



HAL
open science

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

Devaprakash Manoharan, Sivakumar Natesan, Muriel Billamboz, Samir Jawhara

► To cite this version:

Devaprakash Manoharan, Sivakumar Natesan, Muriel Billamboz, Samir Jawhara. Role of Bacteria-Derived Exopolysaccharides in Inflammatory Bowel Disease with a Special Focus on Cyanobacterial Exopolysaccharides. *Advances in Applied Microbiology*, 2024, 4 (1), pp.250-274. 10.3390/applmicrobiol4010017. hal-04454375

HAL Id: hal-04454375

<https://hal.science/hal-04454375v1>

Submitted on 4 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Review

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

Devaprakash Manoharan ¹, Sivakumar Natesan ¹, Muriel Billamboz ^{2,3} and Samir Jawhara ^{4,5,6,*}

¹ Department of Molecular Microbiology, School of Biotechnology, Madurai Kamaraj University, Madurai 625021, Tamil Nadu, India; devprakashm3@gmail.com (D.M.); microshivaak@gmail.com (S.N.)

² INSERM, CHU Lille, Institut Pasteur Lille, U1167-RID-AGE—Facteurs de Risque et Déterminants Moléculaires des Maladies Liées au Vieillessement, University of Lille, 59000 Lille, France; muriel.billamboz@junia.com

³ Laboratory of Sustainable Chemistry and Health, JUNIA, Health and Environment, 59000 Lille, France

⁴ CNRS, UMR 8576-UGSF—Unité de Glycobiologie Structurale et Fonctionnelle, INSERM U1285, 59000 Lille, France

⁵ Faculty of Medicine, University of Lille, 59000 Lille, France

⁶ CHU Lille, Service de Parasitologie Mycologie, Pôle de Biologie Pathologie Génétique, 59000 Lille, France

* Correspondence: samir.jawhara@univ-lille.fr; Tel.: +33-(0)3-2062-3546

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



Citation: Manoharan, D.; Natesan, S.; Billamboz, M.; Jawhara, S. Role of Bacteria-Derived Exopolysaccharides in Inflammatory Bowel Disease with a Special Focus on *Cyanobacterial* Exopolysaccharides. *Appl. Microbiol.* **2024**, *4*, 250–274. <https://doi.org/10.3390/applmicrobiol4010017>

Academic Editor: Ian Connerton

Received: 4 December 2023

Revised: 11 January 2024

Accepted: 15 January 2024

Published: 23 January 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

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-1 β 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).

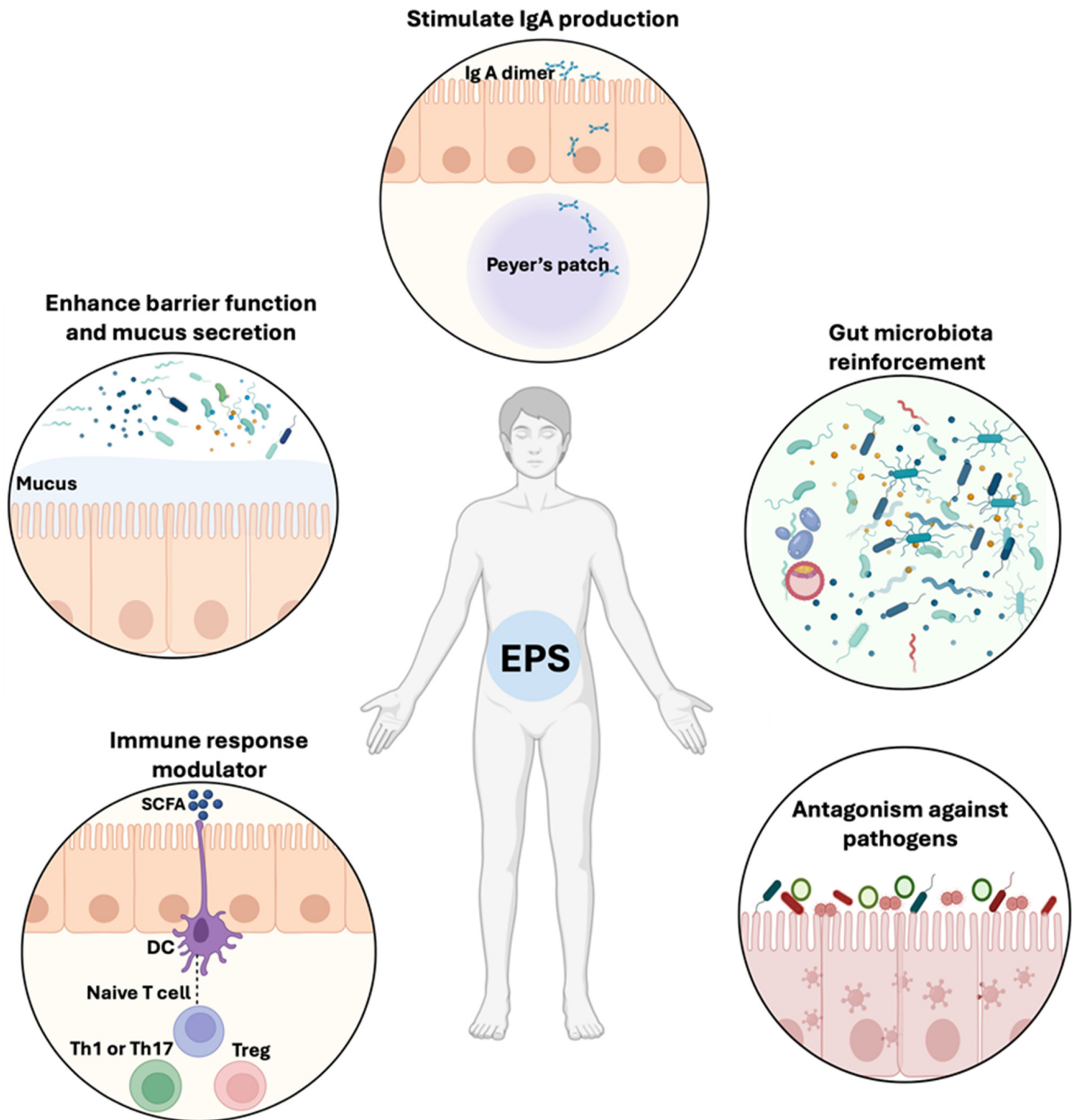


Figure 1. Schematic representation of the beneficial effects of EPSs on gut homeostasis. EPSs from commensal bacteria including *Lactobacillus* and *Bifidobacterium* are involved in the reinforcement of the gut microbiota, the elimination of pathogenic microorganisms (like *C. albicans* and enterotoxigenic *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.

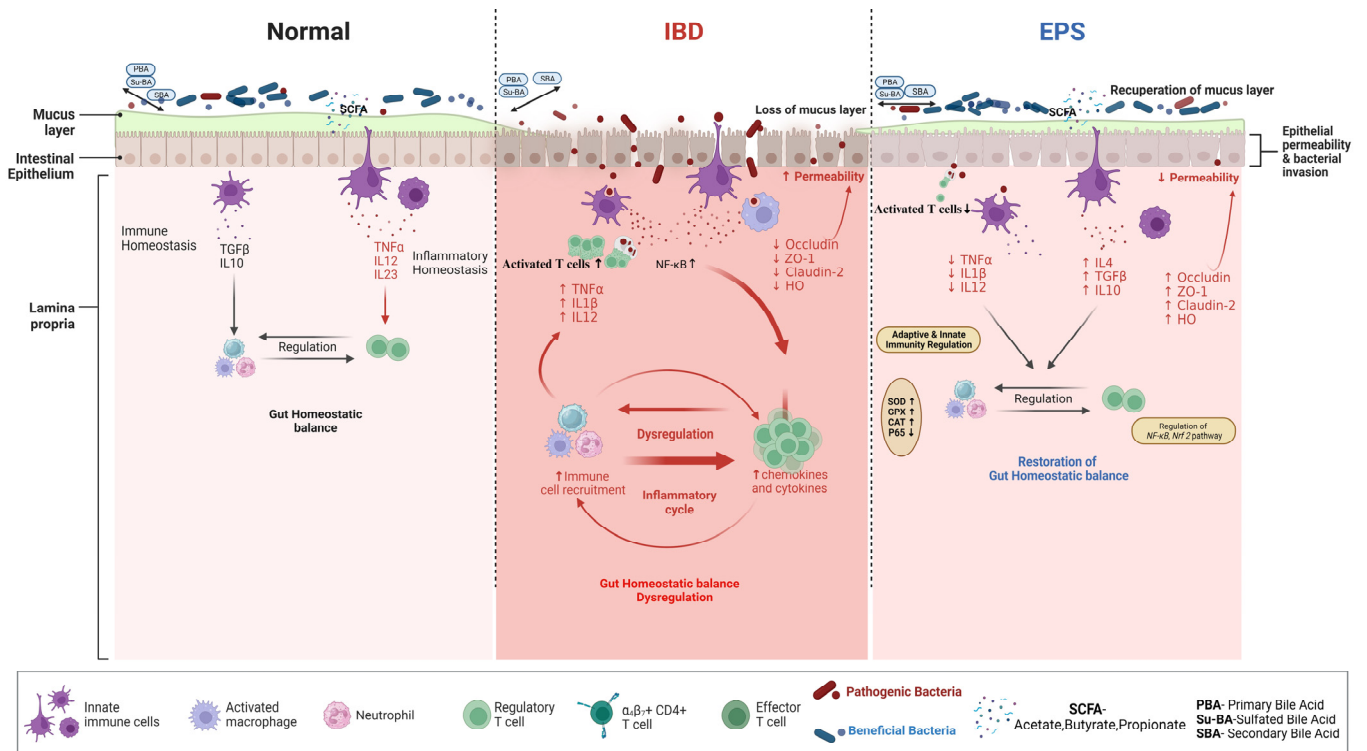


Figure 2. Schematic representation illustrates the mechanisms of EPSs' therapeutic effects on IBD. Immune tolerance maintains the gastrointestinal immune system physiological state, which ensures homeostatic balance. Inflammatory bowel disease (IBD) can cause gut dysbiosis and impaired intestinal barrier 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-1 β , 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-1 β , 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.

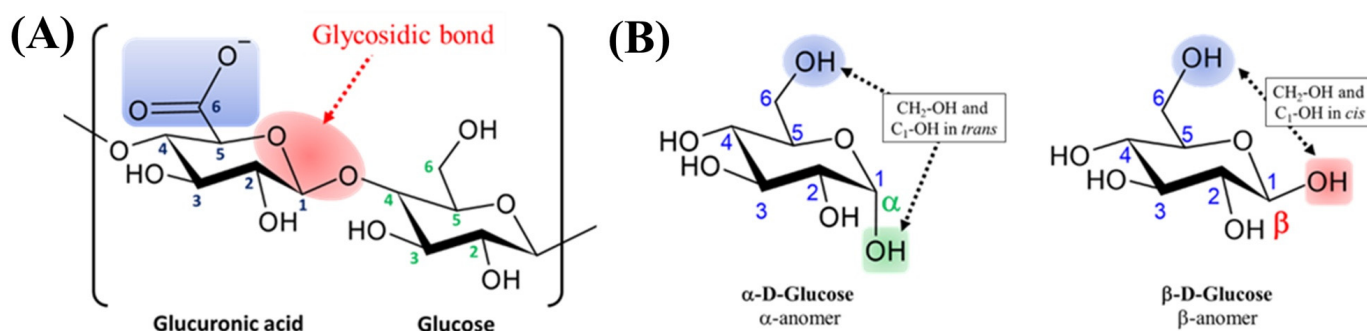


Figure 3. (A) Structure of Glucuronic acid/Glucose disaccharide linked by a glycosidic bond in red; (B) geometry of the two anomers exemplified by Glucose.

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

Table 1. Cont.

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

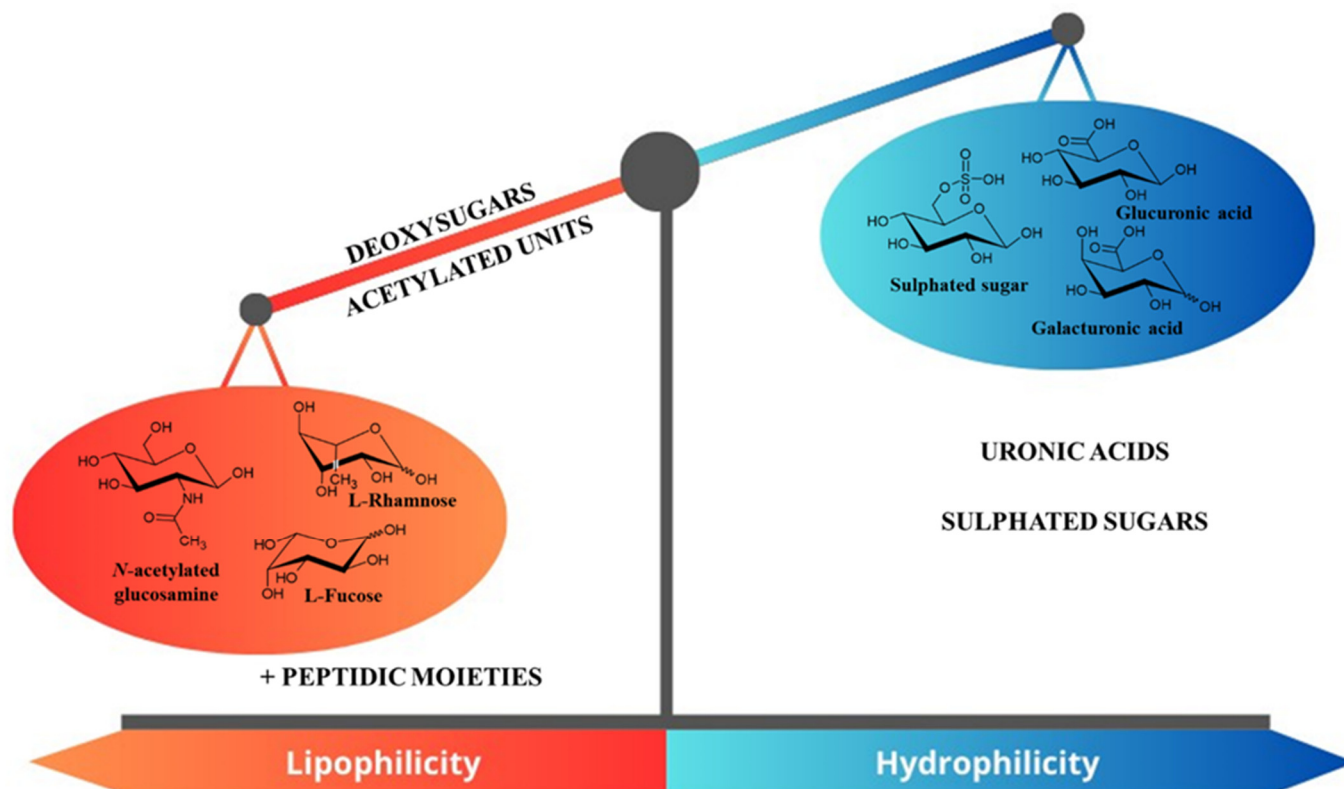


Figure 4. Summary of monomers that influence the global HLB of *Cyanobacterial* EPS.

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 (GlcNAc) 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 decoupled 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.

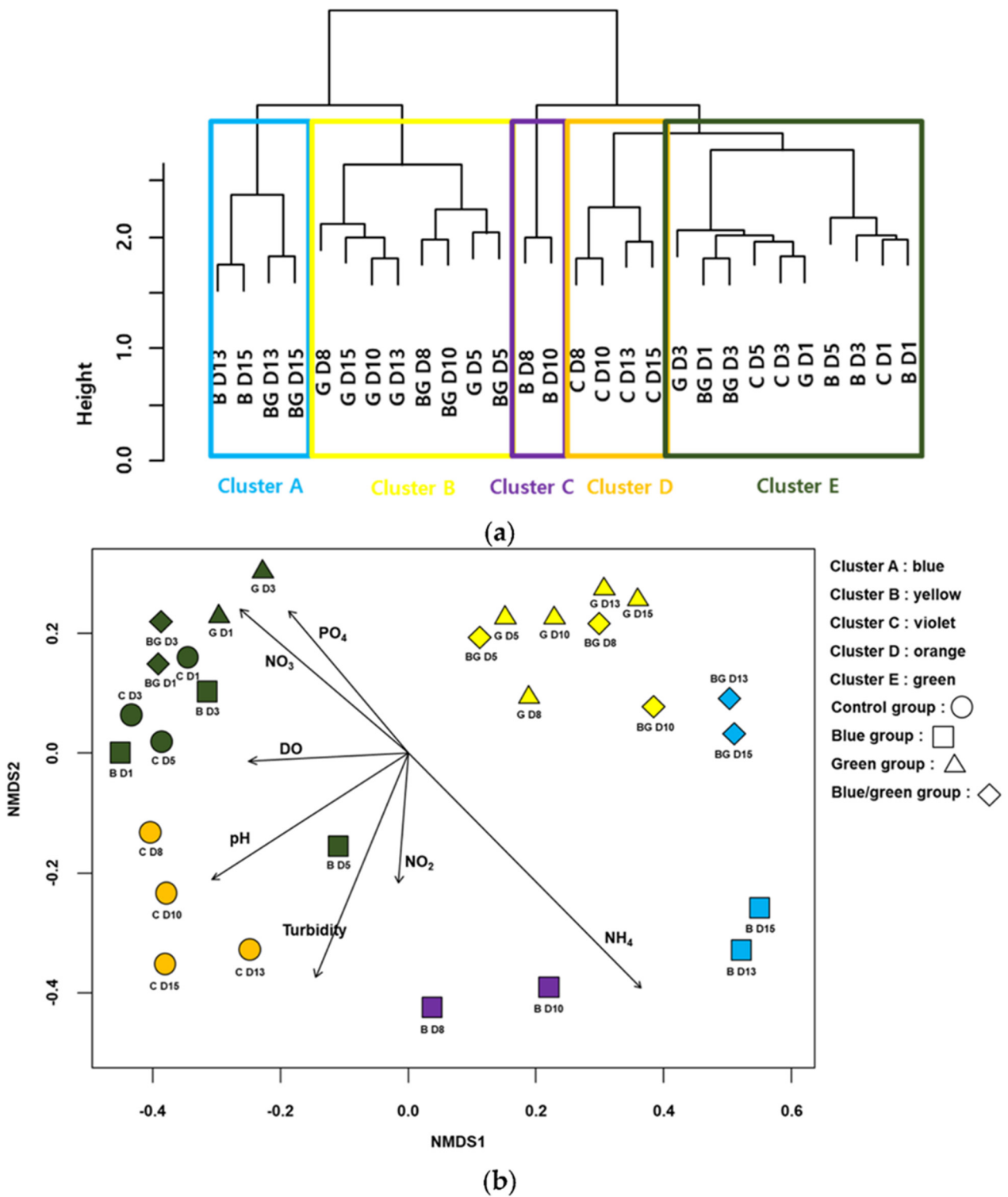


Figure 5. Cluster analysis based on *Cyanobacteria*-associated bacteria assemblages. (a) Non-metric multidimensional scaling (NMDS) ordination of samplings with *Cyanobacteria*-associated bacteria assemblages. (b) Arrows indicate water quality variables significantly related to assemblage compositions ($p < 0.05$). 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*, *Chrysochloris 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% CO₂ compared to ambient air. However, predicting how communities will respond to changes in CO₂ concentration is species-dependent [97]. A particular case concerns the development of subaerial phototrophic biofilms. Due to their ability to fix carbon dioxide (CO₂), *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 CO₂ levels may affect the physiology of these microorganisms, as they use CO₂ 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 CO₂ concentrations [99].

In 2019, Heimann et al. reported the effect of CO₂ on the growth performance and biochemical profiles of the freshwater diazotrophic cyanobacterium *Tolypothrix* sp., for which 15% CO₂-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).

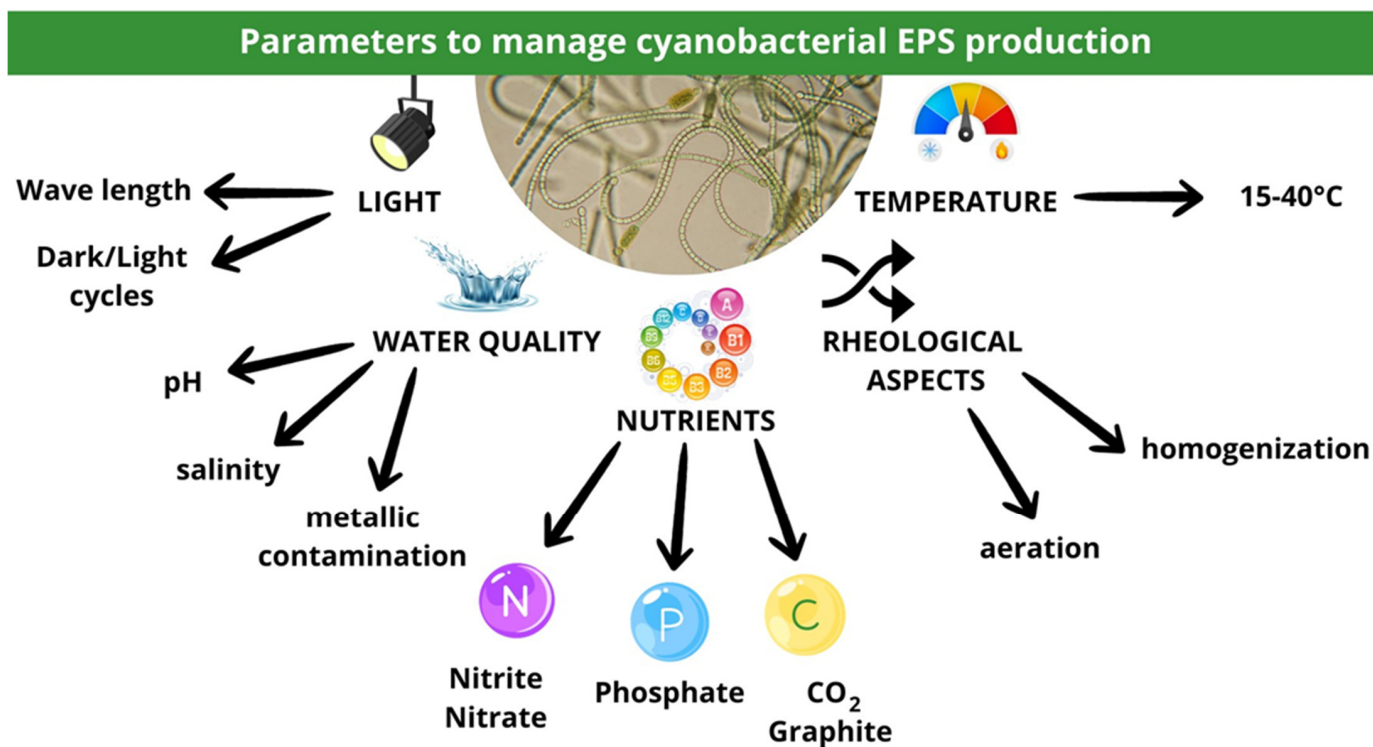


Figure 6. An overview of the main parameters controlling *Cyanobacterial* EPS production.

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% \pm 1.54), lipids (9.36% \pm 1.21), and carbohydrates (66.44% \pm 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 FeCl₃ 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 polyethyleneglycol 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 *Cyanotheca* 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.

Author Contributions: D.M., S.N., M.B. and S.J. writing—original draft preparation; S.J. writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Heyman, M.B.; Kirschner, B.S.; Gold, B.D.; Ferry, G.; Baldassano, R.; Cohen, S.A.; Winter, H.S.; Fain, P.; King, C.; Smith, T.; et al. Children with early-onset inflammatory bowel disease (IBD): Analysis of a pediatric IBD consortium registry. *J. Pediatr.* **2005**, *146*, 35–40. [[CrossRef](#)] [[PubMed](#)]
2. Lewis, J.D.; Abreu, M.T. Diet as a Trigger or Therapy for Inflammatory Bowel Diseases. *Gastroenterology* **2017**, *152*, 398–414.e6. [[CrossRef](#)] [[PubMed](#)]
3. Hildebrandt, M.A.; Hoffmann, C.; Sherrill-Mix, S.A.; Keilbaugh, S.A.; Hamady, M.; Chen, Y.Y.; Knight, R.; Ahima, R.S.; Bushman, F.; Wu, G.D. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* **2009**, *137*, 1716–1724.e1-2. [[CrossRef](#)] [[PubMed](#)]
4. Graham, C.; Mullen, A.; Whelan, K. Obesity and the gastrointestinal microbiota: A review of associations and mechanisms. *Nutr. Rev.* **2015**, *73*, 376–385. [[CrossRef](#)] [[PubMed](#)]
5. Lo, C.H.; Khandpur, N.; Rossato, S.L.; Lochhead, P.; Lopes, E.W.; Burke, K.E.; Richter, J.M.; Song, M.; Ardisson Korat, A.V.; Sun, Q.; et al. Ultra-processed Foods and Risk of Crohn's Disease and Ulcerative Colitis: A Prospective Cohort Study. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, e1323–e1337. [[CrossRef](#)]
6. Ji, Y.; Sakata, Y.; Tso, P. Nutrient-induced inflammation in the intestine. *Curr. Opin. Clin. Nutr. Metab. Care* **2011**, *14*, 315–321. [[CrossRef](#)] [[PubMed](#)]

7. Laugerette, F.; Vors, C.; Geloën, A.; Chauvin, M.A.; Soulage, C.; Lambert-Porcheron, S.; Peretti, N.; Alligier, M.; Burcelin, R.; Laville, M.; et al. Emulsified lipids increase endotoxemia: Possible role in early postprandial low-grade inflammation. *J. Nutr. Biochem.* **2011**, *22*, 53–59. [[CrossRef](#)]
8. Jawhara, S. Healthy Diet and Lifestyle Improve the Gut Microbiota and Help Combat Fungal Infection. *Microorganisms* **2023**, *11*, 1556. [[CrossRef](#)]
9. Martin, R.; Langella, P. Emerging Health Concepts in the Probiotics Field: Streamlining the Definitions. *Front. Microbiol.* **2019**, *10*, 1047. [[CrossRef](#)]
10. Maguire, M.; Maguire, G. Gut dysbiosis, leaky gut, and intestinal epithelial proliferation in neurological disorders: Towards the development of a new therapeutic using amino acids, prebiotics, probiotics, and postbiotics. *Rev. Neurosci.* **2019**, *30*, 179–201. [[CrossRef](#)]
11. Vinderola, G.; Sanders, M.E.; Salminen, S. The Concept of Postbiotics. *Foods* **2022**, *11*, 1077. [[CrossRef](#)] [[PubMed](#)]
12. Martyniak, A.; Medynska-Przeczek, A.; Wedrychowicz, A.; Skoczen, S.; Tomasik, P.J. Prebiotics, Probiotics, Synbiotics, Paraprobiotics and Postbiotic Compounds in IBD. *Biomolecules* **2021**, *11*, 1903. [[CrossRef](#)] [[PubMed](#)]
13. Casillo, A.; Lanzetta, R.; Parrilli, M.; Corsaro, M.M. Exopolysaccharides from Marine and Marine Extremophilic Bacteria: Structures, Properties, Ecological Roles and Applications. *Mar. Drugs* **2018**, *16*, 69. [[CrossRef](#)] [[PubMed](#)]
14. Knowles, E.J.; Castenholz, R.W. Effect of exogenous extracellular polysaccharides on the desiccation and freezing tolerance of rock-inhabiting phototrophic microorganisms. *FEMS Microbiol. Ecol.* **2008**, *66*, 261–270. [[CrossRef](#)]
15. Wang, J.; Salem, D.R.; Sani, R.K. Extremophilic exopolysaccharides: A review and new perspectives on engineering strategies and applications. *Carbohydr. Polym.* **2019**, *205*, 8–26. [[CrossRef](#)]
16. Yan, J.K.; Wang, W.Q.; Wu, J.Y. Recent advances in Cordyceps sinensis polysaccharides: Mycelial fermentation, isolation, structure, and bioactivities: A review. *J. Funct. Foods* **2014**, *6*, 33–47. [[CrossRef](#)]
17. Chung, K.S.; Shin, J.S.; Lee, J.H.; Park, S.E.; Han, H.S.; Rhee, Y.K.; Cho, C.W.; Hong, H.D.; Lee, K.T. Protective effect of exopolysaccharide fraction from *Bacillus subtilis* against dextran sulfate sodium-induced colitis through maintenance of intestinal barrier and suppression of inflammatory responses. *Int. J. Biol. Macromol.* **2021**, *178*, 363–372. [[CrossRef](#)]
18. Angelin, J.; Kavitha, M. Exopolysaccharides from probiotic bacteria and their health potential. *Int. J. Biol. Macromol.* **2020**, *162*, 853–865. [[CrossRef](#)]
19. El-Deeb, N.M.; Yassin, A.M.; Al-Madboly, L.A.; El-Hawiet, A. A novel purified *Lactobacillus acidophilus* 20079 exopolysaccharide, LA-EPS-20079, molecularly regulates both apoptotic and NF-kappaB inflammatory pathways in human colon cancer. *Microb. Cell Fact.* **2018**, *17*, 29. [[CrossRef](#)]
20. Min, W.H.; Fang, X.B.; Wu, T.; Fang, L.; Liu, C.L.; Wang, J. Characterization and antioxidant activity of an acidic exopolysaccharide from *Lactobacillus plantarum* JLAU103. *J. Biosci. Bioeng.* **2019**, *127*, 758–766. [[CrossRef](#)]
21. Li, J.; Li, Q.; Wu, Q.; Gao, N.; Wang, Z.; Yang, Y.; Shan, A. Exopolysaccharides of *Lactobacillus rhamnosus* GG ameliorate Salmonella typhimurium-induced intestinal inflammation via the TLR4/NF-kappaB/MAPK pathway. *J. Anim. Sci. Biotechnol.* **2023**, *14*, 23. [[CrossRef](#)]
22. Paik, W.; Alonzo, F., 3rd; Knight, K.L. Probiotic Exopolysaccharide Protects against Systemic Staphylococcus aureus Infection, Inducing Dual-Functioning Macrophages That Restrict Bacterial Growth and Limit Inflammation. *Infect. Immun.* **2019**, *87*, e00791-18. [[CrossRef](#)] [[PubMed](#)]
23. Xu, X.; Xu, P.; Ma, C.; Tang, J.; Zhang, X. Gut microbiota, host health, and polysaccharides. *Biotechnol. Adv.* **2013**, *31*, 318–337. [[CrossRef](#)] [[PubMed](#)]
24. Matsuzaki, C.; Hayakawa, A.; Matsumoto, K.; Katoh, T.; Yamamoto, K.; Hisa, K. Exopolysaccharides Produced by *Leuconostoc mesenteroides* Strain NTM048 as an Immunostimulant to Enhance the Mucosal Barrier and Influence the Systemic Immune Response. *J. Agric. Food Chem.* **2015**, *63*, 7009–7015. [[CrossRef](#)] [[PubMed](#)]
25. Zhou, X.; Zhang, K.; Qi, W.; Zhou, Y.; Hong, T.; Xiong, T.; Xie, M.; Nie, S. Exopolysaccharides from *Lactobacillus plantarum* NCU116 Enhances Colonic Mucosal Homeostasis by Controlling Epithelial Cell Differentiation and c-Jun/Muc2 Signaling. *J. Agric. Food Chem.* **2019**, *67*, 9831–9839. [[CrossRef](#)] [[PubMed](#)]
26. Jung, J.Y.; Shin, J.S.; Rhee, Y.K.; Cho, C.W.; Lee, M.K.; Hong, H.D.; Lee, K.T. In vitro and in vivo immunostimulatory activity of an exopolysaccharide-enriched fraction from *Bacillus subtilis*. *J. Appl. Microbiol.* **2015**, *118*, 739–752. [[CrossRef](#)] [[PubMed](#)]
27. Gorska, S.; Sandstrom, C.; Wojas-Turek, J.; Rossowska, J.; Pajtasz-Piasecka, E.; Brzozowska, E.; Gamian, A. Structural and immunomodulatory differences among lactobacilli exopolysaccharides isolated from intestines of mice with experimentally induced inflammatory bowel disease. *Sci. Rep.* **2016**, *6*, 37613. [[CrossRef](#)]
28. Di, W.; Zhang, L.; Yi, H.; Han, X.; Zhang, Y.; Xin, L. Exopolysaccharides produced by *Lactobacillus* strains suppress HT-29 cell growth via induction of G0/G1 cell cycle arrest and apoptosis. *Oncol. Lett.* **2018**, *16*, 3577–3586. [[CrossRef](#)]
29. Kiray, E.; Raheel, N.M. A New Approach to Exopolysaccharides of Post Probiotic *Lactobacillus paracasei* L1 Strain: Anti-quarum Sensing Activity. *Balk. Med. J.* **2023**, *40*, 351–357. [[CrossRef](#)]
30. Ksonzekova, P.; Bystricky, P.; Vlckova, S.; Patoprsty, V.; Pulzova, L.; Mudronova, D.; Kubaskova, T.; Csank, T.; Tkacikova, L. Exopolysaccharides of *Lactobacillus reuteri*: Their influence on adherence of *E. coli* to epithelial cells and inflammatory response. *Carbohydr. Polym.* **2016**, *141*, 10–19. [[CrossRef](#)]

31. Xu, R.; Aruhan; Xiu, L.; Sheng, S.; Liang, Y.; Zhang, H.; Liu, Y.; Tong, H.; Du, R.; Wang, X. Exopolysaccharides from *Lactobacillus buchneri* TCP016 Attenuate LPS- and d-GalN-Induced Liver Injury by Modulating the Gut Microbiota. *J. Agric. Food Chem.* **2019**, *67*, 11627–11637. [[CrossRef](#)] [[PubMed](#)]
32. Demoulin, C.F.; Lara, Y.J.; Cornet, L.; Francois, C.; Baurain, D.; Wilmotte, A.; Javaux, E.J. Cyanobacteria evolution: Insight from the fossil record. *Free Radic. Biol. Med.* **2019**, *140*, 206–223. [[CrossRef](#)] [[PubMed](#)]
33. Mehdizadeh Allaf, M.; Peerhossaini, H. Cyanobacteria: Model Microorganisms and Beyond. *Microorganisms* **2022**, *10*, 696. [[CrossRef](#)] [[PubMed](#)]
34. Moore, K.A.; Altus, S.; Tay, J.W.; Meehl, J.B.; Johnson, E.B.; Bortz, D.M.; Cameron, J.C. Mechanical regulation of photosynthesis in cyanobacteria. *Nat. Microbiol.* **2020**, *5*, 757–767. [[CrossRef](#)] [[PubMed](#)]
35. Nunnery, J.K.; Mevers, E.; Gerwick, W.H. Biologically active secondary metabolites from marine cyanobacteria. *Curr. Opin. Biotechnol.* **2010**, *21*, 787–793. [[CrossRef](#)]
36. Jones, A.C.; Monroe, E.A.; Eisman, E.B.; Gerwick, L.; Sherman, D.H.; Gerwick, W.H. The unique mechanistic transformations involved in the biosynthesis of modular natural products from marine cyanobacteria. *Nat. Prod. Rep.* **2010**, *27*, 1048–1065. [[CrossRef](#)]
37. Milligan, K.E.; Marquez, B.L.; Williamson, R.T.; Gerwick, W.H. Lyngbyabellin B, a toxic and antifungal secondary metabolite from the marine cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* **2000**, *63*, 1440–1443. [[CrossRef](#)]
38. Allonsius, C.N.; van den Broek, M.F.L.; De Boeck, I.; Kiekens, S.; Oerlemans, E.F.M.; Kiekens, F.; Foubert, K.; Vandenheuvel, D.; Cos, P.; Delputte, P.; et al. Interplay between *Lactobacillus rhamnosus* GG and *Candida* and the involvement of exopolysaccharides. *Microb. Biotechnol.* **2017**, *10*, 1753–1763. [[CrossRef](#)]
39. Linington, R.G.; Edwards, D.J.; Shuman, C.F.; McPhail, K.L.; Matainaho, T.; Gerwick, W.H. Symplocamide A, a potent cytotoxin and chymotrypsin inhibitor from the marine Cyanobacterium *Symploca* sp. *J. Nat. Prod.* **2008**, *71*, 22–27. [[CrossRef](#)]
40. Zahra, Z.; Choo, D.H.; Lee, H.; Parveen, A. Cyanobacteria: Review of current potentials and applications. *Environments* **2020**, *7*, 13. [[CrossRef](#)]
41. Singh, S.K.; Kaur, R.; Bansal, A.; Kapur, S.; Sundaram, S. Biotechnological exploitation of cyanobacteria and microalgae for bioactive compounds. In *Biotechnological Production of Bioactive Compounds*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 221–259.
42. Cruz, D.; Vasconcelos, V.; Pierre, G.; Michaud, P.; Delattre, C. Exopolysaccharides from cyanobacteria: Strategies for bioprocess development. *Appl. Sci.* **2020**, *10*, 3763. [[CrossRef](#)]
43. Nwodo, U.U.; Grenn, E.; Okoh, A.I. Bacterial exopolysaccharides: Functionality and prospects. *Int. J. Mol. Sci.* **2012**, *13*, 14002–14015. [[CrossRef](#)] [[PubMed](#)]
44. Pereira, S.; Zille, A.; Micheletti, E.; Moradas-Ferreira, P.; De Philippis, R.; Tamagnini, P. Complexity of cyanobacterial exopolysaccharides: Composition, structures, inducing factors and putative genes involved in their biosynthesis and assembly. *FEMS Microbiol. Rev.* **2009**, *33*, 917–941. [[CrossRef](#)]
45. Singh, S.; Sran, S.K.; Pinnaka, A.K.; Choudhury, A.R. Purification, characterization and functional properties of exopolysaccharide from a novel halophilic *Natronotalea sambharensis* sp. nov. *Int. J. Biol. Macromol.* **2019**, *136*, 547–558. [[CrossRef](#)] [[PubMed](#)]
46. De Vuyst, L.; Degeest, B. Heteropolysaccharides from lactic acid bacteria. *FEMS Microbiol. Rev.* **1999**, *23*, 153–177. [[CrossRef](#)] [[PubMed](#)]
47. Rossi, F.; De Philippis, R. Exocellular polysaccharides in Microalgae and Cyanobacteria: Chemical features, role and enzymes and genes involved in their biosynthesis. In *The Physiology of Microalgae*; Springer: Berlin/Heidelberg, Germany, 2016; pp. 565–590.
48. Hu, C.; Liu, Y.; Paulsen, B.S.; Petersen, D.; Klaveness, D. Extracellular carbohydrate polymers from five desert soil algae with different cohesion in the stabilization of fine sand grain. *Carbohydr. Polym.* **2003**, *54*, 33–42. [[CrossRef](#)]
49. Kawaguchi, T.; Decho, A.W. Biochemical characterization of cyanobacterial extracellular polymers (EPS) from modern marine stromatolites. *Prep. Biochem. Biotechnol.* **2000**, *30*, 321–330. [[CrossRef](#)]
50. Kawaguchi, T.; Decho, A.W. Isolation and biochemical characterization of extracellular polymeric secretions (EPS) from modern soft marine stromatolites (bahamas) and its inhibitory effect on CaCO₃ precipitation. *Prep. Biochem. Biotechnol.* **2002**, *32*, 51–63. [[CrossRef](#)]
51. Wang, H.M.; Loganathan, D.; Linhardt, R.J. Determination of the pKa of glucuronic acid and the carboxy groups of heparin by ¹³C-nuclear-magnetic-resonance spectroscopy. *Biochem. J.* **1991**, *278*, 689–695. [[CrossRef](#)]
52. Tamaru, Y.; Takani, Y.; Yoshida, T.; Sakamoto, T. Crucial role of extracellular polysaccharides in desiccation and freezing tolerance in the terrestrial cyanobacterium *Nostoc commune*. *Appl. Environ. Microbiol.* **2005**, *71*, 7327–7333. [[CrossRef](#)]
53. Ruangsomboon, S.; Chidthaisong, A.; Bunnag, B.; Inthorn, D.; Harvey, N.W. Lead (Pb²⁺) adsorption characteristics and sugar composition of capsular polysaccharides of cyanobacterium *Calothrix marchica*. *Songklanakarin J. Sci. Technol.* **2007**, *29*, 529–541.
54. Yoshimura, H.; Kotake, T.; Aohara, T.; Tsumuraya, Y.; Ikeuchi, M.; Ohmori, M. The role of extracellular polysaccharides produced by the terrestrial cyanobacterium *Nostoc* sp. strain HK-01 in NaCl tolerance. *J. Appl. Phycol.* **2012**, *24*, 237–243. [[CrossRef](#)]
55. Yoshimura, H.; Ikeuchi, M.; Ohmori, M. Cell surface-associated proteins in the filamentous cyanobacterium *Anabaena* sp. strain PCC 7120. *Microbes Environ.* **2012**, *27*, 538–543. [[CrossRef](#)]
56. Georgiev, Y.N.; Batsalova, T.G.; Dzhabazov, B.M.; Ognyanov, M.H.; Denev, P.N.; Antonova, D.V.; Wold, C.W.; Yanakieva, I.Z.; Teneva, I.I.; Paulsen, B.S. Immunomodulating polysaccharide complexes and antioxidant metabolites from *Anabaena laxa*, *Oscillatoria limosa* and *Phormidesmis molle*. *Algal Res.* **2021**, *60*, 102538. [[CrossRef](#)]

57. Tseng, C.-C.; Yeh, H.-Y.; Liao, Z.-H.; Hung, S.-W.; Chen, B.; Lee, P.-T.; Nan, F.-H.; Shih, W.-L.; Chang, C.-C.; Lee, M.-C. An in vitro study shows the potential of *Nostoc commune* (Cyanobacteria) polysaccharides extract for wound-healing and anti-allergic use in the cosmetics industry. *J. Funct. Foods* **2021**, *87*, 104754. [[CrossRef](#)]
58. Gong, W.; Gomez Pinchetti, J.L.; Cordeiro, N.; Ouada, H.B. Extracellular polymeric substances produced by the Thermophilic Cyanobacterium *Gloeocapsa gelatinosa*: Characterization and assessment of their antioxidant and metal-chelating activities. *Mar. Drugs* **2022**, *20*, 227. [[CrossRef](#)]
59. Gong, W.; Cordeiro, N.; Pinchetti, J.L.G.; Ouada, H.B. Functional, rheological, and antioxidant properties of extracellular polymeric substances produced by a thermophilic cyanobacterium *Leptolyngbya* sp. *J. Appl. Phycol.* **2022**, *34*, 1423–1434. [[CrossRef](#)]
60. Senousy, H.H.; El-Sheekh, M.M.; Saber, A.A.; Khairy, H.M.; Said, H.A.; Alhoqail, W.A.; Abu-Elsaoud, A.M. Biochemical analyses of ten cyanobacterial and microalgal strains isolated from egyptian habitats, and screening for their potential against some selected phytopathogenic fungal strains. *Agronomy* **2022**, *12*, 1340. [[CrossRef](#)]
61. Ahmed, M.; Moerdijk-Poortvliet, T.C.; Wijnholds, A.; Stal, L.J.; Hasnain, S. Isolation, characterization and localization of extracellular polymeric substances from the cyanobacterium *Arthrospira platensis* strain MMG-9. *Eur. J. Phycol.* **2014**, *49*, 143–150. [[CrossRef](#)]
62. Hussein, M.H.; Abou-ElWafa, G.S.; Shaaban-Dessuuki, S.A.; Hassan, N.I. Characterization and antioxidant activity of exopolysaccharide secreted by *Nostoc carneum*. *Int. J. Pharmacol.* **2015**, *11*, 432–439. [[CrossRef](#)]
63. Lama, L.; Nicolaus, B.; Calandrelli, V.; Manca, M.C.; Romano, I.; Gambacorta, A. Effect of growth conditions on endo-and exopolymer biosynthesis in *Anabaena cylindrica* 10 C. *Phytochemistry* **1996**, *42*, 655–659. [[CrossRef](#)]
64. Moore, B.; Tischer, R. Extracellular polysaccharides of algae: Effects on life-support systems. *Science* **1964**, *145*, 586–587. [[CrossRef](#)] [[PubMed](#)]
65. Nicolaus, B.; Panico, A.; Lama, L.; Romano, I.; Manca, M.C.; De Giulio, A.; Gambacorta, A. Chemical composition and production of exopolysaccharides from representative members of heterocystous and non-heterocystous cyanobacteria. *Phytochemistry* **1999**, *52*, 639–647. [[CrossRef](#)]
66. Richert, L.; Golubic, S.; Guédès, R.L.; Ratiskol, J.; Payri, C.; Guezennec, J. Characterization of exopolysaccharides produced by cyanobacteria isolated from Polynesian microbial mats. *Curr. Microbiol.* **2005**, *51*, 379–384. [[CrossRef](#)] [[PubMed](#)]
67. Rossi, F.; Micheletti, E.; Bruno, L.; Adhikary, S.P.; Albertano, P.; De Philippis, R. Characteristics and role of the exocellular polysaccharides produced by five cyanobacteria isolated from phototrophic biofilms growing on stone monuments. *Biofouling* **2012**, *28*, 215–224. [[CrossRef](#)] [[PubMed](#)]
68. Volk, R.-B.; Venzke, K.; Blaschek, W. Structural investigation of a polysaccharide released by the cyanobacterium *Nostoc insulare*. *J. Appl. Phycol.* **2007**, *19*, 255–262. [[CrossRef](#)]
69. Parikh, A.; Madamwar, D. Partial characterization of extracellular polysaccharides from cyanobacteria. *Bioresour. Technol.* **2006**, *97*, 1822–1827. [[CrossRef](#)]
70. Nunes, C.S.; Rufato, K.B.; Souza, P.R.; de Almeida, E.A.M.S.; da Silva, M.J.V.; Scariot, D.B.; Nakamura, C.V.; Rosa, F.A.; Martins, A.F.; Muniz, E.C. Chitosan/chondroitin sulfate hydrogels prepared in [Hmim][HSO₄] ionic liquid. *Carbohydr. Polym.* **2017**, *170*, 99–106. [[CrossRef](#)]
71. Brown, M.J.; Lester, J.N. Role of bacterial extra-cellular polymers in metal uptake in pure bacterial culture and activated sludge. *Water Res.* **1982**, *16*, 1539–1548. [[CrossRef](#)]
72. Mancuso Nichols, C.A.; Bowman, J.P.; Fuezennec, J. Bacterial exopolysaccharides from extreme marine environments with special consideration of the southern ocean, sea ice, and deep-sea hydrothermal vents: A review. *Mar. Biotechnol.* **2005**, *7*, 253–271. [[CrossRef](#)]
73. De Philippis, R.; Ena, A.; Paperi, R.; Sili, C.; Vincenzini, M. Assessment of the potential of *Nostoc* strains from Pasteur culture collection for the production of polysaccharides of applied interest. *J. Appl. Phycol.* **2000**, *12*, 401–407. [[CrossRef](#)]
74. Micheletti, E.; Pereria, S.; Mannelli, F.; Moradas-Ferreira, P.; Tamagnini, P.; De Philippis, R. Sheathless mutant of the cyanobacterium *Gloeotheca* sp. strain PCC 6909 with increased capacity to remove copper ions from aqueous solutions. *Appl. Environ. Microbiol.* **2008**, *74*, 2797–2804. [[CrossRef](#)] [[PubMed](#)]
75. Fischer, D.; Schlosser, U.G.; Pohl, P. Exopolysaccharide production by cyanobacteria grown in closed photobioreactors and immobilized using white cotton towelling. *J. Appl. Phycol.* **1997**, *9*, 205–213. [[CrossRef](#)]
76. De Philippis, R.; Vincenzini, M. Exocellular polysaccharides from cyanobacteria and their possible applications. *FEMS Microbiol. Rev.* **1998**, *22*, 151–175. [[CrossRef](#)]
77. Tiwari, O.N.; Muthuraj, M.; Bhunia, B.; Bandyopadhyay, T.K.; Annapurna, K.; Sahu, M.; Indrama, T. Biosynthesis, purification and structure-property relationships of new cyanobacterial exopolysaccharides. *Polym. Test.* **2020**, *89*, 106592. [[CrossRef](#)]
78. Bhunia, B.; Uday, U.S.P.; Oinam, G.; Mondal, A.; Bandyopadhyay, T.K.; Tiwari, O.N. Characterization, genetic regulation and production of cyanobacterial exopolysaccharides and its applicability for heavy metal removal. *Carbohydr. Polym.* **2018**, *179*, 228–243. [[CrossRef](#)]
79. Neu, T.R.; Dengler, T.; Jann, B.; Poralla, K. Structural studies of an emulsion-stabilizing exopolysaccharide produced by an adhesive hydrophobic *Rhodococcus* strain. *J. Gen. Microbiol.* **1992**, *138*, 2531–2537. [[CrossRef](#)] [[PubMed](#)]
80. Sheperd, R.; Rockey, J.; Sutherland, I.W.; Roller, S. Novel Bioemulsifiers from microorganisms for use in foods. *J. Biotechnol.* **1995**, *40*, 207–217. [[CrossRef](#)]

81. Alvarez, X.; Alves, A.; Ribeiro, M.P.; Lazzari, M.; Coutinho, P.; Otero, A. Biochemical characterization of *Nostoc* sp. exopolysaccharides and evaluation of potential use in wound healing. *Carbohydr. Polym.* **2021**, *254*, 117303. [[CrossRef](#)]
82. Tiwari, O.N.; Khangembam, R.; Shamjetshabam, M.; Sharma, A.S.; Oinam, G.; Brand, J.J. Characterization and optimization of bioflocculant exopolysaccharide production by cyanobacteria *Nostoc* sp. BTA97 and *Anabaena* sp. BTA990 in culture conditions. *Appl. Biochem. Biotechnol.* **2015**, *176*, 1950–1963. [[CrossRef](#)]
83. Maeda, K.; Okuda, Y.; Enomoto, G.; Watanabe, S.; Ikeuchi, M. Biosynthesis of a sulfated exopolysaccharide, synechan, and bloom formation in the model cyanobacterium *Synechocystis* sp. strain PCC 6803. *eLife* **2021**, *10*, e66538. [[CrossRef](#)]
84. Santos, M.; Pacheco, C.C.; Yao, L.; Hudson, E.P.; Tamagnini, P. CRISPRi as a Tool to Repress Multiple Copies of Extracellular Polymeric Substances (EPS)-Related Genes in the Cyanobacterium *Synechocystis* sp. PCC 6803. *Life* **2021**, *11*, 1198. [[CrossRef](#)]
85. Pereira, S.B.; Santos, M.; Leite, J.P.; Flores, C.; Eisfeld, C.; Buttler, Z.; Mota, R.; Rossi, F.; De Philippis, R.; Gales, L.; et al. The role of the tyrosine kinase Wzc (Slr0923) and the phosphatase Wzb (Slr0328) in the production of extracellular polymeric substances (EPS) by *Synechocystis* PCC 6803. *Microbiologyopen* **2019**, *8*, e00753. [[CrossRef](#)]
86. Singh, S.; Das, S. Screening, production, optimization and characterization of cyanobacterial Polysaccharide. *World J. Microbiol. Biotechnol.* **2011**, *27*, 1971–1980. [[CrossRef](#)]
87. Khangembam, R.; Tiwari, O.N.; Kalita, M. Production of exopolysaccharides by the cyanobacterium *Anabaena* sp. BTA992 and application as bioflocculants. *J. Appl. Biol. Biotechnol.* **2016**, *4*, 8–11.
88. Atta, M.; Idris, A.; Bukhari, A.; Wahidin, S. Intensity of blue LED light: A potential stimulus for biomass and lipid content in fresh water microalgae *Chlorella vulgaris*. *Bioresour. Technol.* **2013**, *148*, 373–378. [[CrossRef](#)]
89. Yang, T.; Lee, C.S.; Cho, J.Y.; Bae, M.J.; Kim, E.J. Comparison of Bacterial Assemblages Associated with Harmful Cyanobacteria under Different Light Conditions. *Microorganisms* **2022**, *10*, 2150. [[CrossRef](#)]
90. Su, C.; Chi, Z.; Lu, W. Optimization of medium and cultivation conditions for enhanced exopolysaccharide yield by marine *Cyanotheca* sp 113. *Chin. J. Oceanol. Limnol.* **2007**, *25*, 411–417. [[CrossRef](#)]
91. Sudo, H.; Burgess, J.G.; Takemasa, H.; Nakamura, N.; Matsunaga, T. Sulfated exopolysaccharide production by the halophilic cyanobacterium *Aphanocapsa* halophytia. *Curr. Microbiol.* **1995**, *30*, 219–222. [[CrossRef](#)]
92. De Philippis, R.; Sili, C.; Tassinato, G.; Vincenzini, M.; Materassi, R. Effects of growth conditions on exopolysaccharide production by *Cynospira capsulata*. *Bioresour. Technol.* **1991**, *38*, 101–104. [[CrossRef](#)]
93. Savadova, K.; Mazur-Marzec, H.; Karosienė, J.; Kasperovičienė, J.; Vitonytė, I.; Toruńska-Sitarz, A.; Koreivienė, J. Effect of Increased Temperature on Native and Alien Nuisance Cyanobacteria from Temperate Lakes: An Experimental Approach. *Toxins* **2018**, *10*, 445. [[CrossRef](#)]
94. Moreno, J.; Vargas, M.A.; Olivares, H.; Rivas, J.; Guerrero, M.G. Exopolysaccharide production by the cyanobacterium *Anabaena* sp. ATCC 33047 in batch and continuous culture. *J. Biotechnol.* **1998**, *60*, 175–182. [[CrossRef](#)]
95. Otero, A.; Vincenzini, M. *Nostoc* (Cyanophyceae) goes nude: Extracellular polysaccharides serve as a sink for reducing power under unbalanced C/N metabolism. *J. Phycol.* **2004**, *40*, 74–81. [[CrossRef](#)]
96. Dineshbabu, G.; Uma, V.S.; Mathimani, T.; Prabakaran, D.; Uma, L. Elevated CO₂ impact on growth and lipid of marine cyanobacterium *Phormidium valderianum* BDU 20041—Towards microalgal carbon sequestration. *Biocatal. Agric. Biotechnol.* **2020**, *25*, 101606. [[CrossRef](#)]
97. Raven, J.A.; Gobler, C.J.; Hansen, P.J. Dynamic CO₂ and pH levels in coastal, estuarine, and inland waters: Theoretical and observed effects on harmful algal blooms. *Harm. Algae* **2020**, *91*, 101594. [[CrossRef](#)]
98. Vázquez-Nion, D.; Fuentes, E.; Prieto, B. Effect of Inorganic Carbon Concentration on the Development of Subaerial Phototrophic Biofilms on Granite. *Coatings* **2020**, *10*, 1049. [[CrossRef](#)]
99. Cheng, Y.S.; Labavitch, J.M.; Vandergheynst, J.S. Elevated CO₂ concentration impacts cell wall polysaccharide composition of green microalgae of the genus *Chlorella*. *Lett. Appl. Microbiol.* **2015**, *60*, 1–7. [[CrossRef](#)]
100. Velu, C.; Cires, S.; Brinkman, D.L.; Heimann, K. Effect of CO₂ and metal-rich waste water on bioproduct potential of the diazotrophic freshwater cyanobacterium. *Heliyon* **2019**, *4*, e01549. [[CrossRef](#)]
101. Pereira, S.B.; Sousa, A.; Santos, M.; Araújo, M.; Serôdio, F.; Granja, P.; Tamagnini, P. Strategies to obtain designer polymers based on cyanobacterial extracellular polymeric substances (EPS). *Int. J. Mol. Sci.* **2019**, *20*, 5693. [[CrossRef](#)]
102. Bhatnagar, M.; Bhatnagar, A. Diversity of polysaccharides in cyanobacteria. *Microbial Diversity in Ecosystem Sustainability and Biotechnological Applications: Volume 1*. In *Microbial Diversity in Normal & Extreme Environments*; Springer: Berlin/Heidelberg, Germany, 2019; pp. 447–496.
103. Oerlemans, M.M.; Akkerman, R.; Ferrari, M.; Walvoort, M.T.; de Vos, P. Benefits of bacteria-derived exopolysaccharides on gastrointestinal microbiota, immunity and health. *J. Funct. Foods* **2021**, *76*, 104289. [[CrossRef](#)]
104. Fanning, S.; Hall, L.J.; van Sinderen, D. *Bifidobacterium breve* UCC2003 surface exopolysaccharide production is a beneficial trait mediating commensal-host interaction through immune modulation and pathogen protection. *Gut Microbes* **2012**, *3*, 420–425. [[CrossRef](#)] [[PubMed](#)]
105. Hachicha, R.; Elleuch, F.; Ben Hlima, H.; Dubessay, P.; de Baynast, H.; Delattre, C.; Pierre, G.; Hachicha, R.; Abdelkafi, S.; Michaud, P. Biomolecules from microalgae and cyanobacteria: Applications and market survey. *Appl. Sci.* **2022**, *12*, 1924. [[CrossRef](#)]
106. Challouf, R.; Trabelsi, L.; Ben Dhieb, R.; El Abed, O.; Yahia, A.; Ghozzi, K.; Ben Ammar, J.; Omran, H.; Ben Ouada, H. Evaluation of cytotoxicity and biological activities in extracellular polysaccharides released by cyanobacterium *Arthrospira platensis*. *Braz. Arch. Biol. Technol.* **2011**, *54*, 831–838. [[CrossRef](#)]

107. Bhatnagar, M.; Parwani, L.; Sharma, V.; Ganguly, J.; Bhatnagar, A. Exopolymers from *Tolypothrix tenuis* and three *Anabaena* sp. (Cyanobacteriaceae) as novel blood clotting agents for wound management. *Carbohydr. Polym.* **2014**, *99*, 692–699. [[CrossRef](#)] [[PubMed](#)]
108. Najdenski, H.M.; Gigova, L.G.; Iliev, I.I.; Pilarski, P.S.; Lukavský, J.; Tsvetkova, I.V.; Ninova, M.S.; Kussovski, V.K. Antibacterial and antifungal activities of selected microalgae and cyanobacteria. *Int. J. Food Sci. Technol.* **2013**, *48*, 1533–1540. [[CrossRef](#)]
109. Mishra, R.; Panda, A.K.; De Mandal, S.; Shakeel, M.; Bisht, S.S.; Khan, J. Natural anti-biofilm agents: Strategies to control biofilm-forming pathogens. *Front. Microbiol.* **2020**, *11*, 566325. [[CrossRef](#)]
110. Gargouch, N.; Elleuch, F.; Karkouch, I.; Tabbene, O.; Pichon, C.; Gardarin, C.; Rihouey, C.; Picton, L.; Abdelkafi, S.; Fendri, I. Potential of exopolysaccharide from *Porphyridium marinum* to contend with bacterial proliferation, biofilm formation, and breast cancer. *Mar. Drugs* **2021**, *19*, 66. [[CrossRef](#)] [[PubMed](#)]
111. Santhakumari, S.; Kannappan, A.; Pandian, S.K.; Thajuddin, N.; Rajendran, R.B.; Ravi, A.V. Inhibitory effect of marine cyanobacterial extract on biofilm formation and virulence factor production of bacterial pathogens causing vibriosis in aquaculture. *J. Appl. Phycol.* **2016**, *28*, 313–324. [[CrossRef](#)]
112. Vasileva, I.; Toshkova-Yotova, T.; Georgieva, Z.; Karcheva, Z.; Petrova, D.; Chaneva, G.; Yocheva, L. Effect of temperature and light on the biochemical profile and antimicrobial activity of *Chroococcus* sp. R-10 (Cyanoprocarvota). *Oxid. Commun.* **2021**, *44*, 723–736.
113. Falaise, C.; François, C.; Travers, M.-A.; Morga, B.; Haure, J.; Tremblay, R.; Turcotte, F.; Pasetto, P.; Gastineau, R.; Hardivillier, Y. Antimicrobial compounds from eukaryotic microalgae against human pathogens and diseases in aquaculture. *Mar. Drugs* **2016**, *14*, 159. [[CrossRef](#)]
114. Wang, W.; Wang, S.-X.; Guan, H.-S. The antiviral activities and mechanisms of marine polysaccharides: An overview. *Mar. Drugs* **2012**, *10*, 2795–2816. [[CrossRef](#)]
115. Andrew, M.; Jayaraman, G. Marine sulfated polysaccharides as potential antiviral drug candidates to treat Corona Virus disease (COVID-19). *Carbohydr. Res.* **2021**, *505*, 108326. [[CrossRef](#)] [[PubMed](#)]
116. Torres, F.G.; Troncoso, O.P.; Pisani, A.; Gatto, F.; Bardi, G. Natural polysaccharide nanomaterials: An overview of their immunological properties. *Int. J. Mol. Sci.* **2019**, *20*, 5092. [[CrossRef](#)] [[PubMed](#)]
117. Homaeigohar, S.; Liu, X.; Elbahri, M. Antiviral polysaccharide and antiviral peptide delivering nanomaterials for prevention and treatment of SARS-CoV-2 caused COVID-19 and other viral diseases. *J. Control. Release* **2023**, *358*, 476–497. [[CrossRef](#)] [[PubMed](#)]
118. Mader, J.; Gallo, A.; Schommartz, T.; Handke, W.; Nagel, C.-H.; Günther, P.; Brune, W.; Reich, K. Calcium spirulan derived from *Spirulina platensis* inhibits herpes simplex virus 1 attachment to human keratinocytes and protects against herpes labialis. *J. Allergy Clin. Immunol.* **2016**, *137*, 197–203.e3. [[CrossRef](#)]
119. Parwani, L.; Bhatt, M.; Singh, J. Potential biotechnological applications of cyanobacterial exopolysaccharides. *Braz. Arch. Biol. Technol.* **2021**, *64*, e21200401. [[CrossRef](#)]
120. Chaisuwan, W.; Jantanasakulwong, K.; Wangtueai, S.; Phimolsiripol, Y.; Chaiyaso, T.; Techapun, C.; Phongthai, S.; You, S.; Regenstein, J.M.; Seesuriyachan, P. Microbial exopolysaccharides for immune enhancement: Fermentation, modifications and bioactivities. *Food Biosci.* **2020**, *35*, 100564. [[CrossRef](#)]
121. Dargahi, N.; Johnson, J.; Donkor, O.; Vasiljevic, T.; Apostolopoulos, V. Immunomodulatory effects of probiotics: Can they be used to treat allergies and autoimmune diseases? *Maturitas* **2019**, *119*, 25–38. [[CrossRef](#)]
122. Kumari, M.; Dasriya, V.L.; Nataraj, B.H.; Nagpal, R.; Behare, P.V. *Lactacaseibacillus rhamnosus*-derived exopolysaccharide attenuates d-Galactose-Induced oxidative stress and inflammatory brain injury and modulates gut microbiota in a mouse model. *Microorganisms* **2022**, *10*, 2046. [[CrossRef](#)]
123. Parwani, L.; Bhatnagar, M.; Bhatnagar, A.; Sharma, V. Antioxidant and iron-chelating activities of cyanobacterial exopolymers with potential for wound healing. *J. Appl. Phycol.* **2014**, *26*, 1473–1482. [[CrossRef](#)]
124. Şengül, N.; Işık, S.; Aslım, B.; Uçar, G.; Demirbağ, A.E. The effect of exopolysaccharide-producing probiotic strains on gut oxidative damage in experimental colitis. *Dig. Dis. Sci.* **2011**, *56*, 707–714. [[CrossRef](#)] [[PubMed](#)]
125. Liu, S.-T.; Wang, S.; Han, N.; Li, M.-Y.; Li, J.; Li, Y.-R.; Jia, S.-R.; Han, P.-P. Effects of H₂O₂ acclimation on the growth, polysaccharide production and tolerance performance of *Nostoc flagelliforme*. *Algal Res.* **2023**, *70*, 102968. [[CrossRef](#)]
126. Uhliariková, I.; Matulová, M.; Capek, P. Optimizing acid hydrolysis for monosaccharide compositional analysis of *Nostoc cf. linckia* acidic exopolysaccharide. *Carbohydr. Res.* **2021**, *508*, 108400. [[CrossRef](#)] [[PubMed](#)]
127. Alberto Vieira Costa, J.; Franco Lucas, B.; Gabrielle Pires Alvarenga, A.; Botelho Moreira, J.; Greque de Moraes, M. Microalgae Polysaccharides: An Overview of Production, Characterization, and Potential Applications. *Polysaccharides* **2021**, *2*, 759–772. [[CrossRef](#)]
128. Tiwari, O.N.; Mondal, A.; Bhunia, B.; kanti Bandyopadhyay, T.; Jaladi, P.; Oinam, G.; Indrama, T. Purification, characterization and biotechnological potential of new exopolysaccharide polymers produced by cyanobacterium *Anabaena* sp. CCC 745. *Polymer* **2019**, *178*, 121695. [[CrossRef](#)]
129. Majdoub, H.; Mansour, M.B.; Chaubet, F.; Roudesli, M.S.; Maaroufi, R.M. Anticoagulant activity of a sulfated polysaccharide from the green alga *Arthrospira platensis*. *Biochim. Biophys. Acta* **2009**, *1790*, 1377–1381. [[CrossRef](#)] [[PubMed](#)]
130. Sun, Y.; Wang, H.; Guo, G.; Pu, Y.; Yan, B. The isolation and antioxidant activity of polysaccharides from the marine microalgae *Isochrysis galbana*. *Carbohydr. Polym.* **2014**, *113*, 22–31. [[CrossRef](#)] [[PubMed](#)]

131. Tannin-Spitz, T.; Bergman, M.; Van-Moppes, D.; Grossman, S.; Arad, S. Antioxidant activity of the polysaccharide of the red microalgae *Porphyridium* sp. *J. Appl. Phycol.* **2005**, *17*, 215–222. [[CrossRef](#)]
132. Sun, L.; Wang, C.; Shi, Q.; Ma, C. Preparation of different molecular weight polysaccharides from *Porphyridium cruentum* and their antioxidant activities. *Int. J. Biol. Macromol.* **2009**, *45*, 42–47. [[CrossRef](#)]
133. Chen, B.; You, W.; Huang, J.; Yu, Y.; Chen, W. Isolation and antioxidant property of the extracellular polysaccharide from *Rhodella reticulata*. *World J. Microbiol. Biotechnol.* **2010**, *26*, 833–840. [[CrossRef](#)]
134. Wang, S.-y.; Jiang, Y.; Meng, C.; Ouyang, Y.-H.; Lin, X.-Z. Preparation of extracellular polysaccharide from fermentation liquor of marine microalgae *Schizochytrium* and study on the bioactivities. *J. Fuzhou Univ.* **2011**, *39*, 786–791.
135. Herrero, M.; Martín-Álvarez, P.J.; Senorans, F.J.; Cifuentes, A.; Ibáñez, E. Optimization of accelerated solvent extraction of antioxidants from *Spirulina platensis* microalga. *Food Chem.* **2005**, *93*, 417–423. [[CrossRef](#)]
136. Li, L.; Gao, Y.; Dai, Y.; Yang, Y.; Wang, X. Scavenging effects of *Spirulina* and polysaccharides *Spirulina platensis* on active oxygens and its antioxidation in vitro. *Chem. Bioeng.* **2007**, *24*, 55–57.
137. Elkomy, R.G.; Ismail, M.M. Crude sulfated polysaccharides extracted from marine cyanobacterium *Oscillatoria simplicissima* with evaluation antioxidant and cytotoxic activities. *Iran. J. Microbiol.* **2021**, *13*, 553. [[CrossRef](#)] [[PubMed](#)]
138. Xu, R.; Shang, N.; Li, P. In vitro and in vivo antioxidant activity of exopolysaccharide fractions from *Bifidobacterium animalis* RH. *Anaerobe* **2011**, *17*, 226–231. [[CrossRef](#)] [[PubMed](#)]
139. Risjani, Y.; Mutmainnah, N.; Manurung, P.; Wulan, S.N.; Yuniarta. Exopolysaccharide from *Porphyridium cruentum* (purpureum) is not toxic and stimulates immune response against vibriosis: The assessment using zebrafish and white shrimp *Litopenaeus vannamei*. *Mar. Drugs* **2021**, *19*, 133. [[CrossRef](#)] [[PubMed](#)]
140. de Jesus Raposo, M.F.; De Morais, R.M.S.C.; de Morais, A.M.M.B. Bioactivity and applications of sulphated polysaccharides from marine microalgae. *Mar. Drugs* **2013**, *11*, 233–252. [[CrossRef](#)] [[PubMed](#)]
141. Caetano, P.A.; do Nascimento, T.C.; Fernandes, A.S.; Nass, P.P.; Vieira, K.R.; Junior, M.R.M.; Jacob-Lopes, E.; Zepka, L.Q. Microalgae-based polysaccharides: Insights on production, applications, analysis, and future challenges. *Biocatal. Agric. Biotechnol.* **2022**, *45*, 102491. [[CrossRef](#)]
142. Cizek-Lenda, M.; Nowak, B.; Śróttek, M.; Gamian, A.; Marcinkiewicz, J. Immunoregulatory potential of exopolysaccharide from *Lactobacillus rhamnosus* KL37. Effects on the production of inflammatory mediators by mouse macrophages. *Int. J. Exp. Pathol.* **2011**, *92*, 382–391. [[CrossRef](#)]
143. Finamore, A.; Roselli, M.; Imbinto, A.; Seeboth, J.; Oswald, I.P.; Mengheri, E. *Lactobacillus amylovorus* inhibits the TLR4 inflammatory signaling triggered by enterotoxigenic *Escherichia coli* via modulation of the negative regulators and involvement of TLR2 in intestinal Caco-2 cells and pig explants. *PLoS ONE* **2014**, *9*, e94891. [[CrossRef](#)]
144. Gouda, M.; Tadda, M.A.; Zhao, Y.; Farmanullah, F.; Chu, B.; Li, X.; He, Y. Microalgae bioactive carbohydrates as a novel sustainable and eco-friendly source of prebiotics: Emerging health functionality and recent technologies for extraction and detection. *Front. Nutr.* **2022**, *9*, 806692. [[CrossRef](#)] [[PubMed](#)]
145. Ozturk, S.; Aslim, B. Modification of exopolysaccharide composition and production by three cyanobacterial isolates under salt stress. *Environ. Sci. Pollut. Res.* **2010**, *17*, 595–602. [[CrossRef](#)] [[PubMed](#)]
146. Zampieri, R.M.; Adessi, A.; Caldara, F.; Codato, A.; Furlan, M.; Rampazzo, C.; De Philippis, R.; La Rocca, N.; Dalla Valle, L. Anti-inflammatory activity of exopolysaccharides from *Phormidium* sp. ETS05, the most abundant cyanobacterium of the therapeutic euganean thermal muds, using the zebrafish model. *Biomolecules* **2020**, *10*, 582. [[CrossRef](#)] [[PubMed](#)]
147. Tabarзад, M.; Atabaki, V.; Hosseinabadi, T. Anti-inflammatory activity of bioactive compounds from microalgae and cyanobacteria by focusing on the mechanisms of action. *Mol. Biol. Rep.* **2020**, *47*, 6193–6205. [[CrossRef](#)]
148. Gao, X.; Zheng, T.; Yuan, X.; Dong, Y.; Liu, C. Biocidal H₂O₂ treatment emphasizes the crucial role of cyanobacterial extracellular polysaccharides against external strong oxidative stress. *Environ. Sci. Pollut. Res.* **2023**, *30*, 60654–60662. [[CrossRef](#)] [[PubMed](#)]
149. Hakansson, A.; Molin, G. Gut microbiota and inflammation. *Nutrients* **2011**, *3*, 637–682. [[CrossRef](#)] [[PubMed](#)]
150. Capek, P.; Matulová, M.; Šutovská, M.; Barboríková, J.; Molitorisová, M.; Kazimierová, I. *Chlorella vulgaris* α-L-arabino-α-L-rhamno-α, β-D-galactan structure and mechanisms of its anti-inflammatory and anti-remodelling effects. *Int. J. Biol. Macromol.* **2020**, *162*, 188–198. [[CrossRef](#)]
151. Uhlíříková, I.; Šutovská, M.; Barboríková, J.; Molitorisová, M.; Kim, H.J.; Park, Y.I.; Matulová, M.; Lukavský, J.; Hromadková, Z.; Capek, P. Structural characteristics and biological effects of exopolysaccharide produced by cyanobacterium *Nostoc* sp. *Int. J. Biol. Macromol.* **2020**, *160*, 364–371. [[CrossRef](#)]
152. Castro-Bravo, N.; Wells, J.M.; Margolles, A.; Ruas-Madiedo, P. Interactions of Surface Exopolysaccharides from *Bifidobacterium* and *Lactobacillus* within the Intestinal Environment. *Front. Microbiol.* **2018**, *9*, 2426. [[CrossRef](#)]
153. Tiwari, S.; Kavitha, D.; Devi, P.B.; Shetty, P.H. Bacterial exopolysaccharides for improvement of technological, functional and rheological properties of yoghurt. *Int. J. Biol. Macromol.* **2021**, *183*, 1585–1595. [[CrossRef](#)]
154. Ananya, A.K.; Ahmad, I.Z. Cyanobacteria “the blue green algae” and its novel applications: A brief review. *Int. J. Innov. Appl. Stud.* **2014**, *7*, 251.
155. Li, J.; Ai, L.; Xu, F.; Hu, X.; Yao, Y.; Wang, L. Structural characterization of exopolysaccharides from *Weissella cibaria* NC516. 11 in distiller grains and its improvement in gluten-free dough. *Int. J. Biol. Macromol.* **2022**, *199*, 17–23. [[CrossRef](#)] [[PubMed](#)]
156. Muninathan, C.; Guruchandran, S.; Viswanath Kalyan, A.J.; Ganesan, N.D. Microbial exopolysaccharides: Role in functional food engineering and gut-health management. *Int. J. Food Sci. Technol.* **2022**, *57*, 27–34. [[CrossRef](#)]

157. Xu, D.; Hu, Y.; Wu, F.; Jin, Y.; Xu, X.; Gänzle, M.G. Comparison of the functionality of exopolysaccharides produced by sourdough lactic acid bacteria in bread and steamed bread. *J. Agric. Food Chem.* **2020**, *68*, 8907–8914. [[CrossRef](#)] [[PubMed](#)]
158. Hamed, I.; Jakobsen, A.N.; Lerfall, J. Sustainable edible packaging systems based on active compounds from food processing byproducts: A review. *Compr. Rev. Food Sci. Food Saf.* **2022**, *21*, 198–226. [[CrossRef](#)]
159. Mishra, P. Cyanobacterial Exopolysaccharide as Natural Sources for Food Packaging Applications. *Innov. Food Technol. Curr. Perspect. Future Goals* **2020**, 171–184. [[CrossRef](#)]
160. Morales-Jiménez, M.; Gouveia, L.; Yáñez-Fernández, J.; Castro-Muñoz, R.; Barragán-Huerta, B.E. Production, preparation and characterization of microalgae-based biopolymer as a potential bioactive film. *Coatings* **2020**, *10*, 120. [[CrossRef](#)]
161. Moradi, M.; Guimarães, J.T.; Sahin, S. Current applications of exopolysaccharides from lactic acid bacteria in the development of food active edible packaging. *Curr. Opin. Food Sci.* **2021**, *40*, 33–39. [[CrossRef](#)]
162. Gouveia, L.; Batista, A.P.; Miranda, A.; Empis, J.; Raymundo, A. *Chlorella vulgaris* biomass used as colouring source in traditional butter cookies. *Innov. Food Sci. Emerg. Technol.* **2007**, *8*, 433–436. [[CrossRef](#)]
163. Bellini, E.; Ciocci, M.; Savio, S.; Antonaroli, S.; Seliktar, D.; Melino, S.; Congestri, R. *Trichormus variabilis* (Cyanobacteria) biomass: From the nutraceutical products to novel EPS-cell/protein carrier systems. *Mar. Drugs* **2018**, *16*, 298. [[CrossRef](#)]
164. Singh, R.; Parihar, P.; Singh, M.; Bajguz, A.; Kumar, J.; Singh, S.; Singh, V.P.; Prasad, S.M. Uncovering potential applications of cyanobacteria and algal metabolites in biology, agriculture and medicine: Current status and future prospects. *Front. Microbiol.* **2017**, *8*, 515. [[CrossRef](#)] [[PubMed](#)]
165. Okajima, M.K.; Sornkamnerd, S.; Kaneko, T. Development of functional bionanocomposites using cyanobacterial polysaccharides. *Chem. Rec.* **2018**, *18*, 1167–1177. [[CrossRef](#)]
166. Moscovici, M. Present and future medical applications of microbial exopolysaccharides. *Front. Microbiol.* **2015**, *6*, 1012. [[CrossRef](#)]
167. Hadji, H.; Bouchemal, K. Advances in the treatment of inflammatory bowel disease: Focus on polysaccharide nanoparticulate drug delivery systems. *Adv. Drug Deliv. Rev.* **2022**, *181*, 114101. [[CrossRef](#)]
168. Estevinho, B.N.; Mota, R.; Leite, J.P.; Tamagnini, P.; Gales, L.; Rocha, F. Application of a cyanobacterial extracellular polymeric substance in the microencapsulation of vitamin B12. *Powder Technol.* **2019**, *343*, 644–651. [[CrossRef](#)]
169. Asgher, M.; Qamar, S.A.; Iqbal, H.M. Microbial exopolysaccharide-based nano-carriers with unique multi-functionalities for biomedical sectors. *Biologia* **2021**, *76*, 673–685. [[CrossRef](#)]
170. Hamidi, M.; Jafari, H.; Siminska-Stanny, J.; Okoro, O.V.; Fatimi, A.; Shavandi, A. Anionic exopolysaccharide from *Cryptococcus laurentii* 70766 as an alternative for alginate for biomedical hydrogels. *Int. J. Biol. Macromol.* **2022**, *212*, 370–380. [[CrossRef](#)]
171. Razzaghi, M.; Navvabi, A.; Homaei, M.B.; Sani, R.; Michaud, P.; Homaei, A. Exopolysaccharides in Drug Delivery Systems. *Microb. Exopolysaccharides Nov. Signif. Biomater.* **2021**, 143–199. [[CrossRef](#)]
172. Sathiyarayanan, G.; Dineshkumar, K.; Yang, Y.-H. Microbial exopolysaccharide-mediated synthesis and stabilization of metal nanoparticles. *Crit. Rev. Microbiol.* **2017**, *43*, 731–752. [[CrossRef](#)] [[PubMed](#)]
173. Saha, I.; Datta, S. Bacterial exopolysaccharides in drug delivery applications. *J. Drug Deliv. Sci. Technol.* **2022**, *74*, 103557. [[CrossRef](#)]
174. Freitas, F.; Torres, C.A.V.; Reis, M.A.M. Engineering aspects of microbial exopolysaccharide production. *Bioresour. Technol.* **2017**, *245 Pt B*, 1674–1683. [[CrossRef](#)]
175. Cheah, Y.T.; Chan, D.J.C. Physiology of microalgal biofilm: A review on prediction of adhesion on substrates. *Bioengineered* **2021**, *12*, 7577–7599. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.