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Review

Role of Bacteria-Derived Exopolysaccharides in Inflammatory Bowel Disease with a Special Focus on *Cyanobacterial* Exopolysaccharides

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Abstract: Instances of inflammatory bowel disease (IBD), a chronic inflammatory condition of the gastrointestinal tract, are rapidly increasing in western and newly industrialized countries. Exopolysaccharides (EPSs) are one of the strategies to enhance the gut microbiota and modulate the immune-inflammatory response deregulation in IBD patients. EPSs are produced by commensal bacteria such as *Lactobacillus* and *Bifidobacterium*. Additionally, *Cyanobacteria* species are promising sources of novel EPS and have potential pharmaceutical and therapeutic applications. The presence of uronic acids and sulphate groups in *Cyanobacterial* EPSs is an important factor that gives EPSs an anionic charge that is not seen in other prokaryotic species. This feature may impact their physico-chemical characteristics and biological properties. Additionally, *Cyanobacterial* EPSs have a wide range of biotechnological applications that include use as thickeners, stabilizers, and gelling agents in the food and pharmaceutical sectors. The present review focuses on the role of EPSs in IBD, with a special focus on EPSs derived from *Cyanobacteria*. This review also covers the biological properties of *Cyanobacterial* EPS in immuno-inflammatory responses and against pathogens as well as its role in biotechnological applications. Overall, *Cyanobacterial* EPSs have therapeutic potential against IBD due to their anti-inflammatory and immunoregulatory properties that can reduce inflammation and regulate the immune response and restore the gut microbiota of patients.

Keywords: exopolysaccharides; inflammatory bowel disease; *Cyanobacteria*; microbiota; uronic acids

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1. Introduction

The westernization of lifestyles and dietary habits over the past few decades has resulted in the spread of inflammatory bowel disease (IBD), which is a chronic inflammatory disease divided into two major types: Crohn's disease and ulcerative colitis [1]. IBD is a multifactorial gut disorder involving immune dysfunction, genetic susceptibility, and environmental factors. The Western-style diet is characterized by a high caloric content combined with large amounts of fat and refined carbohydrates, and has been associated with a significant decrease in the biodiversity of gut microbiota [2]. In light of this issue, it is important to note that the consumption of processed foods in Western countries leads to changes in the gut microbiota [3,4]. This Western food is processed by hulling, heating, and adding preservatives, which all contribute to a reduction in beneficial microorganisms present in food. Furthermore, dietary additives such as emulsifiers, which are regularly

used in processed foods, might also contribute to an increase in the risk of IBD [5]. It has also been found that high-fat diets are linked to dysbiosis, as well as a decrease in the abundance of Bacteroidetes and an increase in the abundance of Firmicutes and Proteobacteria in murine models [3,4].

Western diets rich in fat increase the population of bacteria producing lipopolysaccharides (LPSs), such as Enterobacteriaceae, while reducing the population of bacteria suppressing LPSs, such as Bifidobacterium. Furthermore, this diet alters the intestinal epithelial cells, leading to alterations in the intestinal barrier, including increased intestinal permeability and LPS translocation [6,7].

Different strategies targeted at the gut microbiota have emerged as potential therapeutic approaches [8]. Among them, probiotics have gained the greatest attention as a method to restore the gut microbiota biodiversity in IBD patients. Probiotics are live microorganisms that, when administered in adequate amounts, can confer a health benefit on the host [9]. They can be beneficial in restoring the gut microbiota's composition, which in turn can lead to an improved digestion and absorption of nutrients, as well as improved immunity.

The major beneficial effects of probiotics have been observed to be derived from the metabolites and secreted compounds produced by live microbes rather than simply from the presence of these microorganisms themselves [10]. The compounds derived from probiotic compounds are known as postbiotics. In contrast to probiotics, postbiotics are not dependent on living microorganisms to induce health benefits [11]. The postbiotic components consist of short-chain fatty acids, exopolysaccharides, teichoic acids, vitamins, enzymes, peptides, and bacteriocins. These bioactive compounds appear to instill a wide range of health benefits, including improved immunity, reduced inflammation, and improved digestive health [12].

This review will focus on exopolysaccharides (EPSs) derived from commensal and probiotic bacteria, with a special focus on EPSs derived from *Cyanobacteria*. It will describe how EPSs' composition from different strains of probiotic bacteria differs from that of *Cyanobacteria*. The factors that induce the production of EPSs from *Cyanobacteria* will also be discussed. This review will cover the biological properties of *Cyanobacterial* EPSs regarding immuno-inflammatory responses and against pathogens as well as their role in biotechnological applications. Finally, it will provide insights into the potential of EPS in food products.

2. Role of EPS Derived from Commensal and Probiotic Bacteria in IBD

Recently, more attention has been paid to EPSs produced by probiotic bacteria such as *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, and *Streptococcus* for various applications, including medical applications. EPSs are released into the extracellular environment as capsules which help bacteria survive in extreme environmental conditions. Among their functions are protection from extreme temperature, UV-rays, aridity, salinity, unfavorable pH values, osmotic stress, phagocytosis, and chemical agents (antibiotics, heavy metals, and oxidants) [13–15]. EPSs refer to polysaccharides secreted or produced outside of bacteria during the bacterial growth phase.

These EPSs are identified as homopolysaccharides or heteropolysaccharides according to the composition of their monosaccharides. The major role of EPSs lies in the formation of complex structures by stimulating a variety of microbial interactions [16,17]. EPSs are produced during the growth process of many probiotic bacteria [18]. In some cases, EPSs are linked with the peptidoglycan via N-acetyl-muramic acid, while in other cases, they are more loosely linked and may exist as a slimy secretion.

Furthermore, they have many potential health benefits such as anti-inflammatory properties, pathogen growth-inhibitory properties, immunomodulatory activities, and the regulation of the intestinal barrier [19–21]. The immunological response can only be induced if the EPSs reach the colon intact. Numerous studies have shown that EPSs have

beneficial biological effects in modulating immune responses. Their compositions are so diverse that they induce different immunomodulatory effects according to their composition.

Palik et al. showed that EPS from *Bacillus subtilis* represents a recently discovered probiotic-derived agent that provides protection against systemic *Staphylococcus aureus* infection by increasing the production of ROS as well as limiting the inflammatory activity of immune cells. Furthermore, the authors found that *B. subtilis* EPS is a powerful antibacterial agent [22].

IBD pathogenesis is well known to be associated with increased Th1 and Th17 cells [23]. Additionally, the abnormal and imbalanced function of Treg and Th2 cells occurs at the same time as the dysregulation of cytokine production, which is associated with the development of IBD.

Matsuzaki et al. showed that EPSs stimulated the production of a specific IgA in Peyer's patch cells and influenced the Th1 and Th2 cell-mediated response in splenocytes [24] (Figure 1).

Chung et al. showed that EPSs derived from *Bacillus subtilis* restore intestinal barrier function by modulating tight junction-related proteins (claudin-1, claudin-2, and occludin) and epithelial-mesenchymal transition in DSS induced-colitis mice [17]. EPSs from *Lactobacillus plantarum* promoted colon mucosal healing and homeostasis, enhanced goblet cell differentiation, and increased Muc2 expression, which is the colon's major gel-forming mucin [25] (Figure 1).

Additionally, they modulate the differentiation of T cells in the intestinal tract, and this may result in a relief of IBD symptoms [17]. In line with these observations, B-EPS promoted splenocyte proliferation in response to anti-CD3/CD28-primed splenocytes, confirming its ability to regulate T lymphocyte activation [26].

Gorska et al. analyzed the chemical structures and immunomodulatory properties of EPSs isolated from *Lactobacilli* isolated from mice with induced IBD (IBD "+") and those obtained from healthy mice (IBD "−"). They found that EPSs produced from IBD "+" species are structurally different from those isolated from IBD "−". Further, they observed that EPSs from *L. animalis*/*murinus* 148, *L. animalis*/*murinus* 116, and *L. reuteri* 115 (IBD "+") were all immunologically silent. In addition, they found that different EPS structures leads to different immune responses by dendritic cells, suggesting that, under conditions of gut inflammation, changes in bacteria strains produce EPSs with specific motifs which are not present in lactobacilli IBD+ [27].

The EPSs isolated from *L. casei* SB27 significantly reduced the proliferation of the colon cancer cell HT-29 in vitro [28]. An EPS challenge activated the pro-apoptotic genes Bad and Bax by increasing mRNA expression, along with caspase-8 and caspase-3 [28]. The anti-biofilm activity of three distinct fragments of EPS isolated from the supernatant of *L. fermentum* has been demonstrated in vitro against *Escherichia coli* and *Staphylococcus aureus*, in addition to its anti-oxidant properties and ability to scavenge free radicals [29]. Additionally, EPSs derived from *L. paracasei* inhibit *E. coli* and *S. aureus* biofilms by acting against the quorum-sensing mechanism involved in biofilm formation [29]. Ksonzekova et al. showed that *L. reuteri* EPSs prevent the adhesion of enterotoxigenic *E. coli* to epithelial cells as well as the inflammatory response [30] (Figure 1).

Recent study has shown that EPSs isolated from *L. buchneri* can alleviate experimentally induced liver damage in mice [31]. The mice treated with EPSs also had similar levels of the cytokines TNF-α, IL-6, and IL-1β to the control group and significantly lower levels than the test group. In addition, EPSs increased the number of commensal bacteria and reduced the number of *Helicobacteraceae*, *Enterobacteriaceae*, and *Lachnospiraceae* [31] (Figure 2).

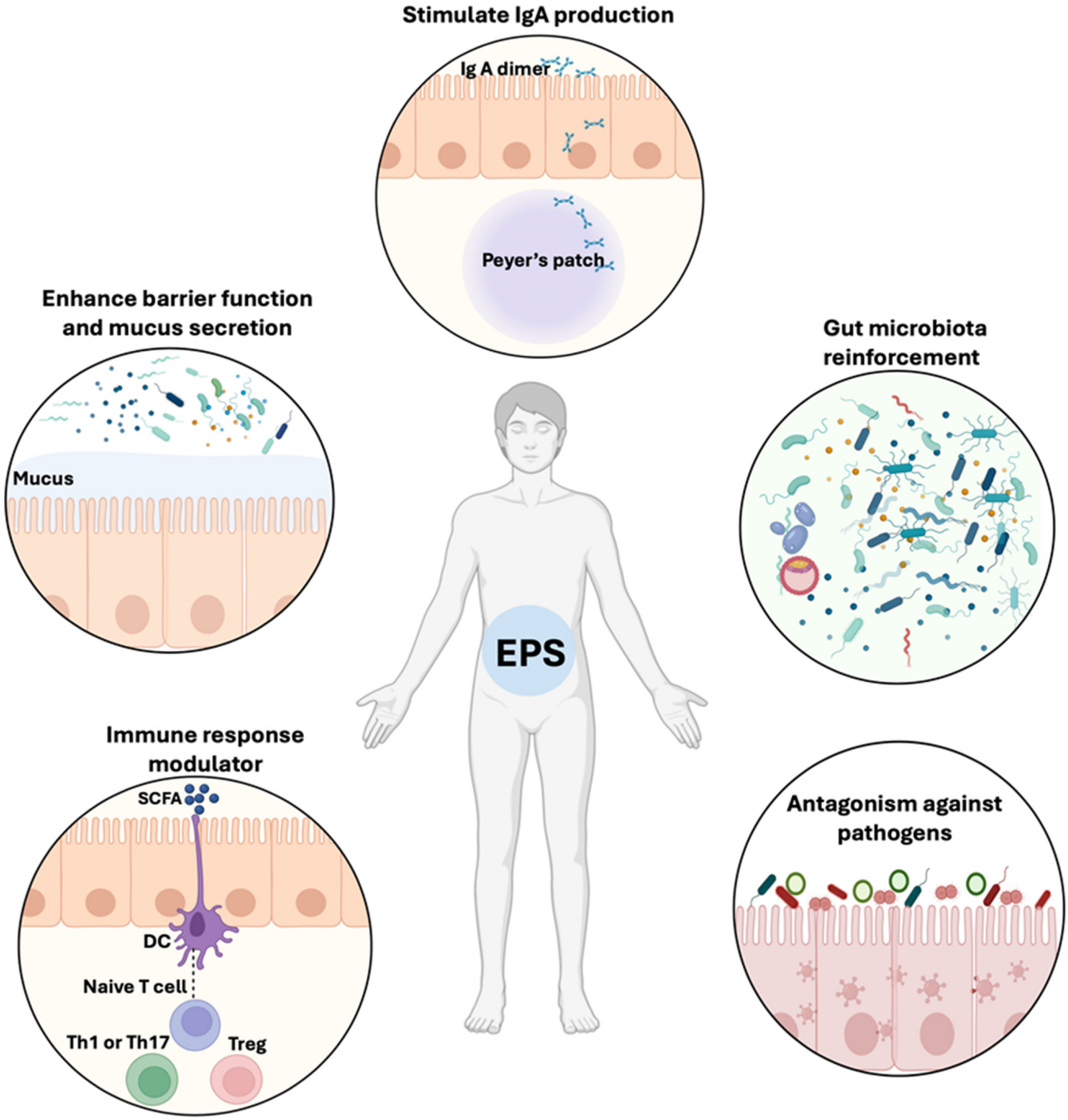

Figure 1. Schematic representation of the beneficial effects of EPSs on gut homeostasis. EPSs from commensal bacteria including *Lactobacillus* and *Bifidobacterium* are involved in the reinforcement of the gut microbiota, the elimination of pathogenic microorganisms (like *C. albicans* and enterotoxigenic *E. coli*), and the modulation of immune response through SCFA production. EPSs increase the function of the intestinal barrier and mucus secretion, as well as IgA dimer production in Peyer's Patches.

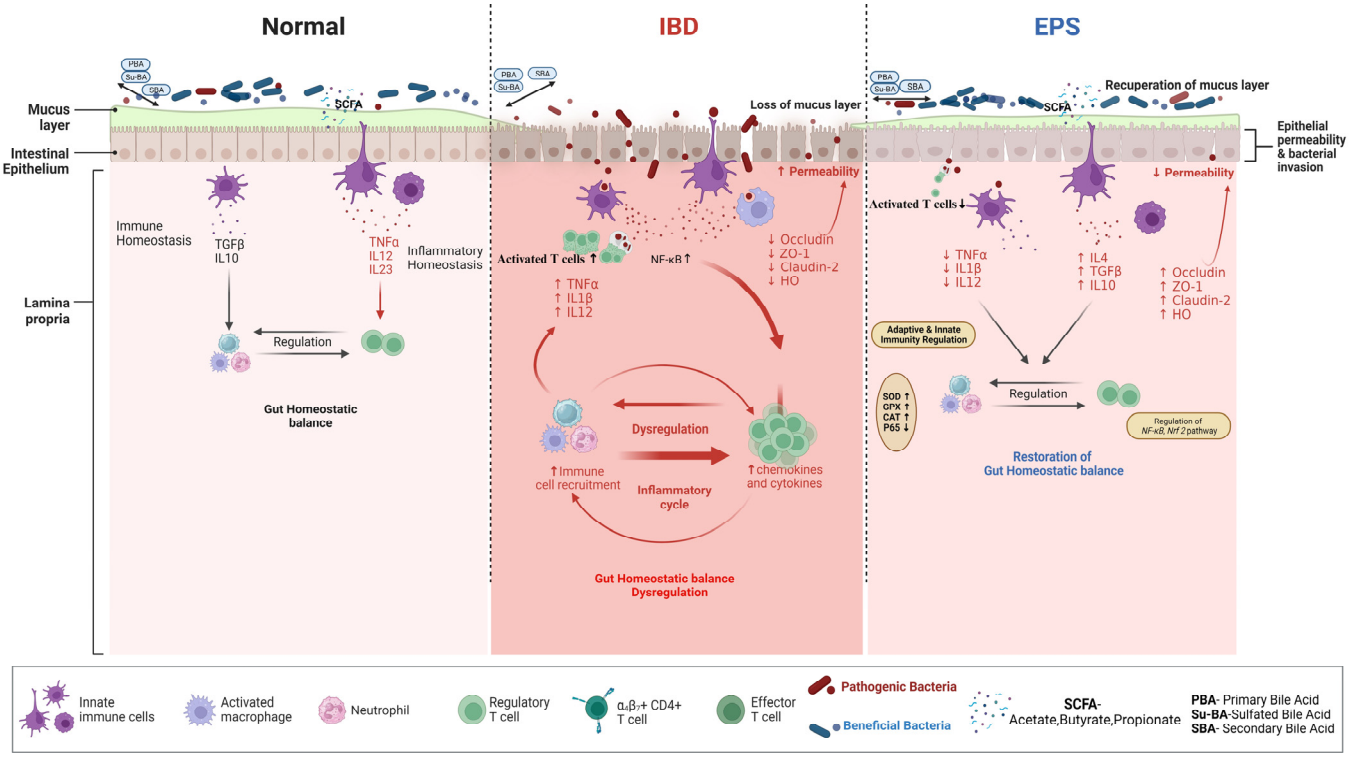

Figure 2. Schematic representation illustrates the mechanisms of EPSs' therapeutic effects on IBD. Immune tolerance maintains the gastrointestinal immune system physiological state, which ensures homeostatic balance. Inflammatory bowel disease (IBD) can cause gut dysbiosis and impaired intestinal barrier function, as well as excessive stimulation of the immune response. An imbalance in the gut microbiota population of the host contributes to leaky gut. This leads to the release of chemokines and cytokines that cause inflammation. An uncontrolled migration of several effector T cell subtypes disrupts the intestinal mucosa, effector, and regulatory T cells in IBD. In the presence of intestinal damage, pathogenic microorganisms are known to translocate from one area to another. Toxins, neuroactive substances, metabolites, and immunogenic peptides resulting from poor digestion can also pass through the leaky gut and cause an immune response and inflammation. The process of inflammation is triggered by several mechanisms, such as soluble inflammatory mediators like TNF-α, IL-1β, and IL-12, as well as cellular mediators like macrophages and cytotoxic T cells. All of these mediators work together to cause local tissue damage and to intensify the inflammation cascade that is already present. Additionally, the bile acid pool is changed under these conditions. After EPSs reach the colon and are metabolized by the gut microbiota, their effects on these receptors attenuate the production of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-12) and modulate macrophages' and helper T cells' polarization towards anti-inflammatory cytokines (IL-10, IL-4, TGF-β). In addition, the EPSs restore the altered gut microbiota community that contributes to the production of SCFAs, which in turn helps in the recovery of the tissues by strengthening the tight junction proteins (Occludin, ZO-1, HO, Claudin-2).

3. Cyanobacterial EPS

Cyanobacteria are a group of prokaryotic microorganisms that are among the oldest life forms on Earth [32]. The *Cyanobacteria* have the capability of producing energy through the process of photosynthesis, which is essential to the survival of other organisms in the water food chain [33]. Additionally, these microorganisms play a crucial role in nutrient cycles, such as the nitrogen cycle. They are involved in the process of converting atmospheric nitrogen into organic nitrogen. Furthermore, they provide a large amount of oxygen, which is essential for the survival of fish, plants, and mammals in the water food chain [34].

Cyanobacteria have been shown to synthesize biotechnological and pharmaceutical compounds with beneficial properties including anticancer, anti-inflammatory, and antibi-

otic ones. *Cyanobacteria* produce a variety of secondary metabolites since they synthesize both non-ribosomal peptides and polyketides [35]. A wide range of *Cyanobacterial* enzymes enable methylation, oxidation, and tailoring, contributing to a wide range of chemically diverse natural products [36].

Marine *Cyanobacteria* compounds are involved in a wide variety of biological interactions with bacteria, fungi, parasites, and invertebrates [37,38]. These interactions are responsible for a range of processes, such as nutrient cycling, bioremediation, and protection against predators. The beneficial effects of marine *Cyanobacteria* compounds on human tumor cell lines have been studied. Human lung cancer cells are highly sensitive to apratoxin D and symplocamide A produced by *Symploca* spp. [39]. It is believed that these compounds cause tumor cells to undergo apoptosis, or programmed cell death, thereby making them incapable of replicating [39].

Cyanobacteria have been identified as a significant source of organic compounds, including lipids, sugars, proteins, antioxidants, nucleic acids, and vitamins and minerals, that are crucial for life [40]. *Cyanobacteria* consist of highly concentrated bioactive substances, including polyunsaturated fatty acids, phycocyanin, carotenoids, peptides, and polysaccharides, and, especially, EPSs, which function as a barrier to protect them from external stresses [41].

The *Cyanobacterial* EPSs can be classified as released exo-polysaccharides (RPSs) or capsular exo-polysaccharides (CPSs). While RPSs are discharged into the extracellular environment, CPSs enclose their cells in the form of a mucilaginous layer [42].

From a chemical perspective, EPSs belong to the polysaccharide class, which is composed of high-molecular-weight biopolymers ranging from 10 to 1000 kDa [43]. To date, observed *Cyanobacterial* EPSs molecular masses have ranged from 80 to 2000 kDa [44]. The carbohydrate polymers are primarily composed of monosaccharide monomers, and they can be linked together by glycosidic bonds to form a whole structure [45] (the red caption in Figure 3A), but they may also contain non-saccharides like phosphate, lactate, acetate or glycerol [44]. Depending on the spatial orientation of this glycosidic bond, two anomers, α and β, can be obtained (Figure 3B). These anomers are stereoisomers with different specific rotations, and thus varied properties.

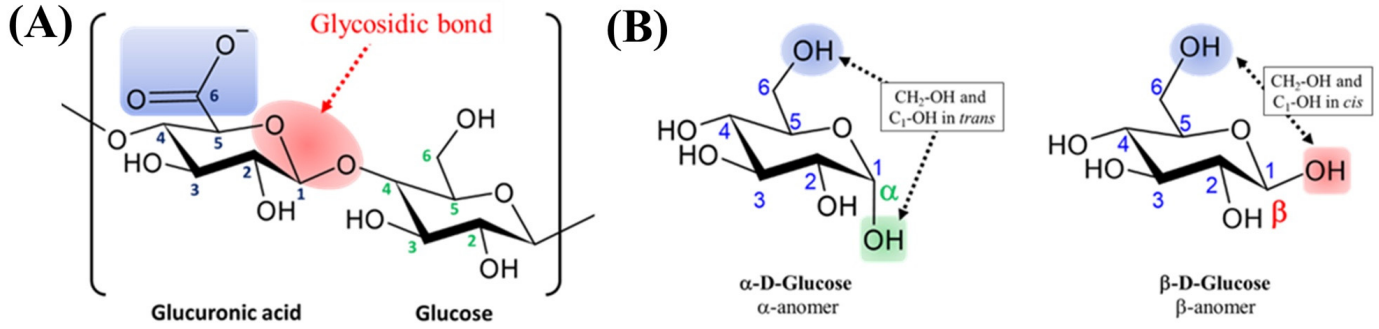

Figure 3. (**A**) Structure of Glucuronic acid/Glucose disaccharide linked by a glycosidic bond in red; (**B**) geometry of the two anomers exemplified by Glucose.

EPSs' physicochemical properties vary according to their source bacterial strain and are related to their inner chemical composition. The microorganism growth conditions affect the amount or type of heteropolysaccharide synthesis or secretion that occurs [46].

Around 75% of the *Cyanobacterial* EPSs described so far belong to the heteropolysaccharide class of biopolymers. In general, heteroglycans, such as hyaluronic acid or agarose, contain two or more different monosaccharide units. The compositions of *Cyanobacterial* EPSs consist of six or more monomers. To date, more than 13 different monosaccharides have been identified in *Cyanobacterial* EPSs: hexoses (glucose, galactose, mannose, and fructose), pentoses (ribose, arabinose, and xylose), deoxyhexoses (fucose, rhamnose, and methyl rhamnose), and uronic acids (glucuronic and galacturonic acids) [47]. Acetylated

or amino-sugars have also been observed, such as N-acetyl glucosamine, 2,3-O-methyl rhamnose, 3-O-methyl rhamnose, 4-O-methyl rhamnose, and 3-O-methyl glucose [48]. Methyl, pyruvyl, and succinyl groups can be present, as well as sulfate groups [42]. Some reports also deal with the presence of polypeptides enriched with amino-acids (glycine, alanine, valine, leucine, isoleucine, and phenylalanine) [49] or proteins rich in aspartic or glutamic acids [50]. Thus, *Cyanobacterial* EPSs have displayed variable compositions, which explains their broad biological and physico-chemical range of applications [44].

To date, around 200 *Cyanobacterial* EPS chemical compositions have been elucidated. Collected reports on *Cyanobacterial* EPSs' monomeric compositions underlined the presence of uronic acid units (Table 1). In addition to the fact that these uronic acid units are rarely found in EPSs produced by other types of bacteria, their presence is a crucial characteristic of *Cyanobacterial* EPSs. The EPSs produced by *Cyanobacteria* also contain sulphate groups. This is a feature that is unique to bacteria but which is also found in the EPSs produced by archaea and eukaryotes.

Uronic acids are a class of sugar acids bearing both carbonyl and carboxylic acid functional groups. The main representative of uronic acids is glucuronic acid, produced from the oxidation of the alcohol function in position 6 in glucose (Figure 3A). The pKa of the carboxylic acid moiety of glucuronic acid measured in a complex structure such as heparin ranged from 2.79 to 3.13 [51], which is similar to that of its monomeric form. In biological conditions, uronic acids are negatively charged.

Table 1. Overview of monosaccharide compositions and their biological applications for different *Cyanobacterial* spp.

Cyanobacteria spp.	Structure	Monosaccharide Composition	Biological Application	Reference
Nostoc punctiforme	Pullulan-like polysaccharide	Glucose, Glucuronic Acid	Carbohydrate storage, desiccation tolerance	[52]
Calothrix marchica	Heteropolysaccharide	Xylose, Fructose, Rhamnose, and Glucuronic Acid	Biosorbent	[53]
Nostoc sp. HK-01	Exopolysaccharide	Fucose, Rhamnose, Arabinose, Galactose, Glucose, Mannose, Xylose, Uronic Acid, Glucuronic Acid	Protect the cells against ion influx and water efflux.	[54]
Anabaena sp. PC-7120	Exopolysaccharide	Fucose, Rhamnose, Arabinose, Galactose, Glucose, Glucuronic Acid	Protect the cells against ion influx and water efflux.	[55]
Anabaena laxa	Polysaccharide complex	Arabinose, Ribose, Rhamnose, Fucose, Xylose, Galactose, Galacturonic Acid	Stimulation on monocytes and granulocytes.	[56]
Nostoc commune	Sulfated Polysaccharide	Glucose, Galactose, Xylose	Wound-healing and anti-allergic cosmetics.	[57]
Gloeocapsagelatinosa	EPS	Arabinose, Fucose, Rhamnose, Xylose, Galactose, Glucose, Mannose, Glucoronic Acid, Galacturonic Acid	Enhanced Anti-oxidant, metal chelating and thermostable.	[58]
Leptolyngbya sp.	EPS	Mannose, Arabinose, Glucose, Rhamnose, Galacturonic Acid	Food and pharmaceutical applications.	[59]
Oscillatoria sancta	Exopolysaccharide	Mannose, Fuccose, Ribose, Arabinose	Biocontrol of plant-infecting fungal pathogens.	[60]

Table 1. *Cont.*

Cyanobacteria spp.	Structure	Monosaccharide Composition	Biological Application	Reference
Arthrospira platensis strain MMG-9	EPS	Fructose, Fucose, Galactose, Glucose (+), Mannose, Rhamnose, Ribose, Xylose, Uronic Acid	-	[61]
Nostoc carneum	EPS	Xylose (+), Glucose, Sul, Uronic Acid	Excellent Anti-oxidant	[62]
Anabaena cylindrica 10C	EPS	Galactose, Glucose, GlucoseA, Mannose, Fucose, Xylose	PHB+PHV Production	[63]
Anabaena flos-aquae	EPS	Glucose, Galactose, Xylose, Ribose	Recycling of growth media	[64]
Chlorogloeopsis spp.	EPS	Rhamnose, Galactose, Arabinose, Glucose, Mannose, Fucose	Inhibition of Avarol toxicity	[65]
Chroococcus submarinus	EPS	Rhamnose, Galactose, Arabinose, Glucose, GlucoseA, GalactoseA, Mannose, Fucose, Xylose, Ribose	-	[66]
Leptolyngbya sp.	EPS	Rhamnose, Glucose, Galactose, GalactoseA, Fucose, Ribose, Xylose	Persistence on lithoid surfaces	[67]
Nostoc insulare	EPS	Arabinose, Glucose, GlucoseA	High viscosity	[68]
Oscillatoria spp.	EPS	Glucose, Xylose, Ribose	Intrinsic viscosity	[69]

Sulfated sugars are also highly present in *Cyanobacterial* EPSs (around 85% of all elucidated structures contain sulphated monomers). In physiological conditions, sulphated biopolymers are anionic (pKa around 2.6, being more acidic than uronic acid moieties). The presence of sulphated sugars and uronic acid units increases the hydrophilicity of the biopolymers, thereby increasing their solubility in water [70].

Both the sulphate groups and the uronic acids contribute to the anionic nature of EPSs, conferring a negative charge on the overall macromolecule and also modulating its adherence properties. Moreover, these anionic moieties are also known for their ability to chelate metallic cations. This capacity is correlated with the steric hindrance around the anionic parts. This hinders their availability, their distribution within the macromolecule, and the subsequent geometry of their metallic complexes [71–74].

On the other hand, some monomers increase EPSs' lipophilicity. Deoxy sugars, such as fucose (6-deoxy-L-galactose) or rhamnose, in which one hydroxyl group has been replaced by a hydrogen atom, are highly present in *Cyanobacterial* EPSs. Fisher et al. reported that the chemical structure of Chroococcus minutus B 41.79 EPS was composed of 14 different units, including uronic acids and deoxy sugars [75]. According to the review by De Philippis and Vincenzini (27), the EPS produced by Cyanothece IR20 was composed by more than 80% of deoxy sugars, which conferred a high hydrophobicity to the EPS [76].

Acetylated sugars, where the hydroxyl group has been acetylated, are more lipophilic than the corresponding HO-monomer. The presence of peptides also increases their lipophilicity.

Overall, the hydrophile/lipophile balance of EPSs depends on the proportion of hydrophilic monomers (uronic acids and sulphated ones) versus the amount of acetylated and desoxy monomers. It is notable that cyanothece CE4 EPS collected from Italian saltworks displayed a high proportion of uronic acids (80.1%) along with deoxy sugars [76]. This composition, with its high level of lipophilic EPSs in combination with a strong charged moiety, contributes to the emulsifying capacity of such EPSs.

Overall, the composition of *Cyanobacterial* EPSs is essential for controlling their hyddophilic/lipophilic balance (HLB)'s compactness or flexibility. This determines their rheological properties and capacity to interact with other compounds such as cations [42,77–80]. Figure 4 summarizes the components that influence EPS HLB.

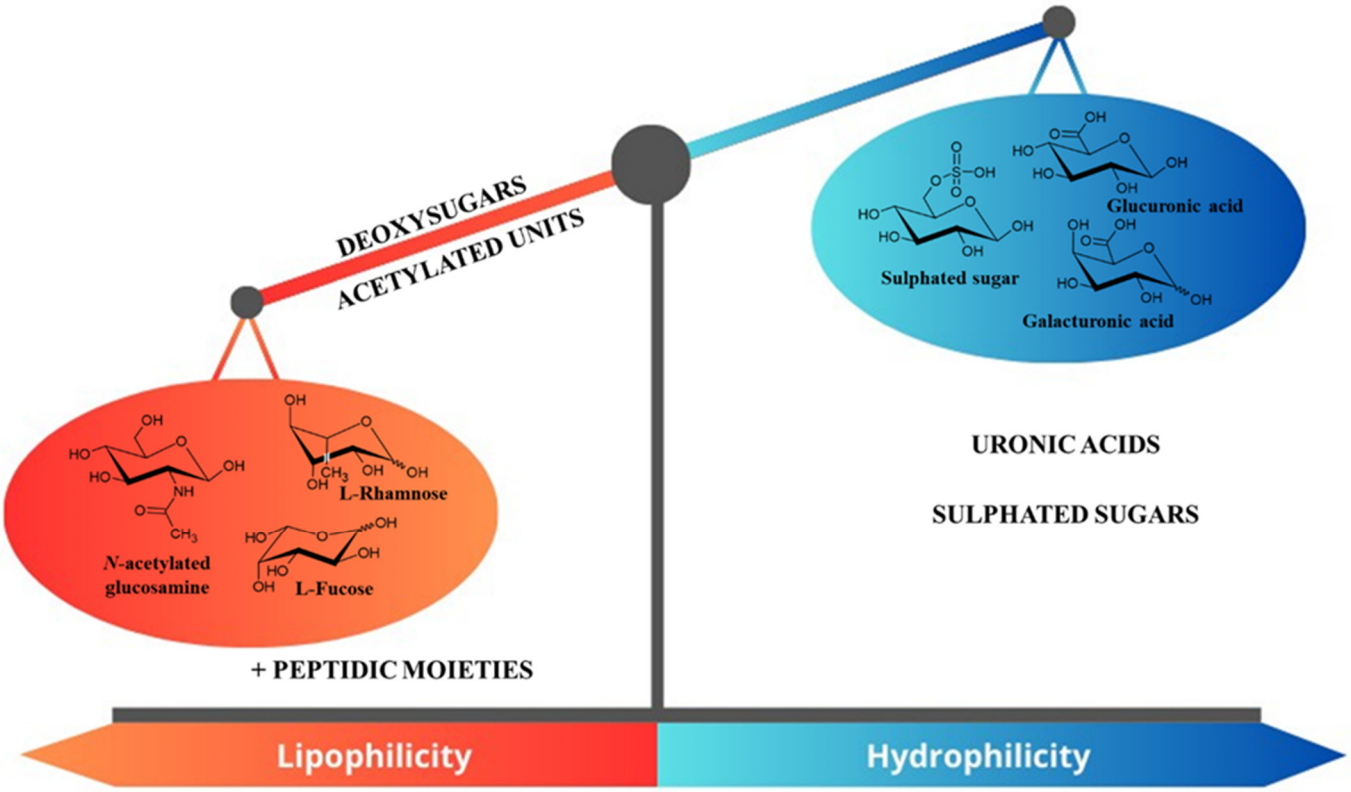

Figure 4. Summary of monomers that influence the global HLB of *Cyanobacterial* EPS.

It was found that polymers will acquire a negative charge from uronic acids, and pullulan-like polysaccharides from *Cyanobacteria* (*Anabaena* and *Nostoc*), which resemble the yeast polysaccharide pullulan in structure, are capable of withstanding desiccation and are also used as reserve food sources [81,82]. The EPSs of glucose, galactose, glucuronic acid, and succinoglycan have been used in *Synechocystis* spp. to stimulate cell motility, which can lead to gliding motility, which is a kind of movement that is necessary for the chemotactic access of the cells. *Cyanobacteria*'s EPSs are rich in glucose, galactosamine, and glucosamine. The initial exploration of *Cyanospira capsulata* EPSs revealed novel N-acetylglucosamine (GIcNAc) and the rare acidic sugar 4-O-[1-carboxyethyl] mannose (4-1 actylman).

A major limitation of *Cyanobacterial* EPSs is that they are difficult to characterize because of their unique structural complexity. To determine the specific chemical structures and contents of EPSs, extensive optimization of the EPS characterization process and sophisticated analytical techniques are required. Since *cyanobacterial* EPSs are heterogeneous, a thorough investigation might be challenging. This heterogeneity is caused by variations in their chain length and complex branching patterns. In addition, it is necessary to establish effective extraction and purification techniques for each common *Cyanobacterial* EPS. The use of different strain-specific EPS extraction methods results in different approaches to using them as standard practice for other *Cyanobacterial* EPSs. It has been found that the genetic manipulation of *cyanobacteria* has a significant effect on EPS production. Therefore, a number of investigations have been carried out to modify *Cyanobacterial* EPSs' characteristics and production [83–85]. However, our understanding of the genetic and enzymatic systems associated with EPS formation is still a very small portion of what has been derived from the complete mechanism.

4. The Factors That Induce the Production of *Cyanobacterial* EPS

This section will focus specifically on the role of temperature, light, and the availability of nutrients such as phosphorus, carbon, or nitrogen, as well as water accessibility, salinity, and pH. These parameters can influence *Cyanobacteria* development and, therefore, EPS

production. In the case of a bioreactor, rheological factors are also important to consider. Indeed, EPS production affects the culture medium. Aeration and/or mixing need to be controlled to ensure the homogeneity of the solution and the distribution of the nutrients. Each parameter must be managed to enhance *Cyanobacteria* growth and develop an efficient bioprocess for *Cyanobacterial* EPS production.

It is important to note that *Cyanobacterial* EPSs exhibit a high degree of chemical diversity. From a process point of view, any change in environmental conditions and the culture process could impact the structure of the produced EPS. This section will present selected studies, discuss their effects on *Cyanobacterial* growth, and attempt to rationalize the data generated by these studies. Globally, these sometimes-divergent reports underline the challenge of establishing a performant bioprocess.

Cyanobacteria are light-powered. The light content influences *Cyanobacteria* growth, as the phototrophic metabolism provides the energy needed for *Cyanobacteria* development. Illumination is one of the major limiting factors controlling *Cyanobacterial* growth [18]. Light intensity (µE), light/dark cycles (L/Dh), and light quality are essential parameters to conduct the bioprocess. Very few reports deal with a systematic study of light influence. It was observed that, in the described processes, some processes used continuous illumination with low or high intensities. In contrast, others selected a balanced L/D cycle up to 12 h/12 h. [82,86,87]. Idris et al. reported that blue-light LED is a stimulus for the growth of the microalgae *Chlorella vulgaris* [88]. However, the conclusion is not so evident for *Cyanobacteria*. Yang et al. assessed the role of light in the growth of *Cyanobacteria* [89]. In this study, the authors established the relationship between two harmful *Cyanobacterial* spp. (*Anabaena* spp. and *Microcystis* spp.) and their associated bacterial assemblages during large-scale cultivation under varied illumination conditions [89]. They performed the experiments under natural light, blue-filtered light, and green-filtered light, as well as under dark conditions. *Anabaena* spp. and *Microcystis* spp. were cultivated in a transparent acrylic tank containing BG-11 medium and a nitrogen source composed of sodium nitrate and ferric ammonium citrate. A set of parameters was recorded over 15 days. The natural light condition (control group) displayed considerable cell growth over the first growth phase of *Cyanobacteria* (from 0 h to 144 h), which was attributed to the proliferation of *Anabaena* spp. Then, from 144 h to 360 h, the cell proliferation of *Microcystis* spp. occurred under natural light conditions but also under blue-light filtered conditions. Moreover, the bacterial communities' compositions were significantly influenced by the irradiated wavelength range. This experiment proved that the dominant *Cyanobacterial* genus in the cultivation system can be tuned by varying the light regimen.

However, light's effect cannot be decorrelated with its impact on environmental and water quality parameters. Indeed, a differential pathway to nitrogen assimilation has been observed between natural light illumination and a blue-filtered light. Nitrogen reductase was applied under natural light conditions, whereas nitrogenase (i.e., the alternative pathway) can be activated under blue-filtered light. In addition, Yang et al. rationalized the impact of environmental conditions on their obtained bacterial communities using a NMDS plot (Figure 5) [89]. The authors clustered the experimental data based on the similarity of this microorganism's composition. The arrows represent the influences of parameters on cluster formation. This study strongly suggests the role of nutrients (orthophosphate PO_4^{3-}, nitrite NO_2^-, and nitrate NO_3^- anions and ammonium NH_4^+), the quantity of dissolved oxygen (DO), the influence of pH, and the importance of rheological properties (turbidity). Depending on the values of these parameters, the bacterial community profile strongly differed, including its EPS content.

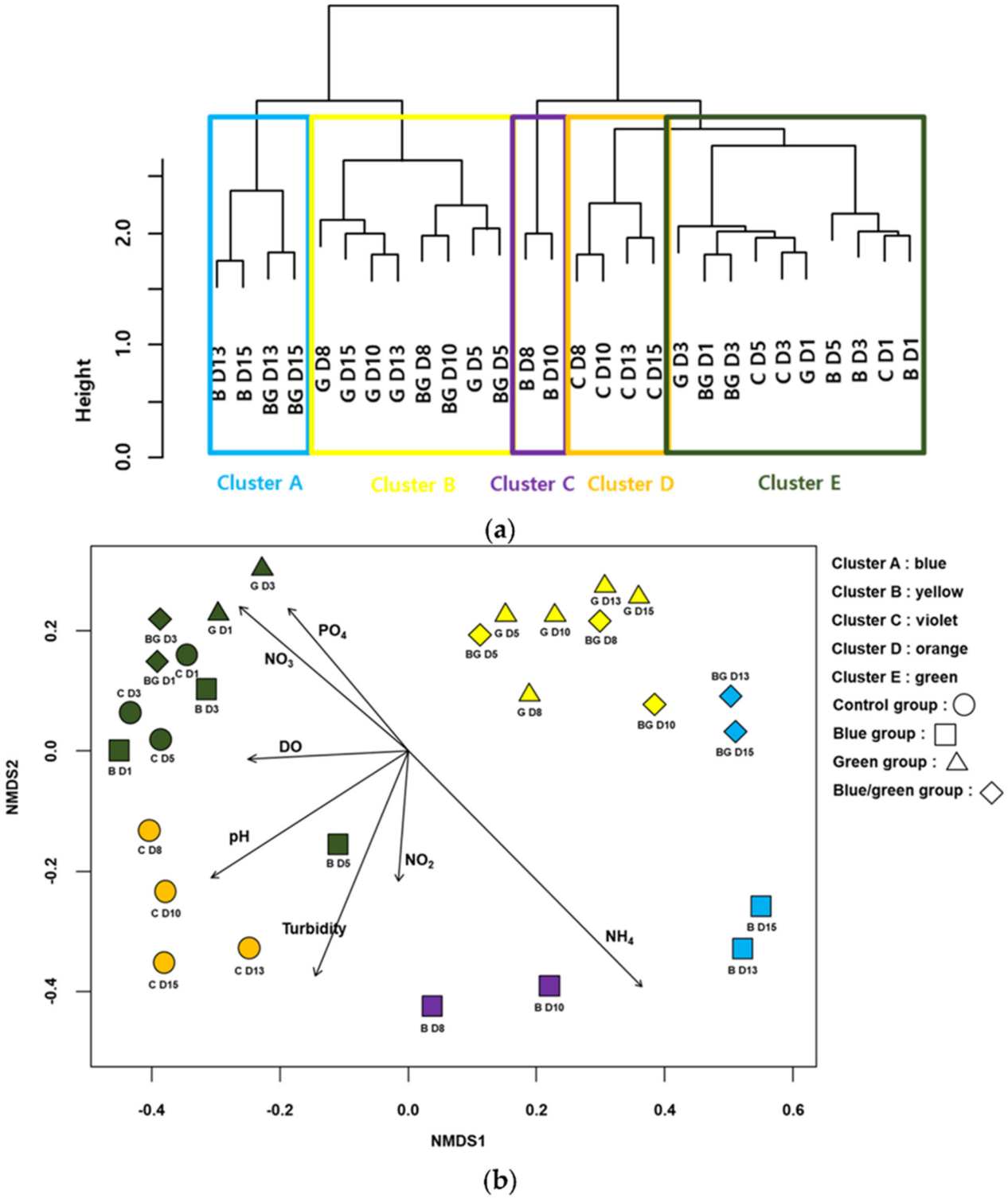

Figure 5. Cluster analysis based on *Cyanobacteria*-associated bacteria assemblages. (**a**) Non-metric multidimensional scaling (NMDS) ordination of samplings with *Cyanobacteria*-associated bacteria assemblages. (**b**) Arrows indicate water quality variables significantly related to assemblage compositions ($p < 0.05$). The longer the arrow length, the higher the correlation coefficients with the NMDS axis. The first letter in the figures indicates the experimental condition (i.e., C: control, B: blue film, G: green film, BC: blue and green light) and the number represents the experimental date (D1: 24 h, D3: 72 h, D5: 14 h, D8: 196 h, D10: 240 h, D13: 312 h, and D15: 360 h). Data from [89] (CC BY 4.0).

The salinity of water is also a crucial parameter. Generally, under salt stress (about [NaCl]~0.5 M), *Cyanobacteria* produce larger amounts of EPS [65,90,91], but some reports exhibited no effect of a NaCl concentration increase or even a negative effect [76,92].

Temperature is a well-known propeller for many enzymatic processes. *Cyanobacteria* are quite special, as they can adapt to a wide range of temperatures, from below 15 °C to above 40 °C. Generally, in bioprocesses, a constant temperature within the mesophile range is applied. Very few reports deal with the effect of temperature on *Cyanobacteria* growth and composition. In 2018, an experimental approach was conducted by Savadova et al. [93]. Studying four strains (*Planktothrix agardhii*, *Aphanizomenon gracile*, *Chrysosporum bergii*, and *Sphaerospermopsis aphanizomenoides*), the authors proved that temperature had an impact on the growth rate of all tested *Cyanobacteria*. Temperature-modulated toxins and oligopeptide production in the strains were studied. Moreover, alien strains adapted well to temperature changes and were more productive than native strains [93]. These conclusions are similar to those of Moreno [94] but contrast with those of Otero and Vincenzini [95], who did not observe any impact of temperature variation. In addition, Nicolaus reported a slight decrease in performance for EPS production in *Spirulina* spp. at temperatures over 30 °C [65].

Carbon content is also an interesting parameter to consider. In 2020, Dineshbabu et al. [96] reported that *Phormidium valderianum* BDU 20041, a marine filamentous cyanobacterium, fixed the carbon and displayed a higher growth rate and biomass productivity from 3% to 15% CO_2 compared to ambient air. However, predicting how communities will respond to changes in CO_2 concentration is species-dependent [97]. A particular case concerns the development of subaerial phototrophic biofilms. Due to their ability to fix carbon dioxide (CO_2), *Cyanobacteria* can colonize bare stone and form subaerial biofilms, mainly composed of a matrix of self-produced extracellular polymeric substances (EPS) [98]. Variations in atmospheric CO_2 levels may affect the physiology of these microorganisms, as they use CO_2 as a source of carbon. However, in a subaerial biofilm, experimental studies proved that EPSs produced by biofilms, measured as the carbohydrate fraction, did not differ clearly between low or high carbon content. This was in relation to either the total or relative number of CFUs [98]. This result highlighted the difference between *Cyanobacteria* and microalgae, as green microalgae of the genus *Chlorella* were significantly affected by elevated CO_2 concentrations [99].

In 2019, Heimann et al. reported the effect of CO_2 on the growth performance and biochemical profiles of the freshwater diazotrophic cyanobacterium *Tolypothrix* sp., for which 15% CO_2-supplementation stimulated carbohydrate production by at least 35% compared to the control, whereas the protein levels did not change. In this study, it is notable that the quality of water, in particular its contamination with metallic residues, did not impact the production rate of *Cyanobacteria* and their metabolites [100].

Overall, many interconnected parameters influence *Cyanobacterial* EPS production. The temperature, pH, nutrients, illumination, and rheology need to be controlled to develop an efficient bioprocess for such *Cyanobacterial* EPSs (Figure 6).

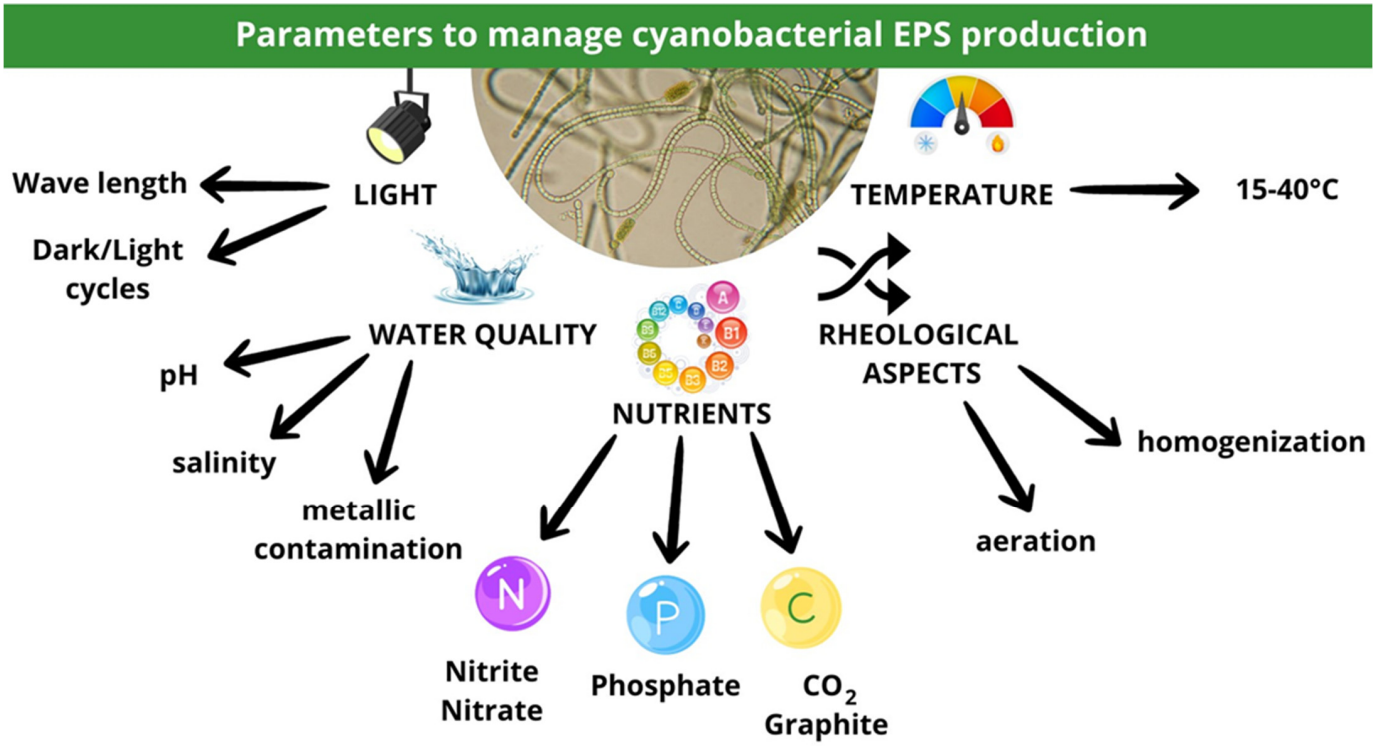

Figure 6. An overview of the main parameters controlling *Cyanobacterial* EPS production.

5. Biological Properties of *Cyanobacterial* EPS on Pathogens

A variety of biological activities can be attributed to *Cyanobacterial* EPSs, depending on their monosaccharide composition as well as the anionic charged molecules [101]. Different studies have revealed that *Cyanobacterial* EPS promotes the growth of certain bacteria, inhibits the growth of others, and acts as a barrier against pathogens [102]. Microbial EPSs are considered non-digestible dietary fibers and are used as a prebiotic supplement to regulate gut microbial homeostasis [103]. *Cyanobacterial* EPSs are a fermentable polysaccharide that is active both as a fermentable polysaccharide and as an antimicrobial against several pathogenic bacteria and fungi [104,105]. The antimicrobial properties of EPS are attributed to the presence of sulphate groups and anionic charges within them. For example, EPSs from various *Arthrospira* spp. have broad spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria. Different monosaccharide compositions of *Cyanobacterial* EPSs are presumably responsible for the differences in antibacterial activity [106].

Bhatnagar et al. reported that EPSs from *Anabaena* spp., and *Tolypothrix* tenuis have inhibitory properties against wound pathogens such as *E. coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. This is possibly due to the presence of a sulphate group in the EPSs [107]. The EPSs of *Gloeocapsa* spp. Were shown to possess strong antibacterial activities against pathogenic bacteria including *S. aureus*, *E. coli*, and *Salmonella enteritidis*, as well as *Candida albicans*. The EPSs of *Synechocystis* spp. inhibited the growth of *P. aeruginosa* [108]. There is also evidence that *Cyanobacterial* EPSs can act as a quorum-sensing inhibitor, thereby preventing pathogenic microbes from forming biofilms [109]. For example, *Phormidium marinum* EPSs prevent the formation of *C. albicans* biofilm, rather than promoting the growth of this fungus [110].

Synechococcus spp. EPSs, being derived from a marine cyanobacterium, have been found to have anti-quorum sensing abilities against aquatic bacterial pathogens such as *Vibrio harveyi* and *Vibrio vulnificus*. This is due to the fact that they inhibit the complex *Vibrio* biofilm architecture [111]. The EPSs of *Chlorococcus* spp. R-10 have been shown to have antibacterial activity against *S. aureus* and *B. subtilis*, both Gram+ bacteria, and minimal inhibition of *C. albicans*, which is a Gram+ bacterium. It has been shown that three Gram+

bacteria (*E. faecalis*, *B. cereus*, and *S. epidermidis*) as well as two Gram-negative bacteria (*P. hauseri* and *A. calcoaceticus*) were resistant to EPS effects [112].

Recently, researchers have revealed the complex structure of polysaccharides found in *Cyanobacteria*'s cell wall. The sulfated polysaccharides found in marine *Cyanobacteria* are rare and rarely generated. They possess probiotic, prebiotic, immunological, and antiviral properties that make them unique [113,114]. Sulfated polysaccharides' varied structural makeup shows exceptional resistance to the COVID-19 virus (SARS-CoV-2) [115]. These polysaccharides inhibit virus transcription and translation in the host cell. This enhances the host's antiviral response as they interfere with the virus's attachment, adsorption, and reproduction within the host cell [116,117]. Sulfated polysaccharide calcium spirulan from *Arthrospira platensis* chelates calcium ions and has antiviral action while maintaining its unique molecular structure [118,119]. EPSs from *Synechocystis* spp. and *Gloecapsa* spp. Gacheva 2007/R-06/1 have shown antibacterial activity against food-borne diseases. A fibrin network is formed by hydrophilic EPSs with anionic groups on their surfaces in bleeding wounds [107]. It was found that EPSs derived from *Anabaena* spp. and *Tolypothrix* spp. showed sustained inhibition of wound infections caused by *E. coli*, *S. aureus*, *P. aeruginosa*, and *B. licheniformis* [119].

6. Biological Properties of *Cyanobacterial* EPS on Immune/Inflammatory Responses

Cyanobacterial EPS modulates host immune responses, including cytokines and the immune response. *Cyanobacterial* EPSs can boost the immune response activity, including macrophages, natural killer cells, and T cells, which can lead to an increased immune response and a stronger defense against infections and illnesses [120,121]. EPSs can reduce inflammation and prevent overreactions of the immune system in allergic reactions, autoimmune diseases, and chronic inflammation [122]. Some *Cyanobacterial* EPSs neutralize inflammation-causing oxidative stress [123]. In addition to their antioxidant properties, *Cyanobacterial* polysaccharides have potential uses in food and medicine [124,125]. As a way to reduce ROS production, stronger DPPH and hydroxyl radical scavenging activities as well as increased levels of SOD, GSH, and MDA in *N. flagelliforme* cells have been observed in *Cyanobacterial* EPSs [125].

It is challenging to determine the relationship between the structure of *Cyanobacterial* polymers and their biological activity due to a lack of structural knowledge [126]. Recently, an analysis of monosaccharide profiles using chromatographic techniques indicated that the anionic charge and presence of sulfate groups explain their substantial biological activity [126,127]. Several studies have shown that *Cyanobacterial* EPSs have a favorable anti-oxidative effect such as those of *Anabaena* spp. [128], *Arthrospira* spp. [129], *Isochrysis galbana* [130], *Nostoc carneum* [62], *Porphyridium* spp., [131] *P. cruentum* [132], *Rhodella reticulata* [133], *Schizochytrium* spp. [134], and *Spirulina platensis* [135,136], and their sulphate groups exhibits high antioxidant properties with sulphate content [137].

Two EPS fractions (EPSa and EPSb) from *B. animalis* RH have been shown to possess strong antioxidative properties, in an in vivo model of aging mice, induced by D-galactose. Both EPS fractions prevented linoleic acid peroxidation and exhibited strong free radical scavenging activity in serums, livers, and brains, suggesting excellent anti-aging properties [138].

The cell wall polysaccharides of *Cyanobacteria* have recently been studied in an attempt to uncover their interesting complex structure. In *Leptolyngbya* spp. EPS, monosaccharides including glucose, rhamnose, mannose, and glucose are present along with proteins (24.20% ± 1.54), lipids (9.36% ± 1.21), and carbohydrates (66.44% ± 2.14) [59]. The monosaccharide backbone of *Porphyridium cruentum*'s cell wall polysaccharides (xylose, galactose, glucose, and glucuronic acid) has immune-stimulating properties in prawns. These monosaccharides have been shown to stimulate the non-specific immune response by enhancing hyaline, granular cells, and phagocytosis, as well as respiratory burst activity [139]. Additionally, sulphated polysaccharides and their derivatives minimize drag as well as being hypolipidaemic or hypoglycemic. Aside from that, sulphated polysac-

charides and their derivatives also act as hypolipidaemics or hypoglycaemics and drag-reducers [140,141]. Probiotic *Lactobacillus* EPS stimulates both pro-inflammatory (Th1) and anti-inflammatory (Th2, Treg) functions and regulates inflammation by decreasing TNF-α-induced IL-8 production in epithelial Caco-2 cells [142,143].

The gut plays a major role in immune responses. Some *Cyanobacterial* EPSs can improve gut health by serving as prebiotics and fostering the development of healthy gut microbiota [144]. *Cyanobacterial* EPS may influence inflammatory reactions. It is possible for these characteristics to vary depending on the strain of *Cyanobacteria* and the composition of the EPS [145]. Some *Cyanobacterial* EPSs inhibit the synthesis of different pro-inflammatory mediators (cytokines and chemokines) [146]. The effect of *Cyanobacterial* EPS on the inflammatory process can be modulated by its ability to regulate the immune response. In addition, EPSs are capable of reducing tissue damage and excessive inflammation by balancing and regulating the immune system [147].

EPSs from *Cyanobacteria* have the ability to reduce the body's oxidative stress by acting as antioxidants. Oxidative stress may contribute to inflammatory reactions, and research has shown that EPSs may reduce inflammation by reducing oxidative stress [148]. *Cyanobacterial* EPSs act as a protective agent against inflammatory disorders such as rheumatoid arthritis and IBD. They alleviate the intensity of the illness and its symptoms [146]. Inflammation can be controlled by maintaining a healthy gut microbiome [149]. The modulation of immune responses to allergens by *Cyanobacterial* EPS has shown potential for reducing allergy responses and allergic inflammation [150].

Cyanobacterial EPSs can inhibit pathogen development and invasion [101]. It has been observed that *Nostoc* EPS can stimulate macrophages to release pro-inflammatory cytokines like TNF-α and IL-6, as well as other critical immune components like prostaglandins (PG) and NO, which indicates that this biopolymer enhances early congenital immunological responses [151]. EPSs, which are significant adhesins, positively impact the ability of beneficial bacteria to colonize the intestinal epithelium. Intestinal epithelial cells attach to EPS, making it possible for microorganisms such as *Lactobacillus* and *Bifidiobacterium* to colonize the gastrointestinal tract and avoid dysbiosis-induced disruption in the gut microbiome. Additionally, beneficial microbiota can adhere to the intestinal mucosa and prevent pathogen adhesion, as well as prevent the growth of harmful intestinal bacteria [152]. A balanced immune response can be regulated by *Cyanobacterial* EPS, thus avoiding immune responses that are either hyperactive or repressed, which could increase inflammation over time [147].

7. Role of *Cyanobacterial* EPS in Biotechnological Applications

EPSs from *Cyanobacteria* have attracted interest due to their diverse biotechnological uses. These applications cover a variety of industries, such as food processing, agriculture, bioremediation, medicine, and more. Potential uses for *Cyanobacterial* EPSs include thickeners, stabilizers, and gelling agents in the food and pharmaceutical sectors. They are used in pharmaceutical formulations and food items to enhance their consistency and texture.

8. The Potential Applications of *Cyanobacterial* EPS in the Food Sector

Cyanobacterial EPSs are non-toxic carbohydrate polymers which exhibit a high structural complexity and biocompatibility, making them useful for food industrial applications such as emulsifiers, stabilizers, and gelling agents, as well as for increasing viscosity in products such as ice cream, cakes, jellies, beverages, and sauces [101].

Due to its stable physical properties, *Cyanobacterial* EPS can be used as a texture enhancer substance for fermented products, especially fermented milk, and to enhance the mouth-feel properties of sauces, soups, and desserts [153]. EPS derived from *Cyanobacteria* is similar to commercial-grade xanthan gum in terms of its pseudoplasticity, elasticity, and rheological properties. Thus, EPS can serve as a stabilizer agent in packed foods. For example, EPSs from *Spirulina platensis* and *Anabaena* spp. are potential alternatives to xanthan gums [119]. *Cyanobacteria* such as *Anabaena*, *Nostoc*, and *Spirulina* are known

for their nutritional properties. Thus, EPSs can be used as food additives. Additionally, *Cyanobacterial* EPSs can be used as emulsifiers in foods, and stabilize water- and oil-based components like mayonnaise and salad dressings [154]. In some food items, EPS can be an alternative to fat and lower the total fat level while preserving desired sensory qualities. To improve the texture of some foods without gluten, *Cyanobacterial* polypeptides can be added. They can be added to dairy-free and vegan goods to enhance their creamy texture, such as plant-based milk substitutes [155].

Many of the EPSs produced by *Cyanobacteria* have prebiotic qualities that encourage the development of healthy gut microbiota. They can be added to functional meals and drinks and improve customer perception. Food items that use EPSs as a source of dietary fiber should have increased nutritional value. They can be added to functional meals and drinks to offer advantages to the body including stronger immunity and better digestive health [156]. By increasing the taste of sweetness in meals, *Cyanobacterial* EPSs can reduce the amount of excess sugar in food products. Many EPSs can improve flavor perception, which makes them useful for both savory and sweet food items. To promote freshness and moisture retention in baked goods, EPSs from *Lactobacilli* spp. enhance the texture and reduce the stalling rate in bread and crumb hardness [157]. Similarly, *Cyanobacterial* EPSs can improve product quality and shelf life.

Food packaging materials used with polysaccharides, proteins, and fats are considered edible packaging materials. These materials can be applied directly to food as a thin coating or direct wrapping without any alteration or loss of nutrients [158]. The biophysical and structural properties of *Cyanobacterial* EPSs make them resistant to environmental gases and yield high tensile properties and elongation, which can prevent mechanical damage to a small degree [159]. To increase the shelf life and decrease spoiling of some commercial foods, EPSs can be used to make edible films and coatings. This is especially important when it comes to fruits, vegetables, and sweets. For instance, *Synechocystis* spp. EPSs have about a 73.3% emulsification index along with inhibition of fungus, *Fusarium verticillioides* (70.2%), and *Fusarium* spp. (61.4%), which is an excellent alternative to plastic food covering [160]. This nature of edible films/coatings acts as a barrier to moisture and other environmental reactions that can reduce the volatile or sensitive nutritive qualities of foods [161]. This includes flavors, vitamins, and antioxidants [161]. Films made with such physically stable EPSs from *Cyanobacteria* prevent deterioration and extend the shelf-life of foods. In addition, *Chlorella vulgaris* biomass has been used in cookie production as a natural colorant and texture enhancer and as a substitute for food-grade synthetic chemicals [162].

9. The Potential Applications of *Cyanobacterial* EPS in the Pharmaceutical Sector

Many *Cyanobacterial* EPSs have been used as a source of film covers for drug encapsulation and the administration of certain medications due to their stability and biocompatibility [163]. Hydrogels can be created from *Cyanobacterial* EPSs which can be used for a variety of applications. The biocompatibility of EPSs and hydrogel-controlled release characteristics enable the creation of drug delivery systems with customized release profiles. The chemical and biological characteristics of *Cyanobacterial* EPSs are comparable to mammalian glycosaminoglycan. These properties make them attractive as pharmaceutical excipients and for drug delivery systems [164].

EPSs are widely used in healthcare and cosmetic products due to their ability to retain moisture and condition the skin. Wound healing can be aided by their capacity to produce bioactive substances, enable gas exchange, and maintain a moist wound environment [165]. EPS hydrogels using $FeCl_3$ gelation have enhanced biocompatibility and significant wound healing abilities. EPS hydrogels derived from *Nostoc* aid in the migration of fibroblasts, which is crucial to the advancement of the regeneration process. They help restore and restructure injured skin [81,107].

EPSs conjugated with medication can effectively target tissue, are well tolerated by tissues, and are less likely to result in tissue damage or adverse reactions, particularly in

cases of gastrointestinal disorders. Along with this, EPS-conjugated nanoparticles can be customized to recognize and bind specific cell types or tissues [166,167]. A hybrid hydrogel was produced by combining the *Thamniochloris variabilis* EPS with synthetic polyethene-glycol diacrylate (PEGDa), which embeds detoxification enzymes with catalytic cysteine residues such as the detoxification enzyme thiosulfate-cyanide sulfur transferase (TST). This shows the possibility of fabricating effective, functional, and non-cytotoxic hydrogels with enzymatic activity for therapeutic applications [163]. In the microencapsulation of vitamin B12 and EPS (extracellular carbohydrate polymer) from *Cyanothece* spp., CCY 0110 was combined with Arabic gum, which resulted in a highly intestinal release of vitamin B12 [168].

The ability to regulate the release of drugs is an important feature of many therapeutic applications, which can be enhanced with the use of *Cyanobacterial* EPS suspensions [42]. Drugs can be protected against environmental conditions that limit their efficiency, including pH variations, enzymatic breakdown, temperature, and exposure to light, by being encapsulated inside an EPS coat [169]. This prolongs medications' shelf life and stability. Aside from that, carboxyl groups in EPSs contribute to the production of hydrogels with pH-sensitive swelling behavior [163]. These hydrogels may exhibit an increased pore size at basic pH and permit protein release from the matrix in the intestinal environment [163]. This may improve protein drug absorption [163]. Hydrogels are three-dimensional, hydrophilic polymers that absorb and retain water. The hydrogel derived from *Cryptococcus laurentii* 70766 EPSs exhibited comparable gelation kinetics, swelling ratios, rheological characteristics, and an extended degradation profile. This was compared to traditional hydrogels based on alginate. Furthermore, there was no discernible negative impact on the survival and proliferation of human macrophage and fibroblast cells [170]. Unlike traditional hydrogels, which are often made from synthetic molecules, recent research has demonstrated that *Cyanobacterial* EPSs have the potential to be employed in the creation of hydrogels that are both eco-friendly and biocompatible. *Cyanobacterial* EPS-mediated hydrogels have been demonstrated to be effective as delivery systems for different medications [163].

Some *Cyanobacterial* EPSs possess mucoadhesive properties, making them effective for mucosal medical administration [171]. These properties enhance the absorption and bioavailability of medication by enabling drug carriers to stick to mucosal surfaces. EPSs can contribute to stabilizing nanoparticles in a colloidal state and reducing metal content [172]. Additionally, EPS-tagged drugs are easily delivered to the appropriate target sites, simply adhering to the mucosal surfaces, resulting in the drug reaching and reacting with them [173].

10. Conclusions

The Western diet is highly associated with processed foods and saturated fats which trigger IBD, a chronic inflammatory disease. This type of diet is characterized by a high caloric content that is associated with a significant decrease in gut microbiota biodiversity. EPSs are one of the strategies to enhance the gut microbiota and immune-inflammatory response deregulation in IBD patients. EPSs, also known as prebiotics, are produced by commensal bacteria such as *Lactobacillus* and *Bifidobacterium*. They are critical in several aspects, including strengthening the gut microbiota, eliminating pathogenic microorganisms, modulating immune responses, and promoting gut health. EPS improves the function of the intestinal barrier and mucus secretion, as well as IgA dimer production in Peyer's patches. These approaches enable improving the abundance of beneficial bacteria populations in the gut, and can help reduce the risk of developing IBD. Additionally, *Cyanobacteria* can be considered a promising source of novel EPSs and have potential pharmaceutical and therapeutic applications. The majority of *Cyanobacterial* EPSs belong to the heteropolysaccharide class of biopolymers, consisting of six or more monomers. The presence of uronic acids and sulphate groups in EPSs is an important factor that gives EPSs an anionic charge that is not seen in other prokaryotic species. This feature may impact their physico-chemical

characteristics and biological properties. *Cyanobacteria* EPSs have antimicrobial properties due to the presence of sulphate groups and anionic charges. Further, EPSs from *Cyanobacteria* have a wide range of biotechnological applications. These applications include food processing, agriculture, bioremediation, medicine, and many more. *Cyanobacterial* EPSs can be used as thickeners, stabilizers, and gelling agents in the food and pharmaceutical industries. They are used in pharmaceutical formulations and food items to enhance consistency and texture. In terms of future research directions, the development of scalable procedures will be key to improving the efficiency of EPS production in the future. This includes characterizing and evaluating *Cyanobacteria* viability and their EPS production on a commercial scale. In addition, it involves refining and improving techniques [174]. There is still much to be explored in relation to the ecological significance of *Cyanobacterial* EPSs in freshwater and aquatic habitats, as well as biofilms. Understanding how these EPSs support *Cyanobacteria* resistance in various environmental conditions will facilitate the development of high-quality and significant *Cyanobacteria*-associated items. Considering how EPSs might affect *Cyanobacteria*'s adherence to surfaces and their ability to form biofilms, as well as their interaction with other microorganisms under various conditions, it would be important to look at the role of EPSs in biofilm formation and structure for a better understanding of EPS function [175]. The development of novel methods for the characterization and use of *Cyanobacterial* EPSs could be achieved due to innovations in the fields of microbiology, biotechnology, chemistry, and materials science. The present review focuses on the role of EPS in IBD, with a special focus on EPSs derived from *Cyanobacteria*. This review also covers the biological properties of *Cyanobacterial* EPSs in immuno-inflammatory responses and against pathogens as well as its role in biotechnological applications. Overall, *Cyanobacterial* EPSs have therapeutic potential against IBD due to their anti-inflammatory and immunoregulatory properties that can reduce inflammation, regulate the immune response, and restore gut microbiota. Thus, EPSs could be expected to be used in the diet and lifestyle of IBD patients.

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