diazotrophic *Cyanothece* sp. (Chi et al. 2007). *Microcystis wesenbergii* represents another unique case where the polymer is exclusively composed of uronic acids (Forni et al. 1997). The heteroglycans, common to most cyanobacteria, are composed of 5–8 monomer repeats (Rossi and De Phillippis 2015); however, a decasaccharide repeating unit has been proposed for *Cyanospira capsulata* (Marra et al. 1990; Garrozo et al. 1995). EPS from *Spirulina platensis* and the thermophilic *Mastigocladus laminosus* have a still complex structure being composed of 15 monomer repeats (Filali Mouhim et al. 1993, Gloaguen et al. 1999). Fourteen monosaccharides have been reported to be present in *Chroococcus minutus* B 41.79 (Fischer et al. 1997). Rossi and De Philippis (2016) in their review on algal polysaccharides have listed the composition of 136 forms of cyanobacteria from various reports. Analysis of this data shows that eight different neutral sugars are generally present in various combinations and molar ratios, with glucose being the most prevalent sugar followed by galactose, fucose, mannose, arabinose, ribose, and fructose. In some cases, sugars such as xylose, galactose, arabinose, or fructose were found to be higher than glucose (Pereira et al. 2009). Pentoses are generally absent in other polysaccharides of prokaryotic origin (Sutherland 1994). The moiety protects the neighboring glycosidic bonds from the more common glycan hydrolases (Helm et al. 2000) and is partially responsible for the gelatinous consistency of the polysaccharide. Presence of either galacturonic acid or glucuronic acid or both in most cyanobacterial polysaccharides along with sulfates vest in negative charges and thus impart adhesivity to the macromolecule (De Philippis et al. 2000; Mancuso Nichols et al. 2005).

Sulfated sugars are involved in cell recognition and adhesion that are crucial in biofilm formation and complexation of metal ions (Tease and Walker 1987). They also provide stability over a range of temperature, pH, and salinity degrees (Arad and Levy-Ontman 2013). Sulfated polysaccharides have been shown to have numerous bioactivities of medicinal value. For cyanobacteria living in alkaline habitats like *Microcystis flos-aquae* C3–40, the polysaccharide capsule accumulates iron and manganese that are necessary for cyanobacterial growth but are relatively insoluble in aerobic alkaline conditions (Parker et al. 1996). Gehrke et al. (1998) showed that

iron species complexed by EPS allow bacteria to attach on pyrite and that Fe (III)-ions complexed by uronic acids in the EPS were needed to dissolve pyrite.

Uronic acid is a highly hydrophilic substance and contributes to the highly absorptive character of the EPS that can absorb over 95% water by weight (Decho 1994). This is critical for the survival of cyanobacteria through desiccation. Hydrophilic moieties provide minerals, nutrients, and water to the growing cell (Rossi et al. 2012a, b). Uronic acids are present in nearly 90% polymers and can reach up to 20–30% of the released polysaccharide dry weight (De Philippis et al. 2007; Laurienzo 2010). Polymers containing nosturonic acid or uronic acids with lactyl moieties play a pivotal role in the ability of organisms to survive extreme environments as in *Nostoc commune* DRH-1, a desiccation-tolerant cyanobacterium that can survive −400 MPa (0% humidity) for centuries (Potts 1994). Such functional groups act as a spacer arm or linker that aid adherence important for biofilm formation and act as molecular scaffolds for covalent attachment of UV-absorbing pigments and other antioxidative compounds. Lactyl-containing mannose monomers have been reported in *Cyanospira capsulata*, a filamentous heterocystous form that grows in saline lakes (Garozzo et al. 1998).

Cellulose, an insoluble polysaccharide of linear β-1,4-glucan, is present in the sheath, slime tubes, or EPS of *Oscillatoria* sp. UTEX 2435, *Oscillatoria princeps*, *Nostoc* sp. UTEX 2209, *Gloeocapsa* sp. UTEX L795, *Scytonema hofmanni* UTEX 2349, *Anabaena* sp. UTEX 2576, *Phormidium autumnale* UTEX 1580A, *Synechocystis* sp., *Nostoc* sp. PCC7120, *Crinalium epipsammum*, and *Synechococcus* 7002 (de Winder et al. 1990, Nobles et al. 2001; Zhao et al. 2015). Depending on the extent of inter- and intramolecular hydrogen bonding, cellulose exhibits varying degrees of crystallinity (O'Sullivan 1997). It could have roles in gliding motility of hormogonia, desiccation tolerance, nitrogen-fixing efficiency of heterocysts, enhancing viability of akinetes, or protection from UV light and could serve as a means of attachment to the host plant in the formation of symbiotic relationships (Matthysse 1983; Nobles et al. 2001). Synthesis of cellulose in cyanobacteria has been correlated to the presence of cellulose synthase gene *CesA* which has homology with the cellulose synthase in vascular plants. Cellulose occurs possibly as a laminated layer between the inner and outer membrane and is an important component of the extracellular glycocalyx in *Synechococcus* PCC7002 (Zhao et al. 2015). The thermophilic cyanobacterium *Thermosynechococcus vulcanus* undergoes cell aggregation in response to light stress under suboptimal temperatures induced by cellulose accumulation in the wall (Kawano et al. 2011).

Other rare monosaccharides identified in the EPS of cyanobacteria include methylated sugars, amino sugars like N-acetyl glucosamine, 2,3-O-methyl rhamnose, and acofriose as found in spirulan. 2-O-methyl D-xylose has been reported in the sheath of *Gloeothece* sp. PCC 6501 (Weckesser et al. 1987). N-acetyl fucosamine is found in large amounts in the arabinofucan EPS of *Synechocystis aquatilis* (Flamm and Blaschek 2014). Other methylated sugars like 4-O-methyl rhamnose and 3-O-methyl glucose have also been reported (Hu et al. 2003) (reviewed by Delattre et al. 2016). Methyl sugars perhaps play a role in certain recognition events (Staudacher 2012). The sugar moiety of EPS from *Wollea*

saccata was reported to have 60% hexoses and 31% 6-deoxyhexoses and 9% of pentoses with 40 types of methylated sugar derivatives suggestive of a very complex structure (Šutovská et al. 2017).

Certain cyanobacterial EPS contain peptides and ester-linked acetyl groups (up to 12% of EPS dry weight) (De Phillipis et al. 1998; Richert et al. 2005). These components along with deoxy-sugars like rhamnose and fucose confer hydrophobic character on the EPS affecting its rheological, emulsifying, and adhesive properties (Shepherd et al. 1995). Fattom and Shilo (1984) demonstrated that all benthic cyanobacteria are hydrophobic, while all planktonic forms are hydrophilic. Presence of cations was found to be necessary for the expression of hydrophobicity with divalent cations being more effective than monovalents. Multivalent ions induce gel formation (De Philippis et al. 1993). Metal ion sequestration or immobilization also protects the cells from its toxic species and at times provides for certain ions essential for growth. Some cyanobacteria are capable of modifying EPS from hydrophobic to hydrophilic character and can detach from surfaces as observed in *Phormidium* sp. when conditions become inappropriate (Fattom and Shilo 1985). Others have both hydrophilic and hydrophobic fractions that enable adhesion as well as water storage (Rossi et al. 2012a, b). Such amphiphilic exopolymers help stabilization of emulsions or act as flocculants (Fattom and Shilo 1985). Aggregation and flocculation of suspended particles by flocculants allow for light penetration to the sediment-water interface, thus facilitating survival and growth of benthic cyanobacteria that occupy a low-light zone. The flocculant may also carry nutrients to this zone (Bender et al. 1994; Fattom and Shilo 1984). Emulcyan, a sulfated heteropolysaccharide synthesized by *Phormidium* J-1, contains fatty acids and proteins that contribute variable degrees of hydrophobicity to the macromolecule (Bar-Or and Shilo 1987).

Adhesivity is an important character in mat formation and creating associations with plants as in *Nostoc* and wheat roots (Gantar et al. 1995) and symbiosis in *Anabaena azollae* (Robins et al. 1986). Polypeptides enriched with alanine, glycine, isoleucine, leucine, phenylalanine, and valine have been reported in the EPS of *Cyanospira capsulata* and *Nostoc calcicola* (Flaibani et al. 1989; Marra et al. 1990). *Schizothrix* sp. is a dominant cyanobacterium in the marine stromatolites found on the margins of Exuma Sound, Bahamas. The EPS released by this organism contains 2.5% protein, specifically enriched with aspartic and glutamic acid. These proteins act as nucleation centers for $CaCO_3$ precipitation. Changes in the EPS composition and stereochemistry lead to $CaCO_3$ polymorphisms (Kawaguchi and Decho 2002). The coccoid cyanobacterium *Solentia* (order Pleurocapsales) is an important component of stromatolite climax community that bores into the grains. The cell and its polysaccharidic sheath elongate as the cell divides and glides into the hole. Micrite composed of aragonite needles (<4 μm long) deposited on this sheath acts as a cement to form well-indurated layers (Reid et al. 2000; Dupraz et al. 2009). Other non-saccharidic components include phosphates, acetates, pyruvates, lipids, and DNA (De Philippis and Vincenzini 1998; Pereira et al. 2009).

The high number of different monosaccharides and their derivatives found in the cyanobacterial EPS, variety of substituent groups, linkages, and a broad range of possible macromolecular structures gives incalculable structural diversity and

functional variability to polysaccharides. According to a calculation by Werz et al. (2007), a trimer composed of 10 most frequently occurring mammalian monosaccharides alone may arrange in 126,000 possible combinations. With enormous versatility of their armor, cyanobacteria have an edge over other organisms against environmental stresses and thus occupy a special trophic status in the most extreme environments on earth.

EPS excretion serves multiple functions, including nutrient storage (organic compounds containing C, N, or P and trace metals), structural organization, and buffering against environmental stressors (Flemming and Wingender 2010). Studies on *Nostoc commune* have showed that EPS prevents membrane fusion, during periods of desiccation and subsequent rehydration. This, along with the synthesis of osmotica like trehalose and sucrose, may be the key mechanism in desiccation survival (Hill et al. 1997).

The highly hygroscopic EPS of *Chroococcidiopsis* maintains prolonged moisture around the cells, releasing it slowly (Caiola et al. 1996). A recent study on three strains of *Nostoc*, viz., *N. commune*, *N. verrucosum*, and *N. sphaericum*, that produce massive extracellular matrices showed that only EPS does not render desiccation tolerance. Expression of a 36kD Wsp A (water stress protein) and Sod F (superoxide dismutase) in *N. commune* was responsible for the tolerance, while the other strains without them were sensitive to desiccation (Sakamoto et al. 2018). Wsp A, perhaps, dynamically coordinates the flexibility and rigidity of the EPS matrix in response to desiccation-rehydration (Liu et al. 2017). The presence of capsules helps evade grazers as observed in *Phormidium* (Pajdak-Stós et al. 2001) and enhance nitrogen fixation by reducing oxygen permeability to nitrogenase as reported in the heterocysts of various species of *Nostoc* (Bergman et al. 1997; Soule et al. 2016) and in non-heterocystous forms like *Gloeothece* (Kallas et al. 1983). EPS of cyanobacteria also contains diverse phytochemicals. Presence of mycosporine-like amino acids in EPS has been reported by several authors. *Nostoc commune*, *Arthrospira platensis*, and *Microcoleus* sp. and *Leptolyngbya* sp. have been reported to actively secrete and accumulate them in their capsular polysaccharides (Bohm et al. 1995; Trabelsi et al. 2009, 2016). Radical scavengers have been reported in the EPS of *Anabaena* sp., *Tolypothrix tenuis*, *Phormidium*, *Nostoc*, *Oscillatoria*, and *Calothrix* (Parwani et al. 2014; Babić et al. 2015). The activity was attributed to the presence of phenolic acids, vitamin C, and flavonoids in *Leptolyngbya* (Trabelsi et al. 2016). *Anabaena* PCC 7120 and *Oscillatoria angustissima* have been reported to produce intra- as well as extracellular polysaccharides as a means of protection to toxic species (El-Sheekh et al. 2012). Cyanobacterial sheaths play an important role in enabling the microbe to survive environments subject to extensive mineralization. The sheath of *Calothrix* sp. was reportedly impermeable to particles sized $\geq$11 nm diameter, thus restricting silicification to the outer surface of the sheath preserving the cell wall and cytoplasmic functions (Phoenix et al. 2000; Benning and Mountain 2004). In natural environments, the complex EPS harbor numerous heterotrophic bacteria and undergo arrangement, rearrangement, dissociation, and resynthesis in a dynamic process buying time for acclimatization of the organism to changing

environment. It contributes to the structural stability of biofilms and mats, helps adhesion and attachment to substrate, and is implicated in cyanobacterial locomotion.

15.5.1 Transparent Exopolymeric Particles (TEPs)

Cyanobacterial exopolysaccharides vary in molecular structure depending on the producing species (Pereira et al. 2009). The sheaths of *Anabaena* C5 and *Nostoc* 2S9B have a sheetlike appearance, while *Anabaena* sheds its sheath by tearing off, leaving behind the nude filaments throughout the lifecycle, but the sheath of *Nostoc* is linked to hormogonia release which when liberated leave behind empty shells (Gantar et al. 1995). When the cell coating/mucilage detaches from the surface, it may further coagulate, gelate, or anneal to form submicron gels that further coagulate to form particulate (0.4–300 μm) TEP or colloidal TEP (0.05–0.4 μm) that can be visualized by Alcian blue staining. TEP can directly form from the fragmentation of capsules throughout the growth phase as observed in *Anabaena spiroides* or under nutrient limitation and on senescence following cellular lysis (Grossart et al. 1997; Berman and Viner-Mozzini 2001; Bittar and Vieira 2010; Verdugo and Santschi 2010; Berman-Frank et al. 2016) with dominance of the colloidal fraction (Villacorte et al. 2015). They can also develop abiotically by gelation, coagulation, or bubble adsorption (Chin et al. 1998; Passow 2000; Mari et al. 2017) under certain environmental conditions from dissolved fibrillar polysaccharides released from various planktonic organisms. TEPs exist as blobs, clouds, sheets, filaments, or clumps and have been detected in various aquatic ecosystems like rivers, lakes, groundwater, wastewater, brackish water, and seawater where they significantly contribute to the trophic structure, carbon cycling, and export nutrients to deep waters (Passow and Alldredge 1994; Passow 2000, 2002; Engel 2004; Berman-Frank et al. 2007).

The TEP macrogels (Verdugo et al. 2004) are composed of highly surface-active polysaccharides (Mopper et al. 1995) and thus have a strong tendency to form hydrogen bonds and bridge with ions like Na^{2+}, Ca^{2+}, and other metals. As a result, TEPs are usually extremely sticky, about two to four orders of magnitude stickier than phytoplankton or mineral particles with a high probability of attachment upon collision (Passow 2002; Engel 2004; Mari and Dam 2004; Liu et al. 2018).

Visible aggregates of TEP (>1 mm) have been reported in tank cultures of nutrient-depleted *Synechococcus* sp. (Deng et al. 2016) that sink at velocities of more than 400 m d^{-1} in seawater. *Microcystis* sp. has been reported to produce 15 pg Xanthan equivalents of TEP per cell (Liu et al. 2014). Interaction of this EPS with Ca^{2+} has been reported to induce colony formation in this bloom-forming cyanobacterium (Sato et al. 2017). *Crocosphaera*, a marine diazotrophic cyanobacterium, produces EPS and TEP constitutively during the exponential growth phase as has also been reported for *Anabaena flos-aquae* (Surosz et al. 2006; Sohm et al. 2011), while *Phaeocystis antarctica* produces them in stationary and death phase (Hong et al. 1997) and *Nostoc* under N limitation (Otero and Vincenzini 2004). Cyanobacterial blooms significantly contribute to the TEP pool (Bertocchi et al.

1990; Gloaguen et al. 1995) and are known TEP precursors (Passow 2000). Positive coupling between programmed cell death during bloom termination and Fe starvation and TEP production has been reported for *Trichodesmium* blooms (Berman-Frank et al. 2007). TEP concentrations reaching 1474 ± 226 μg xanthan gum equivalents L^{-1} have been reported in stationary phase cultures of *Prochlorococcus* sp., a picocyanobacterium-dominant primary producer in the oligotrophic ocean (Iuculano et al. 2017).

Because of their high abundance and unique properties, TEPs play a major role in the dynamics of the aquatic ecosystems. For example, as gel-like free swimming particles, TEP and TEP precursors show lectin-like property which can enable them to act as a chemical conditioning layer and to agglutinate bacteria (Li et al. 2015). It has been shown that about 0.5–25% of all bacteria present in seawater and freshwater were attached onto TEP. This suggests that free swimming TEPs are hotspots of intense microbial and chemical activity and act as a carrier to transport bacteria in aquatic environments. Evidence suggests that TEP can play an active role in the development of aquatic biofilms (Berman et al. 2011; Bar-Zeev et al. 2012) enhance surface biofouling and cycle nutrients vertically in deep waters (Passow 2002). Additionally, these particles together with their associated flora and fauna can serve as food packages for protists, microzooplankton, and even larval fish (Grossart et al. 1998). TEP-based aggregates or marine-snow containing TEP typically have high carbon (C)-nitrogen (N) ratios (Berman-Frank and Dubinsky 1999), which can also fuel N_2 fixation by heterotrophic diazotrophs (Rahav et al. 2013; Benavides et al. 2015).

15.5.2 Factors Affecting EPS Production

Composition of all structural and storage polysaccharides is more or less constant, yet EPS show a high amount of compositional flexibility. They also show a wide range of cellular N:P ratios, ranging from 5:1 to 100:1 depending on the type of nutrient that was in short supply, deviating a lot from the Redfield ratio of 106:16:1 (Geider and Roche 2002; Rabouille et al. 2017). This flexibility explains the capacity of these simple life forms to survive in nutrient extremes. The overconsumption of carbon is exuded as EPS. EPS production by phytoplankton is highly variable, from 1 to 99.9% of the net photosynthetically fixed organic carbon, depending on species and environmental conditions (Bertilsson and Jones 2003). Besides nutrient availability, other abiotic factors like light, temperature, pH, salinity, C:N ratio, nutrient source, batch or continuous cultivation, aeration, dilution, and availability of micronutrients also affect EPS production. Generally, exopolysaccharide production increases under stress, but what is stress to an organism may be a normal situation for another. Therefore, the responses are largely strain dependent.

An increase in EPS pool has been reported with increase in irradiance in *Crocosphaera watsonii* while the growth becomes saturated, and a similar response is observed at a low irradiance with nearly 30% of carbon occurring in TEPs (Rabouille et al. 2017). Increase in EPS with light intensity has also been reported in *Cyanothece* sp. (Su et al. 2007), *Aphanocapsa halophyta* MN11 (Matsunaga et al.

1996), *Gloeocapsa gelatinosa* (Raungsomboon et al. 2006), *Anabaena* ATCC 33047 (Moreno et al. 1998), and *Nostoc* sp. (Otero and Vincenzini 2003, 2004). The spectrum of energy also affects EPS productivity. Red and blue wavelengths were shown to enhance EPS production in *Nostoc flagelliforme* (Han et al. 2014) by altering carbon allocation and increasing carbon flow into the sugar nucleotide synthesis pathway (Han et al. 2018). Light was found to be the key factor in *Cyanothece* CCY0110 EPS production with a maximal yield being 1.77 gL^{-1} at 50 $\mu E\ m^{-2}\ s^{-1}$ (Mota et al. 2013). Light intensity and temperature have a synergistic effect (Carvalho et al. 2009). Temperature affects nutrient uptake, membrane fluidity, and photosynthetic rate and thus the EPS production. While a positive effect of temperature was observed on EPS production by *Anabaena* ATCC33047 (Moreno et al. 1998), no effect was observed in *Nostoc* sp. PCC 7936 (Otero and Vincenzini 2003, 2004).

Increase in salt concentrations increased EPS production in *Cyanothece* sp. ATCC51142, *Synechocystis* sp., *Spirulina*, and *Anabaena* PC1 (Nicolaus et al. 1999, Pereira et al. 2009; Ozturk and Aslim 2010), but *Cyanothece* CCY0110 being a marine form did not show much response (Mota et al. 2013). EPS content in *Synechococcus* strain CCAP1405 increases with salinity and age of cultures (Bemal and Anil 2018). *Spirulina subsalsa* showed a 2.5% increase in EPS in the stationary phase (Chakraborty et al. 2015) which suggests that nutrient starvation is needed to induce a response in this organism. The composition of the EPS also changes with a change in molar ratios of the monomers and composition.

Increase in C:N ratio has a critical role in EPS production. Usually, the presence of combined nitrogen even in diazotrophic forms enhanced EPS productivity perhaps because nitrogen fixation itself is an energy-intensive process (Kumar et al. 2007, Pereira et al. 2009). Reaction to N starvation is strain specific. An increase in EPS on N limitation has been reported in *Anacystis nidulan*s and *Microcoleus vaginatus* (Chen et al. 2006). A study on 15 *Cyanothece* species by De Philippis et al. (1998) showed that while a few strains showed an increase in intracellular carbohydrate, others showed increase in extracellular carbohydrate under N limitation. Response depended on the source of nitrogen in case of *Anabaena cylindrica* (Lama et al. 1996) and *A. flosaquae* (Tischer and Davis 1971). Excess nitrogen as nitrate generally does not affect significantly as it is the most easily metabolizable source. Urea was found to be the best nitrogen source for EPS production in *Nostoc flagelliforme* (Han et al. 2017). *Phormidium tenue* (Hu et al. 2003), *Spirulina subsalsa* (Chakraborty et al. 2015), and *Nostoc* sp. (Otero and Vincenzini 2003) showed an increase in EPS on N starvation, while no change was reported in *Synechocystis* (Panoff et al. 1988), *Cyanothece capsulata* (De Philippis et al. 1998), *Phormidium* (Fattom and Shilo 1984), and *Crocosphaera watsonii* (Sohm et al. 2011), and a negative effect was observed in *Phormidium laminosum* (Fresnedo and Serra 1992) (reviewed by Pereira et al. 2009).

Cade Menun and Paytan (2010) suggested a lower threshold value of phosphorous concentration at which carbohydrate accumulation is observed in *Spirulina platensis* (Markou et al. 2012). Increase in EPS in P starvation is reported in *Cyanothece* 16SOM-2 (De Philippis et al. 1993), *Synechococcus* sp. (Roux 1996),

Spirulina (Nicholaus et al. 1999), and *Anabaena* sp. (Huang et al. 2007), while no effect was observed in *Phormidium* J1 (Rossi and De Philippis 2016) and *Cyanospira capsulata* (De Phillipis et al. 1991), and a decrease has been reported in *Anabaena cylindrica* (Lama et al. 1996).

Concentration of divalent ions also affects EPS synthesis as observed in *Anabaena* sp. PCC7120 (Singh et al. 2016) in response to calcium chloride. High EPS production was observed at the inhibitory concentration of 10 mM, which suggests release of EPS as a means of chelation of the ion to protect the cell.

The composition of the EPS may vary with the age of the culture both quantitatively and qualitatively as observed for the sulfated polysaccharides produced by *Synechocystis* strains (Panoff et al. 1988) and *Spirulina platensis* PCC8005. *Spirulina* showed a decrease in the amount of galactose with culture aging, while *Synechocystis* showed variation in molar ratios, and one strain formed an additional polymer on aging (Filali Mouhim et al. 1993). On the other hand, the exopolysaccharide from *Cyanospira capsulata* showed no alteration in composition even after 10 years of cultivation (De Philippis and Vincenzini 1998). *Cyanothece* 16Som2 on continuous culturing for 5 years showed an additional sugar, rhamnose with variation in molar ratio in its EPS (De Philippis et al. 1998).

15.5.3 Rheological Behavior

Most cyanobacterial polysaccharides are polyelectrolytes. The charged groups ensure strong hydration. They may contain over 95% water by weight. A 20–40-fold increase in the weight of colonies of *Nostoc commune* was observed by Shaw et al. (2003) with most of it absorbed by the extracellular glycan. The EPS from *Anabaena* sp., *A. anomala*, *and A. oryzae* absorbs 25.9, 7.16, and 12.3 g H_2O g^{-1} polymer, while the polymer from *Tolypothrix tenuis* absorbs only 9.35 g (Bhatnagar et al. 2014b). Sacran absorbs an exorbitant amount of 6100 mL water per gram polysaccharide. The absorbing capacity is however dependent on the ionic strength of the solvent and decreases to 2700 ml in saline (Mitsumata 2018).

Polysaccharides do not form a true solution in water; however, on hydration, some of them undergo conformational transitions entering secondary, tertiary, and quaternary interactions (Rees 1982). These inter- and intramolecular interactions lead to characteristic hydrodynamic behavior such as viscoelasticity or gel-like properties. Viscoelastic behavior of EPS is responsible for the cell's mechanical integrity and is required for normal cell functioning, cellular homeostasis, cell-cell communication, stress response, and locomotive function (Bhat et al. 2012). An understanding of the flow behavior not only is relevant to industrial applicability of these polysaccharides but also gives an insight into the structure of the macromolecule. The viscosity and flow behavior (rheology) of the polysaccharides change in response to a number of variables, viz., the structure of the polysaccharide, size, concentration, temperature, pH, ionic strength, and shear. For Newtonian fluids, at constant temperature and pressure, viscosity does not vary with shear rate. On the other hand, for most non-Newtonian fluids, viscosity decreases with increase in

shear and are thus classified as pseudoplastic as against dilatant fluids that show increase in viscosity on increasing shear. Fluids that show increase in viscosity on constant shear with time are called rheopectic, while the ones that show a decrease are called thixotropic.

Cyanobacterial polysaccharides are characterized by high molecular weight (MW) that contributes to the viscosity which in certain cases is even greater than xanthan (Rossi and De Philippis 2015). *Cyanospira capsulata* has been reported to produce EPS with a molecular weight of 4.5 MDa, the highest reported so far. Table 15.3 summarizes some reported MW. Viscosities of cyanobacterial EPS may vary from as low as 0.9 cps as in *Nostoc calcicola* (Bhatnagar et al. 2014a) to 400 cps

Table 15.3 Molecular mass of cyanobacterial exopolysaccharides

Species	Apparent molecular mass (kDa)	References
A. circularis PCC 6720	>1200	Bar-Or and Shilo (1987)
A. halophytica GR02	2100	Morris et al. (2001)
Anabaena anomala	864	Bhatnagar et al. (2014b)
Anabaena circularis PCC 6720	41,200	Bar-Or & Shilo (1987)
Anabaena oryzae	539	Bhatnagar et al. (2014b)
Anabaena sp	3679	Bhatnagar et al. (2014b)
Anabaena sp. ATCC 33047	1350	Moreno et al. (2000)
Anabaena spiroides	2000	Colombo et al. (2004)
Aphanothece sacrum	1.6×10^4	Okajima et al. (2012)
Aphanothece stagnina	3.14×10^4	Le Nguyen et al. (2012)
Arthrospira platensis	81–98	Tseng and Zhao (1994)
C. capsulata ATCC 43193	1400–1900	Vincenzini et al. (1993)
C. minutus B 41.79	1200–1600	Fischer et al. (1997)
Cyanothece sp.	4.5×10^4	Ohki et al. (2014)
Gloeocystis vesiculosa	680	Halaj et al. (2018)
Microcoleus vaginatus	380	Hu et al. (2003)
Nostoc insulare 54.79	540–1300	Fischer et al. (1997)
Nostoc sp.	460	Hu et al. (2003)
Nostoc sphaeroids	131	Liu et al. (2018)
Oscillatoria sp.	200	Bender et al. (1994)
Phormidium versicolor NCC466 (CFv-PS)	63.79	Belhaj et al. (2018)
Phormidium J-1	1200	Bar-Or and Shilo (1987)
Phormidum 94a	2000	Vicente-Garcia et al. (2004)
Phormidum tenue	380	Hu et al. (2003)
Schizothrix sp.	300	Kawaguchi and Decho (2002)
Scytonema javanicum	110–380	Hu et al. (2003)
Tolypothrix tenuis	1953	Bhatnagar et al. (2014a, b)

in *Cyanothece* CE4 (De Philippis et al. 2001). EPS from *Nostoc calcicola*, a low-viscosity polymer (55–65 cps), showed a truly pseudoplastic, non-Newtonian, time-independent behavior with good recovery from shear (Bhatnagar et al. 2014a). Non-Newtonian shear-thinning properties have been reported for many other cyanobacteria also like *Spirulina platensis* (Filali Mouhim et al. 1993), *Anabaena halophytica* GRO2 EPS (Morris et al. 2001), *Cyanospira capsulata* (Lapasin et al. 1992), *Limnothrix redekei* (Moreno et al. 2000), *Anabaena variabilis* (Bhatnagar et al. 2012), *Nostoc carneum* (Hussain et al. 2015), and *Nostoc minutum* (Pereyra and Ferrari 2016). EPS from *Phormidium* 94a shows a Newtonian behavior at low EPS concentration changing to pseudoplastic above 0.1% solution and increasing hydration times perhaps due to increase in hydrogen bonding leading to a strong polymer network and viscosity (Vicente-Garcıa et al. 2004). Aqueous dispersions (0.1% w/v) of polysaccharide produced by *Cyanothece* strains were comparable to xanthan (De Philippis et al. 1998). Mancuso Nichols et al. (2009) screened 800 algal cultures for exosaccharide production and isolated the cyanobacterium *Microcystis aeruginosa* f. *flos-aquae* that showed highest viscosity (6.55 cps, equivalent to 1.16 g L^{-1} xanthan gum) in the medium. Parikh and Madamwar (2006) studied four cyanobacterial strains: *Cyanothece* sp., *Oscillatoria* sp., *Nostoc* sp., and *Nostoc carneum*. All the polysaccharides were low-viscosity products (6.9–18.4 cps) and showed decline in reduced viscosity with 0.1 M NaCl and precipitated with 0.1 M $CaCl_2$. A biphasic effect of metal ion concentration on the polysaccharide produced by *Microcystis flos-aquae* has been reported. The polysaccharide viscosity increased with increasing metal ion concentration ($CdC1_2$, $Pb(NO_3)_2$, $FeC1_3 > MnCl_2 > CuC1_2 > CaC1_2 > NaCl$) reaching a maxima and then decreased with further addition of that ion (Parker et al. 1996).

Kinematic viscosity of *Nostoc* strains (*Nostoc commune*, *Nostoc flagelliforme*, and *Nostoc sphaeroides*) grown in the field was found to be higher than the suspension cultures grown under controlled condition (Huang et al. 1998). Apparent viscosity curves of EPS from *Arthrospira* sp. showed three phases. The first phase was characterized by Newtonian behavior at zero shear with viscosity reaching up to 10^2 Pa.s at 5% concentration. Beyond a critical shear value, the flow behavior became rheo-fluidifiant followed thereafter by another Newtonian region at a high shear rate (Chentir et al. 2017).

Polysaccharide properties are integrals of many factors. The primary structure of a polysaccharide is the main sequence of covalently linked sugar monomers. The constitutively fixed bond lengths and angles controlling the ring orientations comprise a secondary structure (configuration). In solution, polymer chains align themselves to adopt an orientation with lowest energy that may be ordered or disordered. Two general ordered conformations are ribbon-like and helix conformations. Polysaccharide with ribbon-like conformation is most easily aligned and closely packed through numerous hydrogen bonds and van der Waals forces. The resultant compact structures essentially prevent solvent penetration and retain insolubility in water. The ribbon-like conformation is the least soluble followed by the hollow helix, while polysaccharides with disordered conformation of a random coil are the most soluble. Stiff structure that hinders the intermolecular association remains extended and

usually leads to a higher solubility. Branched structure and presence of charged groups (carboxylate group, sulfate, or phosphate groups) increase solubility, while structural characters that promote the intermolecular association lead to poor solubility, such as linear chain, large molecular weight, and other regular structural characters. Zhang et al. (2007) reported the order of chain flexibility of glucan as (1,4) β > (1,3) α > (1,4) α > (1,3) β > (1–6) α > (1–6) β, while β glucans are inherently flexible. Besides molecular structure, concentration, degree of polymerization, polydispersity, solvent characteristics, and temperature also affect the polysaccharide conformation. In poor solvents, interactions of chain segments with themselves are favored resulting in aggregation. In good solvent, interactions between solvent and chain segments are favorable resulting in extended conformations and high solubility. Stability in aqueous environments can only be achieved when interchain and intrachain interactions are favorable. Therefore, two or more stranded associations of helices, of ribbons, or of helices with ribbons are found. These can be regarded as tertiary and higher levels of structure (Rees and Welsch 1977). Native polysaccharides can link up further to form three-dimensional networks resulting in gels that help maintain hydration and integrity of the cells. An increase in viscosity coincides with an increase in surface. The most extended conformation is the random coil and thus exposes more surface area than does a helix and a single helix exposes more than a double helix. With the structural complexity observed in cyanobacterial polysaccharides, an immensely wide variety of solution behaviors are expected. However, very few studies have been conducted. Since cyanobacterial polysaccharides are generally polyelectrolytes, their conformation depends on the ionic strength of the solvent and their concentrations. In very dilute salt-free solutions, these macromolecules thus tend to adopt an extended rod-like conformation; however, conformations ranging from rigid rod to random coils have been reported.

A rigid/extra-rigid rod-type conformation has been envisaged for the exopolysaccharide from *Aphanothece halophytica* GR02 (AH-EPS) (Morris et al. 2001). Polysaccharides extracted from four filamentous cyanobacteria, viz., *Microcoleus vaginatus*, *Scytonema javanicum*, *Phormidium tenue*, and *Nostoc* sp., show a conformation intermediate to a stiff rod and a random coil (stiff coil or a flexible rod) (Hokpusta et al. 2003), while EPS of *Anabaena* sp. ATCC 33047 takes up an intermediate structure between a random coil polysaccharide and a weak gel. Rheological studies on *Cyanospira capsulata* EPS show two different viscoelastic responses at sufficiently high concentrations and molecular weights (Cesàro et al. 1990; Garozzo et al. 1995, 1998). The solution conformation of the EPS is that of a random coil with moderate flexibility. As the concentration increases, overlapping and entanglement coupling occurs along with flickering interchain cross-reactions between semi-flexible segments creating order in the system. Further increase leads to formation of an entanglement network locally stabilized through specific non-covalent intermolecular interactions leading to a weak gel-like consistency (Cesàro et al. 1990; Navarini et al. 1992). The gelatinous EPS of *Nostoc commune* that grows in extreme conditions of desiccation is a biological gel that shows properties of both physical and chemical gels. The gel shows a reversible stress

softening behavior perhaps due to intensive physical crosslinking that makes it behave as an elastomer, limiting the relaxation of individual chains.

Sacran, a megamolecular suprapolysaccharide produced by *Aphanothece sacrum*, is an extremely high molecular weight (>1.6×10^7 g mol^{-1}) polysaccharide composed of five major monosaccharides (glucose, xylose, rhamnose, galactose, and mannose) (Okajima et al. 2009; Ohki et al. 2018). Sacran shows a very low overlap concentration of 0.004% indicating its megamolecular structure. The chains are not fully extended in pure water and take double-helical conformation at concentrations (c) >0.09 wt %, form a weak gel at c > 0.25 wt%, and finally form huge domains of liquid crystalline gels considered to be an aggregate of highly ordered helices, forming self-orienting micro-rods longer than 3 μm at c > 0.2 wt% (Mitsumata et al. 2013). During the drying process of the sacran solution, the rigid polysaccharides exhibit self-orientation and self-assemble to build a rod-like microdomain in micrometer scale (~1 μm of outer diameter and > 20 μm length) which have not been reported for any other soluble polysaccharides. Under certain conditions, clear twisting structures are formed (Okeyoshi et al. 2016; Budpud et al. 2018).

15.6 Industrial Applications

Cyanobacteria are gaining attention of the industry due to the ease of production with minimum cheap supplements, eco-friendly nature, and immense functional versatility that is difficult to reproduce synthetically. Though the productivity is lesser than other bacteria and fungi, their unique composition and interesting properties drive research in the field. Their potential for application in some areas is discussed here.

15.6.1 Lipopolysaccharides

Cyanobacterial lipopolysaccharides are generally considered as toxins and are attributed with a range of pathological effects. They can cause strong allergic reactions and skin and eye irritations and can induce symptoms of influenza like rigors, uneasiness, headaches, arthralgia, somnolence, marginal loss of memory, and diarrhea (Jakubowska and Szelag-Wasielewska 2015). However, cyanobacterial lipopolysaccharides are reported to be ten times less harmful than other bacterial variants. LPS from *Oscillatoria* sp. has been reported to activate cells of the immune system (Mayer et al. 2011, 2016; Ohkouchi et al. 2015). An exception was reported by Best et al. (2002) who investigated the potential of isolated cyanobacterial LPS to reduce the activity of glutathione S-transferases (GSTs) in zebra fish embryos which was found to be greater than LPS from *E. coli* or *Salmonella typhimurium*. Reduction in GST decreased utilization of glutathione, and glutathione depletion prevented LPS-induced inflammation as observed in case of lung injury (Nathens et al. 1998). It also has a protective effect on various models of apoptotic and necrotic liver injury

(Hentze et al. 1999, 2000). This property of cyanobacterial EPS has been proposed as a novel anti-inflammatory pharmacotherapy (Szászi et al. 2005; Stewart et al. 2006).

An LPS-related molecule derived from the cyanobacterium *Oscillatoria planktothrix* FP1, termed CyP, acts as a TLR4 receptor antagonist and blocks toxicity associated with other Gram-negative bacteria (Carillo et al. 2014; Swanson Mungerson et al. 2017). It acts as a competitive inhibitor of *Escherichia coli* LPS binding to the receptor complex on human dendritic cells (Macagno et al. 2006). Inhibition of cytokine production by Cyp in septicemia induced by *Neisseria meningitidis* in a human whole-blood model was reported by Jemmett et al. (2008) which thus can be considered as a new adjunctive therapy for treating septicemia. LPS preparations from *Oscillatoria planktothrix* sp. have also been proposed for the treatment and/or prevention of bacterial gum diseases primarily caused by *Actinobacillum actinomycetemcomitans*, *Tannerella forsythia*, *Treponema denticola*, and, more importantly, *Porphyromonas gingivalis* that causes gingivitis and periodontitis (pyorrhea) (Molteni 2011). CyP actively inhibits the proinflammatory cytokines induced by LPS in vitro even when added several hours after LPS exposure (Macagno et al. 2006). Furthermore, the effect was not species specific since it was reportedly active in human, mouse, and porcine cells (Jemmett et al. 2008; Thorgersen et al. 2008). Thus, the potential of CyP can be exploited for the treatment of noninfectious diseases, in which detrimental TLR4-driven inflammatory processes induced by endogenous ligands play a pivotal role. TLR4 antagonism by CyP can help in delaying seizures and reducing recurrence in animal models of neurological and neurodegenerative diseases such as in epilepsy and models of amyotrophic lateral sclerosis and Alzheimer's diseases (Marosso et al. 2010; Iori et al. 2017; Molteni et al. 2016).

15.6.2 Exopolysaccharides

The immense structural variability in cyanobacterial exopolysaccharides manifests into functional versatility. Due to various sol-gel properties resident in these polysaccharides, they are variously used as thickening, emulsifying, gelling agents and stabilizers in food industry (Delattre et al. 2011; Kraan 2012). Xanthan is widely used in the food industry for its rheological behavior. EPS from *Cyanospira capsulata* and *Anabaena halophytica* GRO2 show xanthan-like physical properties (Cesàro et al. 1990; Navarini et al. 1990, 1992; Morris et al. 2001), while *Anabaena* sp. ATCC 33047 EPS is similar in properties to Alkemir 110 that is widely used in the food industry as a stabilizer (Moreno et al. 2000). *Microcystis flos-aquae* C3–40 resembles the plant polysaccharide pectin in its composition. Pectin is used as a gelling agent but requires intensive processing. Thus, the ease of preparation of the cyanobacterial polymer is a promising alternative. The exopolysaccharides of *Nostoc commune* are often used as a dietary ingredient in countries such as China and Peru (Johnson et al. 2008). These polymers have been suggested for applications as bioemulsifiers in cosmetics, swelling agents in food industry, and stabilizers in

textile and pharmaceutical industry. They can also be of use as industrial gums owing to their capacity to form weak gels (Parikh and Madamwar 2006).

Humectants that are commonly used in the cosmetic industry are glycerin, sodium pyrrolidone carboxylic acid, propylene glycol, and urea (Rawlings et al. 2004). These chemicals though have appreciable water absorption ability, and their retention ability is poor, thereby necessitating the use of occlusive agents to minimize transepidermal loss (Zhao et al. 2013) which may impart undesirable odor and greasy texture (Kraft and Lynde 2005). Though generally considered safe, they may trigger adverse skin reactions particularly in people with dermatitis (Zesch 1982). Cosmetic industry therefore has a demand for safer, nonirritant alternatives (Lodén et al. 2002). Amphipathic cyanobacterial exopolysaccharides trap water and protect live cells during periods of desiccation by retarding water loss (Tamaru et al. 2005). The exopolysaccharides of *Nostoc commune* exhibit a moisture absorption rate of 28% on exposure to 43% relative humidity for 24 h, which was much higher than that of chitosan (6.3%) and urea (5.8%) (Li et al. 2011). Sacran, a giant anionic polysaccharide extracted from the cyanobacterium *Aphanothece sacrum*, exhibits tenfold higher moisture retention than hyaluronic acid. This gummy polysaccharide consists of 11 different monosaccharides with ~12% carboxyl and ~11% sulfate groups per sugar chain (Okajima et al. 2008; Derikvand et al. 2017). Due to their excellent water-holding capacity, cyanobacterial EPS has great potential for being exploited as humectants in the skin care industry without the need of occlusive agents.

Another feature which makes cyanobacterial exopolysaccharides suitable for skin care is its antioxidant activity that, besides giving protection, also slows down the aging process. EPS capable of scavenging both superoxide anions and hydroxyl radicals in vitro (Li et al. 2011) can also mitigate oxidative damage induced by paraquat (Li et al. 2011). Sed et al. (2017) proposed extraction of exopolysaccharides for cosmetic use from spent culture systems of *Arthrospira platensis* that also exhibited antioxidant activity.

Cyanobacterial polysaccharides have also garnered interest in commercialization due to their potential in medicine. Scytonemin, a commercialized extracellular pigment present in the sheath of *Scytonema,* controls the cell cycle by regulating mitotic spindle formation and activity of kinases. It also inhibits proliferation of human endothelial and fibroblast cells (Stevenson et al. 2002). Polysaccharides from *Phormidium versicolor* (NCC466) protect liver tissues from cadmium toxicity (Belhaj et al. 2018). Consequent to their excellent biocompatibility, stability, efficacy, nontoxicity, biodegradability, low cost, and distinctive physicochemical properties, sulfated cyanobacterial polysaccharides can be used as nanocarriers for bioimaging and therapeutic applications (Radonić et al. 2010). Spirulan that exists as calcium (CaSp)/sodium spirulan (NaSp) is a sulfated polysaccharide prepared from *Arthrospira platensis*. It exhibits antithrombin activity by the activation of heparin cofactors (Hayakawa et al. 2003). Depolymerized NaSp can function as a precursor of the agents that prevent atherosclerosis as it acts as a potent inhibitor of arterial smooth muscle cell proliferation in vitro (Kaji et al. 2004) and selectively inhibits the entry of enveloped viruses and is reported to be active against HIV-1, HCMV, HSV-1, measles virus, mumps virus, and influenza A virus (Hayashi et al.

1996; Ayehuni et al. 1998; Hayashi 2008). TK V3 polysaccharide, another variant, was shown to inhibit replication of HIV, HCMV, HSV-1, human herpesvirus type 6 (HHV-6), and VACV, but not the enveloped viruses Epstein-Barr virus and influenza A virus (Kolender et al. 1997). Mansour et al. (2011) found that the polysaccharides isolated from *Gloeocapsa turgidus* and *Synechococcus cedrorum* had higher antiviral activity against rabies virus than that against herpes-1 virus. The exopolysaccharide from *Aphanothece halophytica* has antiviral activity against influenza virus A (H1N1), which shows 30% inhibition of pneumonia in infected mice (Zheng et al. 2006). Nostoflan from *Nostoc flagelliforme* shows antiviral activity against a variety of enveloped viruses whose cell receptors are carbohydrates such as influenza virus, herpes simplex virus-1, HSV-2, and human cytomegalovirus (Kanekiyo et al. 2005, 2007). EPS from *Nostoc commune* shows antimicrobial activity against *Escherichia coli*, *Bacillus anthracis*, *Staphylococcus aureus*, *Bacillus subtilis*, *Serratia marcescens, Aspergillus niger,* and *Candida albicans* (Qian et al. 2012; Matsui et al. 2012; Liao et al. 2015; Li and Guo 2018). The polysaccharides from *Synechocystis* sp., *Gloeocapsa* sp., and *Nostoc entophytum* inhibit the growth of selected pathogenic bacteria and the fungus *Candida albicans* (Najdenski et al. 2013). *Phormidium versicolor* polysaccharides have been reported to be active against Gram-positive and Gram-negative bacteria as well as fungi (Belhaj et al. 2017). The elastomeric gel synthesized by *N. commune* can also be exploited for producing hydrogel films and scaffolds for tissue regeneration. The polysaccharides can also constitute scaffolds for tissue/organ regeneration in regenerative medicine (Nielsen et al. 2010; Kurd and Samavati 2015; Rodriguez et al. 2017).

Wounded skin exhibits a rise in the oxidant levels which can trigger chronicity of wounds especially in diabetic patients, and carcinogenesis and promote tumor progression via cell proliferation and cell death pathways. Reactive oxygen species (ROS) are also associated with various degenerative diseases; inflammation; and disorders such as cardiovascular disease, immune function decline, and aging (Rahman et al. 2012; Zhang et al. 2015). Nostoglycan reduces reactive oxygen species level and can suppress the proliferation of several types of tumor cells and induce apoptosis of human lung adenocarcinoma A549 cells via caspase-3 activation (Li et al. 2018). Spirulan inhibits pulmonary metastasis by preventing adhesion and proliferation of tumor cells (Mishima et al. 1998). Attempts are being made to prepare nanoformulations for commercialization against cancer (Bajpai et al. 2018). Potential of cyanobacterial polysaccharides in wound healing as a function of antioxidant activity has also been reported in *Anabaena anomala*, *A. variabilis*, *A. oryzae*, and *Tolypothrix tenuis* (Bhatnagar et al. 2014b). These hemostatic polymers were proposed to be used in the recovery from hemorrhagic wounds. Antioxidant activities have been reported in *Phormidium versicolor* (NCC 466) ECP also (Belhaj et al. 2017).

High molecular weight polysaccharidic preparation from the *Arthrospira*, called Immulina, has been commercialized as it exhibits significant immunostimulatory activity by raising TNFα, IFNγ, and IL-6 blood levels (Løbner et al. 2008; Nielsen et al. 2010). It is 100–1000 x more active as monocyte activation factor in vitro than

the polysaccharide preparations that were being used at the time in clinical settings for cancer immunotherapy (Løbner et al. 2008). Brevitoxin, another polysaccharide isolated from *Aphanizomenon flos-aquae* is reported to be immunostimulatory (Pugh et al. 2001).

The complex polysaccharide of *Wollea saccata* is antitussive and bronchodilatory with the effect being equal to or better than salbutamol but lesser than codeine (Šutovská et al. 2017). Antidiabetic activity in intracellular and extracellular polysaccharides has been reported in *Oscillatoria* sp., *Leptolyngbya* sp., *Pseudanabaena* sp., *Lyngbya* sp., *Coelastrella* sp., *Aphanothece* sp., *Synechococcus* sp., and *Chroococcus* sp. (Priatni et al. 2016). Sacran when applied topically shows reduced transepidermal water loss in dry skin human subjects and displays antiallergic effects similar to hydrocortisone and tacrolimus in animal experiments. It decreases the severity of atopic dermatitis (AD) skin lesions, itch, and sleep disorder in AD patients and thus may serve as an alternative adjuvant and therapeutic antiallergic agent (Motoyama et al. 2018). Heteropolysaccharides from *Phormidium versicolor* NCC466 (CFv-PS) displayed strong antioxidant and hepatoprotective activity against cadmium toxicity (Belhaj et al. 2018).

Another area of interest in cyanobacterial polysaccharides is nanoparticle synthesis. Silver nanoparticle synthesis with antibacterial activity has been reported in cell-free extracts of *Limnothrix* sp., *Anabaena* sp., *Synechocystis* sp., and *Nostoc commune* attributed to extracellular polysaccharides (Morsy et al. 2014; Patel et al. 2015). *Lyngbya majuscula* reduces gold to form nanoparticles. Nucleation occurs on the cell surface, and surface-active molecules are suggested to be involved in metal ion reduction and stabilization (Bakir et al. 2018).

Anionic polysaccharides rich in uronic acids can be developed as biosorbents for easy metal recovery. *Limnothrix* sp. KO05 and *Synechocystis* sp. PCC6803 EPS have been demonstrated to be instrumental in biosorbing cadmium (Haghigi et al. 2017; Shen et al. 2018). Preferential adsorption of uranium by functional groups of the marine unicellular cyanobacterium *Synechococcus elongatus* BDU130911 has been reported by Vijayaraghavan et al. (2018). Heterogels of sacran with polyvinyl alcohol have been explored for selective neodynium (rare earth metal) sorption (Okajima et al. 2010). Selectivity toward neodymium over other earth metals has also been reported in sacran-sepiolite composites (Alcantara et al. 2014). Bionanocomposite with sacran chains complexed with multiwall carbon nanotubes has been synthesized that form hardened hydrogel beads with metals and can be collected by electrophoresis for metal recovery (Okajima et al. 2013).

An exopolysaccharide with properties of a good hydrophobic dispersant, an excellent emulsifier, as well as a flocculant has been isolated from a strain of *Cyanothece epiphytica*. Its potential as a biolubricant with characteristics better than the conventional lubricant "grease" has been proposed for tribological applications (Borah et al. 2018). Halophilic cyanobacteria like *Cyanothece* sp. ATCC 51142, *Aphanocapsa halophytica*, and *Synechococcus* sp., producing copious amounts of EPS (Matsunaga et al. 1996; Moreno et al. 1998; Shah et al. 1999) can be relevant to oil recovery as they can decrease surface tension, thereby increasing solubility and mobility (Abed et al. 2009).

Adhesivity in cyanobacteria by virtue of the polysaccharidic sheath has always been viewed as a nuisance for their role in biofilm formation; however, their potential in wastewater remediation through turf scrubbing has been recognized and adopted by numerous companies like Hydromentia, BioProcess Algae, OneWater Inc., and Green Shift Corp. Biofilm formation as a source of biomass for biofuel production has also been recognized (Choudhary et al. 2017). A xanthan analogue excreted by the cyanobacteria CSIRO505 has been evaluated for its adhesive property and was described as fourfold effective for wood (maple) bonding (1.5 MPa shear strength) compared to commercial PVAc glue (Mancuso Nichols et al. 2009). Role of EPS as a molecular glue in photosynthetic algal microbial fuel cells, to generate electricity in a carbon neutral fashion, is also being explored. An electrogenic response to light has been observed from sheathed cyanobacteria (*Phormidium*, *Nostoc*, *Spirulina*, *Anabaena*, and *Lyngbya*) indicating that mucilaginous sheaths do not insulate or prevent electrogenic activity (Pisciotta et al. 2010). Further the role of EPS in direct electron transfer to the electrode and thus efficient energy production has been reported for the chlorophyte, *Scenedesmus* sp. SB1 (Angelaalincy et al. 2017), that may have analogy in cyanobacteria and still needs to be explored.

15.6.3 Glycogen

Glycogen extracted from natural sources is used in the cosmetics industry as an emollient and hydrating agent (Marchitto et al. 2010), as an antiaging agent in combination with a protein and a flavonoid (Mausner 1992), as a humectant (Jialun et al. 2018), and as a lubricant in ophthalmic solutions (Cavallo et al. 2002).

Monodisperse glycogen or phytoglycogen nanoparticles and their derivatives are polyfunctional additives suitable for use in aqueous- or alcohol-based pharmaceutical or food formulations (Korenevski et al. 2016), as rheological modifiers (including modulation of thixotropic behavior), stabilizers of organic and biological materials, and photostabilizers in sunscreens. Some of the products having glycogen as one component are Dermosaccharides® GY, Oxygen® complex LS 9641, and VitaplexTM LS 9799 by BSF; Amino-Glyco kviar, Bio-Hydractyl, Cobiodefender EMR, Glycoenergyzer, Hairdensyl complex, and Hydrotensyl complex by Cobiosa; Marine spheres by Chemir; and PhytoSpherix by Mirexus Biotechnologies (SpecialChem c2018).

Amphoteric glycogen hydrogels using phosphorylase-catalyzed enzymatic polymerization have been prepared for biomedical applications (Izawa et al. 2009, Kadokawa 2018). Hussain et al. (2018a,b) synthesized self-healing ultrastretchable glycogen hydrogels with good mechanical properties. Patra et al. (2016) synthesized stimuli-responsive glycogen/N isopropylamide hydrogels by free radical polymerization using ethylene glycol dimethylacrylate as a crosslinker for colon-specific delivery of ornidazole and 5-aminosalicylic acid. Russo et al. (2014) describe a high-quality slow-release pharmaceutical formulation made of glycogen and alginate. Monodisperse spherical hyperbranched nano-polysaccharidic glycogen

nanoballs have been synthesized by Takahashi et al. (2011) as a new building block for biomedical engineering and to act as chaperone in protein engineering. Though these preparations are resourced from other sources, cyanobacterial glycogen can also be used on similar lines.

Interest in glycogen metabolism in cyanobacteria as a promising alternative for biofuel production has also been explored. Möllers et al. (2014) demonstrated that cyanobacterial biomass could be used as an efficient feedstock for bioethanol production since it has simplified cell walls and glycogen as the main storage polymer which is far easier to mobilize than starch, the main storage polymer for eukaryotic algae.

Efflux engineering involving inactivation of pathways leading to glycogen synthesis has been tried in *Synechococcus* sp. PCC 7002, *S. elongatus* PCC7942, and *Synechocystis* sp. PCC 6803 wherein knocking out the enzymes necessary for glycogen polymerization led to increased leakage of nonspecific carbohydrates, organic acids, and a number of metabolites, including key intermediates of carbon metabolism and compatible solutes (Carrieri et al. 2012; Grundel et al. 2012; Hickman et al. 2013; Xu et al. 2013; Hays and Ducat 2015). *Synechococcus elongatus* UTEX 2973 (Syn2973), the fastest-growing cyanobacterium, appears to hold promise for the biofuel industry as this engineered strain can secrete 35.5 mg sucrose L^{-1} h^{-1} and accumulate glycogen at the rate of 0.75 g L^{-1} d^{-1} under nitrogen-replete conditions (Song et al. 2016). *Synechococcus* sp. PCC 7942 has also been genetically modified to secrete noncrystalline cellulose, which may be converted to ethanol by yeast fermentation (Nobles and Brown 2008) and *Synechococcus* sp. (Ducat et al. 2012). *Synechococcus* sp. PCC 7002 has been engineered to produce mannitol that gave a yield of 10% of cell dry weight and after genetic inactivation of glycogen the production of mannitol increased to 30% (Jacobsen and Frigaard 2014). Similarly, production of other chemicals such as isoprene in *Synechocystis* sp. PCC 6803 (Bentley et al. 2014) and lauric acid in *Synechococcus* sp. PCC 7002 (Work et al. 2015) has been attempted in glycogenless strains.

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