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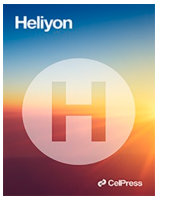

Microbial exopolysaccharides in the biomedical and pharmaceutical industries

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ABSTRACT

The most significant and renewable class of polymeric materials are extracellular exopolysaccharides (EPSs) produced by microorganisms. Because of their diverse chemical and structural makeup, EPSs play a variety of functions in a variety of industries, including the agricultural industry, dairy industry, biofilms, cosmetics, and others, demonstrating their biotechnological significance. EPSs are typically utilized in high-value applications, and current research has focused heavily on them because of their biocompatibility, biodegradability, and compatibility with both people and the environment. Due to their high production costs, only a few microbial EPSs have been commercially successful. The emergence of financial barriers and the growing significance of microbial EPSs in industrial and medical biotechnology has increased interest in exopolysaccharides. Since exopolysaccharides can be altered in a variety of ways, their use is expected to increase across a wide range of industries in the coming years. This review introduces some significant EPSs and their composites while concentrating on their biomedical uses.

1. Introduction

A wide variety of structural, useful, and profitable polysaccharides are produced by microbial cells (both Eukaryotic and Prokaryotic), which can be homopolymeric or heteropolymeric in makeup. Exopolysaccharides (EPSs) are the name given to these polymeric molecules [1,2]. Homopolymeric EPSs molecules are constructed of repeating units of a single monosaccharide, often glucose or fructose, as opposed to heteropolysaccharides, which are typically branched and consisting of repeating units of more than one monosaccharide, primarily glucose, fructose, galactose, etc., with various non-carbohydrate groups [3]. These homopolysaccharides and heteropolysaccharides have diverse industrial applications and health properties as indicated in Fig. 1.

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Exopolysaccharides (EPSs), a biopolymer with important structural and functional properties, are released by various prokaryotic and eukaryotic microorganisms, including fungi and algae, in response to biotic and abiotic stresses and to survive in hostile settings [3–5]. Microbial EPSs are exciting in a range of industrial areas due to their exceptional material properties and less toxic, fully biodegradable, and biocompatible makeup. A promising template for the quick production of metallic nanoparticles has recently been found in microbial EPSs, and EPSs-mediated metal reduction techniques are emerging as straightforward, safe, and ecologically friendly green chemistry methods [6]. Microbial polymers were first used in the 1960s, and since then, their commercial utilization has increased significantly [7]. Microbial EPSs are crucial for cellular relationships, nutrition, and both micro- and macro environments. Organisms that produce EPSs do better in oligotrophic environments and can maintain nutrient concentrations below the minimum necessary in the absence of EPSs [8,9]. EPSs are complex, high-molecular-weight polymers composed of different types of sugar monomers. The biosynthesis of EPSs is typically carried out by a group of enzymes encoded by a set of genes within a biosynthetic gene cluster (BGC) in the genome of the producing microorganism [3,5]. The biosynthesis of EPSs is regulated by several factors, including environmental conditions, growth stage, and nutrient availability [10]. With the advent of synthetic biology, it has become possible to engineer microorganisms to produce specific EPSs with desired properties. This approach typically involves modifying the biosynthetic pathways of the microorganisms by introducing or deleting genes within the BGC or by controlling the expression of these genes using synthetic promoters [11]. The use of synthetic biology in EPSs production has several advantages over traditional methods. For example, it allows for the production of EPSs with tailored properties, such as improved solubility, increased stability, and enhanced functionality. It also enables the production of EPSs at scale, which is important for commercial applications [6].

In summary, the genetic basis for producing EPSs is critical for understanding the biosynthesis and regulation of these complex molecules. In the context of synthetic biology, the genetic basis for EPSs production is essential for the development of new and

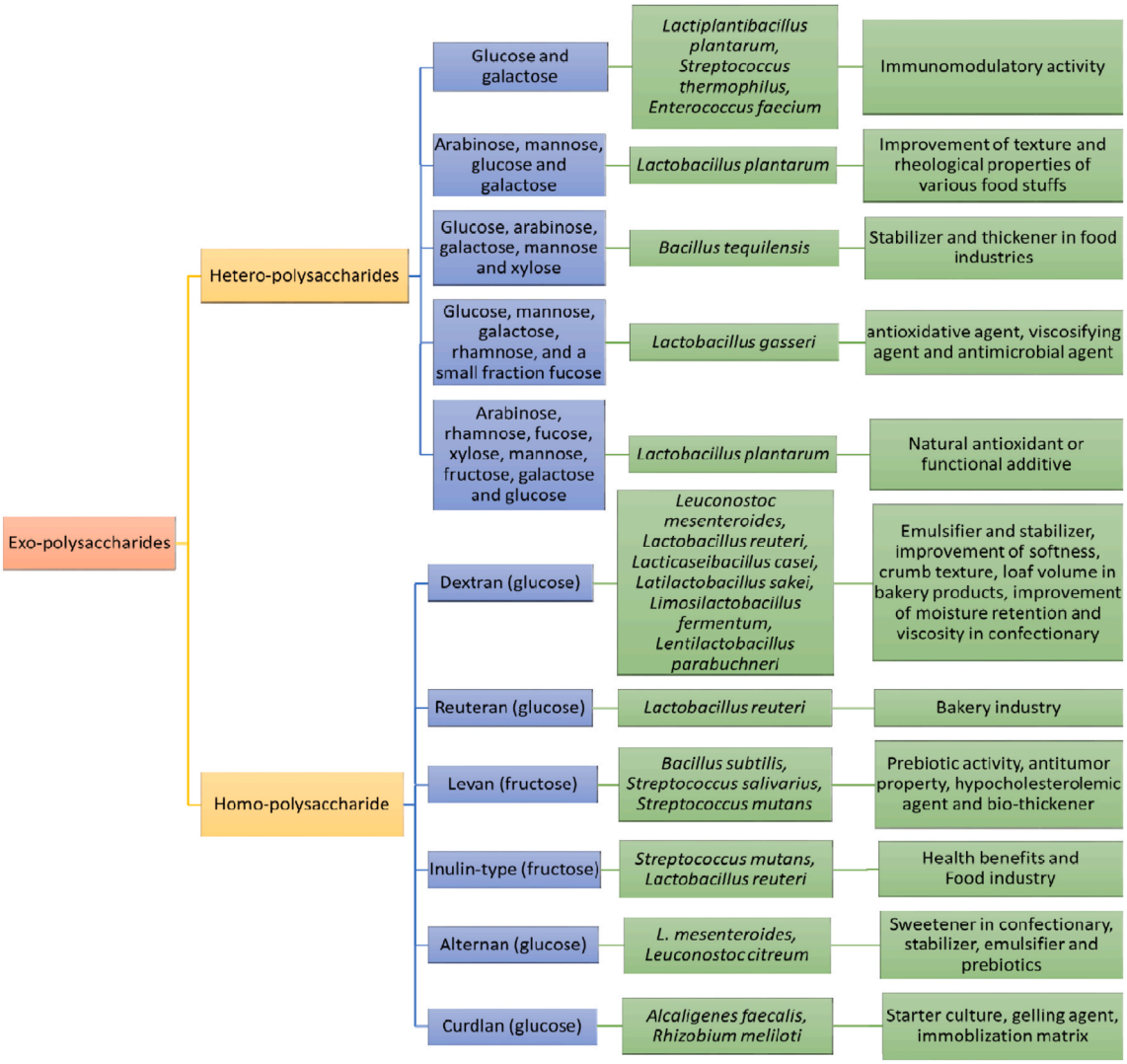


Fig. 1. Industrial applications and health properties of some homopolysaccharides and heteropolyssacharides.

improved EPSs with tailored properties and for the production of these molecules at scale [12,13]. Because of their interesting and seductive qualities, microbial polysaccharides are utilized as bio-absorbents, bio-flocculants, and drug delivery agents in the pharmaceutical industries [14]. Polysaccharides are used in the green manufacturing of silver nanoparticles because they are more beneficial than synthetic polymers. The interaction of metal ions with the hydroxyl groups of EPSs has a significant impact on the form and size of a nanoparticle [15]. Their applications range from the laboratory through the clinical to tableting and include orthopedic surgery, tissue engineering, the implantation of medical devices and artificial organs, prostheses, dentistry, bone repair, and many other fields of medicine [16]. Table 1 shows various industrial applications of microbial EPSs [10,13,16–18,19,20,21,22].

Additionally, they facilitate the controlled slow release of drugs into the body, which is a therapeutic and pharmaceutical use [17,18]. As well as being used for disease treatment, they can also be used for skin rejuvenation and wound healing [23]. A number of these polysaccharides are commercially available industrial products, while others are still being developed several of the findings of recent research on these topics are discussed in the current review [24].

2. EPSs composites

EPSs are abundant in natural sources, biodegradable, non-toxic, and biocompatible. It has been extensively researched how combining EPSs with natural and synthetic polymers affects the characteristics of such materials. Few EPSs and their composites were covered here [25].

2.1. Xanthan

Xanthan, an extracellular polysaccharide comprised of a homopolysaccharide D-glucose backbone and tri-saccharide side chains that have been modified with different levels of O-acetyl and pyruvic acid acetal, is produced by the bacteria *Xanthomonas campestris* [26]. Xanthan demonstrates notable emulsion stabilizing, particle suspension, and recoverable shear-thinning activity with high viscosities even at low concentrations. The culinary additive xanthan gum is used to make soft meals (ice cream, cheese). It is also used in the oil industry to enhance oil recovery. Xanthan can also be used to make water-based paints and dental pastes. Many sectors employ xanthan, including the creation of paints, cosmetics, pharmaceuticals, printing inks, cleaning up crude oil, and the manufacture of insecticides, detergents, and paints [27,28]. Dental pastes and water-based paints can also be created using xanthan. Many industries, such as the manufacturing of pesticides and detergents, the production of paints, the production of cosmetics and pharmaceuticals, the production of printing inks, the recovery of crude oil, and the sector of food production also depend on microorganisms for the synthesis of a variety of products [27,28]. The shear-thinning properties of xanthan are used by the paint industry because xanthan-containing paints are highly viscous at low shear rates and do not drip off the brush. Additionally, the solution's use in drilling muds for oil wells acts as a lubricant for drilling equipment [29].

- **Alginate**: Xanthan can be blended with alginate by encapsulation. Alginate (Alg), is a linear polysaccharide made of brown algae-derived 1 → 4 linked β-(*d*)-guluronic(G) and α-(l)-mannuronic (M) acids [30,31].
- **Chitosan:** Gallic acid is made biochemically from the enzyme 3,4,5-trihydroxy benzoic acid. dihydro shikimate. It is prevalent in various plant species, particularly berries. foods such as cereals, tea, wine, citrus fruits, and plants that are found naturally in ester or salt as well as in free. The goal of microencapsulation is to preserve the compound's bioactivity. Microencapsulation using the lyophilisation process in a polymer matrix preserved its biological activity and managed release [25].

2.2. Gellan

Sphingomonas paucimobilis (formally known as *Pseudomonas elodea*), is used in the aerobic fermentation procedure to produce gellan gum, an extracellular polymer with exceptional physical and chemical properties. It is made up of 1,3-D-glucose, 1,4-D-glucuronic acid, 1,4-D-glucose, and 1,4-L-rhamnose, four monosaccharide molecules [32]. Deacylation can transform native gellan gum from soft, elastic thermo-reversible gels to harder, more brittle gels with higher thermal stability [33]. Gellan gum is a bacterial polysaccharide with high commercial potential for food, pharmaceuticals, and, in particular, environmental bioremediation due to its excellent

Table 1
Industrial applications of microbial EPSs.

EPSs	Application	Reference
Xanthan	Emulsion, stabilization, suspension agent in foods, Foam stabilizing agent in foods Crystal formation inhibitor in foods, for controlling viscosity in the oil drilling mud and inkjet printing	[16,17]
Bacterial cellulose	Moisture retention during wound dressings, High acoustic diaphragms in sound reproduction	[10]
Hyaluronic acid	Hydrating agent in cosmetics, pharmaceuticals. Replacement for synovial fluid and vitreous humour in biomedicine	[13]
Emulsan	Emulsifier, vaccine adjuvant	[18]
Gellan	Gelling agent in foods, Food coatings, Various Paper coating and water flocculent	[22]
Curdlan	Used as a thickener, stabilizer and texturizer in the food industry	[10]
Pullulan	In food science, pharmacy, health care, lithography, and many other fields	[20,21]
Xylose	Used as a diabetic sweetener in food and beverage.	[19]

rheological properties [34]. Gellan gum has also been reported to be useful in the bioremediation of contaminated soils and aquifers. This gum is utilized to improve viscosity, and stabilize, or modify temperature constancy. Additionally, despite its subpar efficiency, it can be employed to increase cell proliferation. interactions or covalently bonded mechanical characteristics. Surface engineering tests must be carried out in this situation, formerly to alter the polymer's functional groups and enable an effective drug attachment. Due to its mucoadhesive qualities and ability to maintain cells at the site of implantation while promoting cell development, GG has been utilized extensively to make hydrogels for DDSs [33,35].

The capacity of GG to adhere, multiply, and differentiate cells on its surface makes it a polymer with great potential for tissue engineering. It also provides a passage between order and disorder that enables the creation of hydrogels using several methods that have distinct characteristics. Furthermore, GG is utilized to create particles and polyelectrolyte complexes that delay the release of drugs. Nevertheless, the majority of applications for GG include blends or composites due to their low mechanical resistance and high polyelectrolyte content. These characteristics preclude its use because it is the only polysaccharide in fibres and scaffolds [17,29]. Gellan gum is a high molecular weight polysaccharide produced by the bacterium *Sphingomonas elodea*. Its chemical structure consists of a linear tetrasaccharide repeating unit of two glucoses, one glucuronic acid, and one rhamnose, with acetyl and glyceryl groups attached to the glucose residues [29]. The acetyl and glyceryl substituents are responsible for the unique properties of gellan gum, such as its ability to form strong, elastic gels at low concentrations, its resistance to enzymatic degradation, and its ability to stabilize emulsions and suspensions. The acetyl groups also contribute to the solubility of gellan gum in hot water, allowing it to be easily dispersed in aqueous systems [27]. Gellan gum is widely used in the food, pharmaceutical, and biotechnology industries as a thickener, stabilizer, and gelling agent due to its unique properties. Its chemical composition and structure make it a versatile ingredient with a range of functional properties that can be tailored to suit specific applications [34].

2.3. Clavan

Clavan, which is composed of tetrasaccharide repeating units of glucose, galactose, fucose, and pyruvic acid in the molar ratios of 1:1:2:1, is one of the richest polymers in the uncommon sugar fucose. *Clavibacter* strains, particularly *Clavibacter michiganensis*, are responsible for its production [36]. The polysaccharide clavan, which contains L-fructose, may be used to treat rheumatoid arthritis, prevent the colonization of the lung by tumor cells, regulate the production of white blood cells, control the synthesis of antigens for the production of antibodies, and moisturize the skin in cosmeceuticals [37].

2.4. Dextran and its composites

Dextrans are glucans, which are glucose polymers and include 1 → 6 glycosidic connections. Additionally, certain dextran's contain connections that are α 1 → 2, α 1 → 3 and a 1 → 4 Dextrans' molecular dimensions are between 15,000 and 500,000 [38]. In the commercial manufacture of dextran, batches of mesenteroides are fermented using a culture media that includes sucrose, organic nitrogen, and organic phosphate. After crude dextran is produced, it is precipitated using alcohol and then subjected to acid hydrolysis [33,39,40].

- **Poly (vinylamine)**: A polyvinyl amine/bis (ethyl Vinylamine) ether) microgel (PVAM-BEVAME MG) is pH-neutral and has a high amine concentration. Composite made of poly (vinylamine) microgel and dextran was created by McCann et al. [41] hydrogels that include Dexox and MG particles (MG-Dexox gel). This polymer has a wide range of uses, including controlled drug delivery systems, membrane production, polymer recycling, and packaging. Studies on PVA's physical gel-forming abilities, changes in crystallinity and swelling behaviour, and dissolving mechanisms have been conducted. PVA is bio inertness and has a wide range of medicinal applications, including synthetic vitreous, haemodialysis, Nano filtration, artificial pancreas, and implanted medical devices [42]. One promising application of PVA_m is in drug delivery systems. PVA_m can form stable complexes with negatively charged drugs, such as DNA, siRNA, and proteins, through electrostatic interactions. These complexes can protect the drugs from degradation and facilitate their delivery into target cells. For example, PVA_m has been used to deliver siRNA to silence the expression of specific genes in cancer cells. PVA_m has also been investigated as a coating material for biomedical implants, such as stents and catheters. The cationic nature of PVA_m can promote cell adhesion and proliferation, leading to improved tissue integration and reduced inflammation [43,44].
- **Poly (ε-caprolactone):** Dextran-Poly (ε -caprolactone) (Dex-PCL) copolymers can be used to successfully produce stable particles with a nanometric diameter using an emulsion/evaporation technique. The PCL was confined in the core, and the dextran layer was securely bonded to the nanoparticle surface. Drugs that are insoluble in water are stored in the hydrophobic core, which is typically made of a biodegradable polymer like poly(-caprolactone), improving their apparent solubility in water. This also provides a defence against deterioration in the case of labile medications [45]. According to Wei et al. [46], polycaprolactone is a desirable biomedical polymer because of its slow biodegradability, good biocompatibility, good drug permeability, and comparatively low production cost. PCL has been used in basic research and approved for use in some clinical settings, including drug delivery systems, tissue regeneration, and wound healing [46,47]. Hydrogels for biological applications are made using polycaprolactone and dextran. The poor mechanical performance of hydrogels has limited their use in biological applications to bone tissue engineering. The application of tough hydrogels with strong and elastic properties has garnered a lot of interest, but this has been constrained by their deterioration [48].

2.5. Hyaluronic acid with its composites

A linear polymer called hyaluronic acid (HA) has important biological, rheological, structural, and physiological activities. HA can be produced through bacterial fermentation using strains of *Streptococcus* sp. and *Bacillus* sp [49,50]. The production process typically involves the following steps in Fig. 2.

- *Seed culture preparation:* The selected bacterial strain is cultured in a nutrient-rich medium until it reaches the desired cell density.
- *Fermentation:* The seed culture is then transferred to a larger fermenter containing a medium optimized for HA production. The fermentation conditions, such as temperature, pH, and agitation, are carefully controlled to ensure optimal bacterial growth and HA production. *Streptococcus zooepidemicus* typically produced HA at a pH and temperature of 7.0 and 37 °C, respectively.
- *Harvesting:* Once the fermentation is complete, the bacterial cells are harvested by centrifugation or filtration to separate the cells from the HA-containing broth.
- *Purification:* The HA is then extracted from the broth using a combination of enzymatic and chemical treatments, followed by filtration and ion exchange chromatography. The purified HA can be further processed into various molecular weight fractions for specific applications.
- Formulation: Finally, the purified HA is formulated into various products, such as dermal fillers, ophthalmic solutions, and joint injections [49]. Fig. 3 shows a schematic presentation of hyaluronic acid production using *Streptococcus zooepidemicus* [51].

It is believed to have characteristics that can have an impact. the treatment of cancer, angiogenesis, wound healing, cell motility, and cell adhesion, and has numerous uses in the cosmetic industry in artificial tears, and in the medical field as skin moisturizers Treatment for osteoarthritis as a substitute for eye fluid in ophthalmic surgery, joint lubricant, and adhesion prevention surgery on the abdomen, healing of wounds, and surface coating [52]. Hyaluronic acid (HA) is produced through bacterial fermentation, mainly by strains of *Streptococcus* sp. and *Bacillus* sp. The production process involves the use of a growth medium containing a carbon source (e.g., glucose), nitrogen source (e.g., yeast extract), and salts. The bacteria are cultured in the growth medium under controlled conditions, such as pH and temperature, for several days. After fermentation, the HA is extracted and purified from the culture medium using various methods, such as filtration, centrifugation, and precipitation. Finally, the purified HA is formulated into various products for use in the medical, cosmetic, and pharmaceutical industries [49,51].

- **Polyacrylic acid:** There are two ways to functionalize native polysaccharides using grafting, "Grafting to" and "grafting from" are examples of grafting techniques. The salt of sodium in Grafting polymers such as polyacrylic acid (PAA) is used. Nakagawaa et al. [53] created a biocompatible calcium salt of HA grafted with PAA (HA-g-PAA).
- **Chitosan**: Chitosan NPs are most successfully produced using ionotropic gelation. Pentasodium tripolyphosphate (TPP) is used in this method to ionically cross-link chitosan chains while cargo molecules are present. The ionotropic gelation technique involves dissolving chitosan in an acidic solution, often acetic acid, to produce positively charged chitosan molecules. TPP contains phosphate groups that can interact with the amine groups of chitosan, forming ionic crosslinks between the chitosan chains. This leads to the formation of chitosan nanoparticles. The addition of TPP to the chitosan solution results in the formation of chitosan-TPP complexes, which can entrap cargo molecules, such as drugs or proteins, during nanoparticle formation [54]. The cargo molecules are trapped within the chitosan-TPP complex, allowing them to be delivered to their target site. This method has several advantages, including the ability to encapsulate a wide range of cargo molecules, ease of scalability, and low cost. However, the

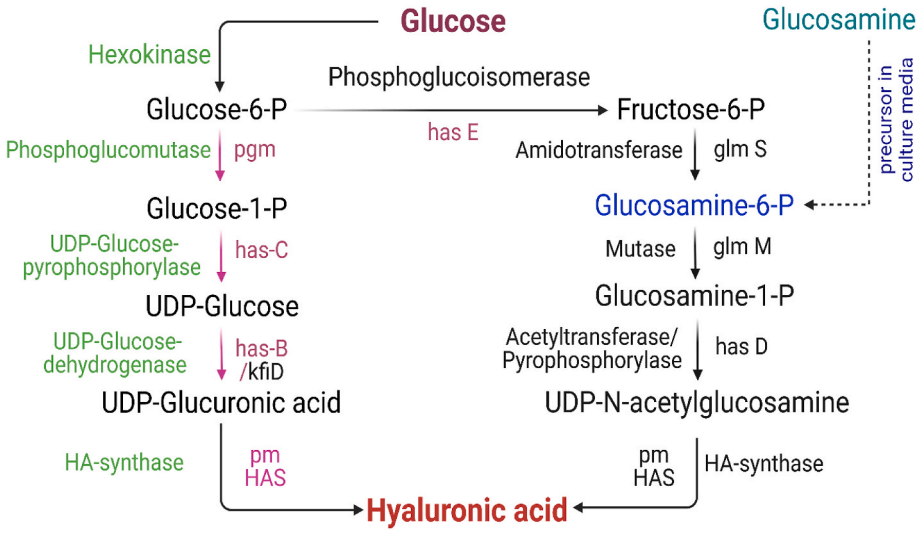


Fig. 2. Hyaluronic acid production processes or steps.

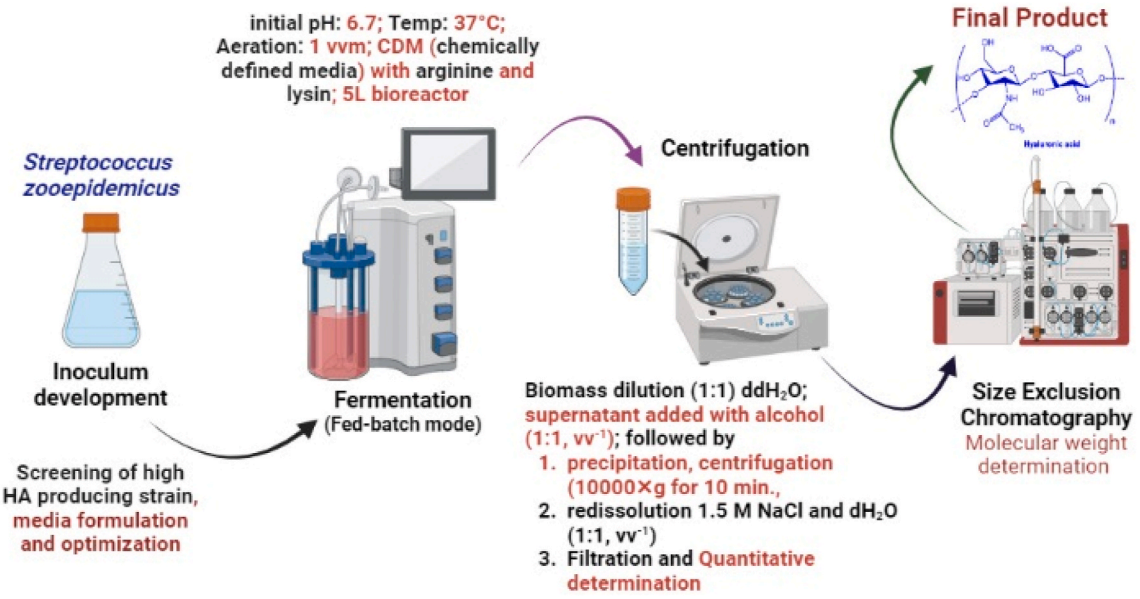


Fig. 3. Schematic presentation of hyaluronic acid production using *Streptococcus zooepidemicus*.

method also has some limitations, such as batch-to-batch variability in particle size and low drug loading capacity. Overall, ionotropic gelation with TPP is a commonly used method for preparing chitosan nanoparticles for drug delivery applications [55]. The physicochemical characteristics of chitosan NPs were enhanced by adding HA [52,56].

- **Gelatin:** Gelatin, a collagen product that has partially disintegrated, is thought to have a lower antigenicity than collagen. Furthermore, it includes amino acids and is more affordable than collagen. The amino acid sequences that can improve cell adhesion, like the RGD of collagen [57]. Therefore, to create 3-D models, gelatin has been combined with various natural or synthetic biomaterials. scaffolds created via a variety of techniques for diverse tissue engineering purposes [58,59]. Gelatin and

Table 2
Exopolysaccharides LAB producers and their corresponding applications.

S·N.	Bacterial strain	Source	Applications	Reference
1	*Leuconostoc mesenteroides*	Fermented sourdough	Levan up-regulates anti-inflammatory cytokine IL-4	[13]
2	*Lactobacillus bulgaricus*	Bulgarian yoghurt	EPS activated NK cells, with the contribution of INF-γ, IL-12, IL-18 cytokines via MyD88-driven signaling in mice	[70]
3	*Lactobacillus plantarum*	Tunisian traditional fermented food	EPS induced gene expression in immunity and antioxidant responses in fish	[13]
4	*Lactobacillus helveticus* LZ-R-5	Tibetan kefir	In-vitro immunomodulatory activity	[69]
5	*Lactobacillus plantarum* H31	Pickled cabbage	Reduce α-amylase activity and up-regulation of GLUT-4, AKT-2 and AMPK gene expression in insulin-resistant HepG2 cells	[65]
6	*Lactobacillus plantarum*	Chinese Paocai	*c*-EPS significantly inhibited the proliferation of HepG-2, BGC-823, especially HT-29 tumor cells	[13]
7	*Lactobacillus plantarum 86, Weisella confusa AI10, Pediococcus parvulus AI1, Weisella cibaria 142*	Indian fermented foods	Antibacterial activity *E. coli*	[13]
8	*Lactobacillus plantarum LRCC5310*	Kimchi	In-vitro anti-viral activity against Rota virus induced diarrhea and regulates inflammatory response	[71]
9	*Lactobacillus plantarum HY*	Sichuan pickle	Antioxidant activity and α-amylase inhibitory activity	[66]
10	*Leuconostoc citreum* L3C1E7	Artisanal cheese	Suppresses allergen-specific IgE synthesis and may alleviate Th2-mediated allergic symptoms	[13]
11	*Lactobacillus plantarum JLK0142*	Tofu	Improvement of the intestinal immunoglobulin A(IgA) content and the serum levels of the cytokines, IL-2 and TNF-α	[64,73]
12	*Lactobacillus paracasei M7*	Human breast milk	Antioxidant, *anti*-biofilm and hypocholesterolemic activity	[68]
13	*Lactobacillus plantarum WLPL04*	Breast milk	Inhibits the adhesion of *E. colianti* O157:H7 to HT-29 cells, antitumor activity and anti-tumor activity against pathogens	[13]
14	*Lactobacillus plantarum MTCC9510*	Curd	Antitumor activity and immunomodulatory activities	[72]
15	*Lactobacillus gasseri*	Human vagina	L-EPS of *L. gasseri* strains inhibit proliferation and induce apoptosis in HeLa cells in strain dependent manner	[67]
16	*Enterococcus faecium WEFA23*	Healthy infant's feces	Antioxidant activity and strong inhibition against the adhesion of *Listeriamono cytogenes* CMCC54007 on HT-29 cells	[65]

HA, two biopolymers, could be used to create macropore-sized elastic cryogels. appropriate as scaffolding materials for adipose tissue engineering [58].

- **Collagen:** The creation, maintenance, and repair of connective tissues depend heavily on collagen and the protection of organs and tissues. Productively, human-like collagen (HLC) is expressed by *Escherichia coli* recombinant strain BL21 [19]. To create HA/HLC hydrogels, cross-linked HA/HLC using 1, 4-butanedioldiglycidyl ether (BDDE) is recommended [25].

Exopolysaccharides have recently attracted interest from a variety of sectors, including agriculture (preservatives, bioherbicides, and microbicides), and health (medicine and pharmaceuticals, and cosmetics), all of which are important to human activities. Additionally, to surgeries, biopsies, diagnoses, and many other procedures, the medications also contain preventative and antibacterial treatments. As natural, non-toxic materials, EPSs are changing how people receive medical care around the world through a variety of means [60].

Exopolysaccharides are made by both bacteria and fungi, however, it is still unclear which produces EPS more effectively because fungi have greater structural and cellular complexity than bacteria. In the past, endophytic fungi and mushrooms have been widely employed as important sources of beneficial industrial exopolysaccharides [61]. Exopolysaccharides are obtained from sources including bacteria and archaea bacteria [62]. Dextran, xanthan, and gellan gum are the three exopolysaccharides that are frequently made by prokaryotes. Additionally, discovered to be effective EPS makers are thermophilic bacteria like *Geobacillus sthermodenitrificans* and *Bacillus thermantarcticus*. Exopolysaccharides in the form of surface biofilm from thermophilic and halophilic archaea, including *Thermococcus, Sulfolobus, Archaeglobus fulgidus*, and *Thermococcus litoralis,* respectively [63]. Myxobacteria primarily create polysaccharides for their ability to move, as well as for defence against phagotrophic and dehydration [13,64,65,66,67,68,69,70,71,72,73] Table 2.

3. EPSs applications in the biomedical and health sector

The pharmaceutical industry's acceptance and use of EPSs have recently created a new possibility for researchers to make use of novel bacteria. EPSs can be changed by blending or combining natural and synthetic materials [23]. Lactic acid bacteria (LAB), a group of bacteria that produce lactic acid as a metabolic by-product, have been widely studied for their EPSs production abilities [20,74]. Numerous investigations have shown that LAB is capable of creating a variety of antimicrobial molecules, such as bacteriocins, diacetyl, organic acid, carbon dioxide, and certain other low-molecular-weight substances like reuterin, reutericyclin, and antifungal peptides [59]. In addition to these substances, EPSs produced by LAB have been well documented by numerous researchers for their capacity to display antagonistic effects versus pathogenic bacteria. Under in-vitro conditions, the *Lactobacillus rhamnosus* that produces EPSs and was isolated from human breast milk had high antibacterial activity against pathogenic *Escherichia coli* and *Salmonella typhimurium* [75,76]. Instead of preventing pathogenic bacteria from proliferating, EPSs from the probiotic bacterium *Bifidobacterium longum* inhibit cell division [21].

A few of the metabolites created by LAB are lactic acid, acetic acid, ethanol, flavourings, bacteriocins, and exopolysaccharides (EPSs). Both EPSs and LAB can play a part in the probiotic properties of fermented items, influencing the quality of the finished goods

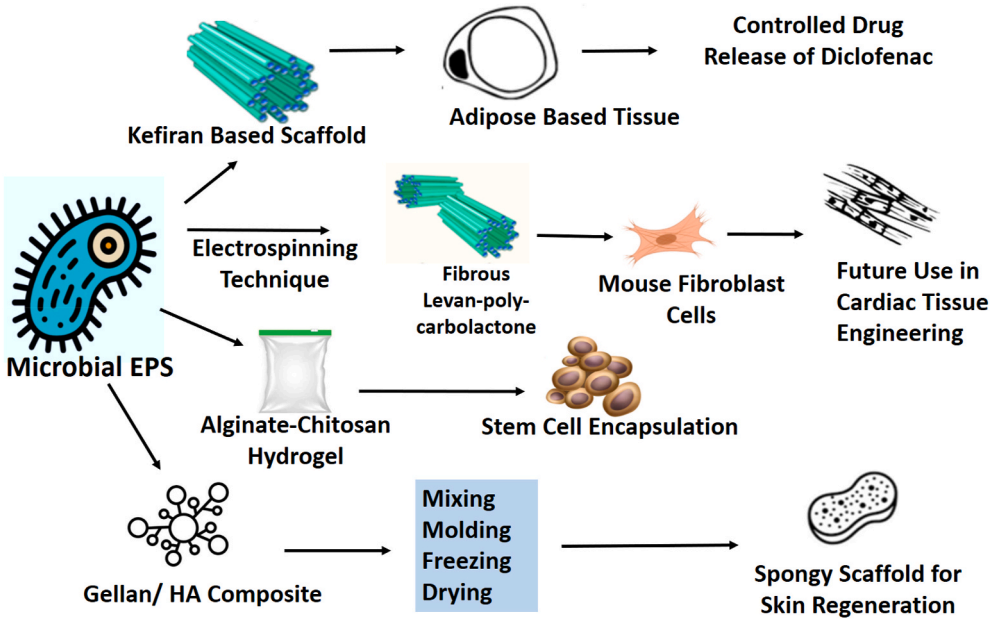
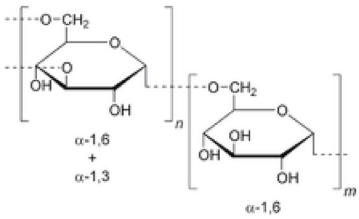
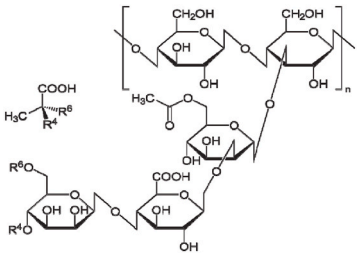
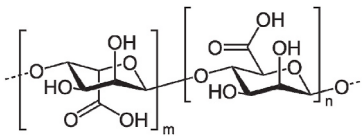
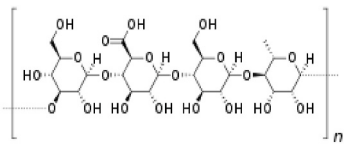
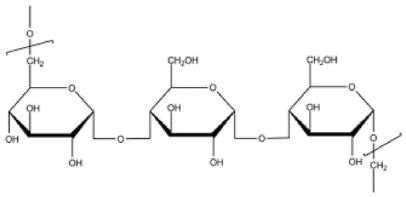
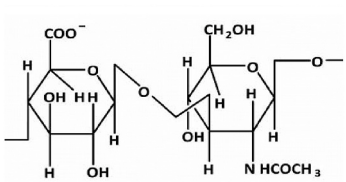


Fig. 4. Microbial EPSs and composites as scaffold in tissue engineering.

[77]. By adding to the texture, flavour, and perfume of fermented items, EPSs enhance food's physicochemical properties while shielding the cell from external harm. Additionally, the addition of viscosity, structural enhancement, stabilizing effects, and water-binding qualities in fermented goods are all impacted by EPSs. The food industry uses EPSs as a commercial stabilizer due to these qualities. EPSs can be significant for human health in addition to their technological benefits. As an illustration, it was claimed that EPSs synthesized by LAB had antioxidant, anticancer, and anti-inflammatory properties [78]. As microorganisms grow, they release long-chain polysaccharides with or without branched sugar units. The production of EPSs can be divided into two types: homo-polysaccharides containing a single monosaccharide and heteropolysaccharides containing more than two monosaccharides [79]. Sugars such as glucose, galactose, and rhamnose make up the homopolysaccharide unit of EPSs. The best-known LAB-producing homopolysaccharides are *Leuconostoc mesenteroides* and *Streptococcus mutans* (Fig. 4). *Lactococcus lactis*, *Streptococcus sobrinus Streptococcus gordonii Streptococcus thermophilus*, and *Lactobacillus* spp. viz. *Lactococcus lactis, Lactobacillus casei, Lactobacillus helveticus, Lactobacillus delbrueckii* subsp. *bulgaricus and Lactobacillus rhamnosus and Lactobacillus kefiranofaciens* are examples of heteropolysaccharide-producing LAB [64,22]. Metabolites produced by LAB are not only protective of cells against external factors, but they are also beneficial for human health.

The production of EPS plays an important role in LAB's antioxidant, immunomodulatory, and anticancer properties. Fig. 4

Table 3
Applications of EPS in health care.

EPS	Chemical structure	Monomer composition	Main producing microorganism	Applications	Reference
Dextran		Glucose	*Leuconostoc mesenteroides*	Expander of blood plasma (regulate wound shock)	[18]
Xanthan		Glucose (2), mannose (2), acetate, pyruvate, glucuronic acid,	*Xanthomonas campestris*	Suspension stabilizer, Thickener agent in pharmaceutical creams and other suspensions Controlled release carrier	[26]
Alginate		Mannuronic acid, acetate guluronic acid	*Azotobacter vinelandii, Pseudomonas aeruginosa*	Antacid (anti-reflux) stomach protectors, dental impressions, microspheres for drug delivery, and fibres in wound haemostatic dressing and bandage	[30,31]
Gellan		Glucose, glucuronic acid, rhamnose, glycerate, acetate	*Sphingomonas paucimobilis*	Excipient in oral, ophthalmic, and nasal drug formulations, for controlled tablet disintegration.	[33–35]
Pullulan		Maltotriose	*Aureobasidium pullulans*	Tablet granulation and coating, binder. Oxygen impermeable film forming, non-animal capsules, oral, and wound healing products	[18]
Hyaluronic acid		Glucuronic acid and N-acetyl-glucosamine	*Streptococcus equisimilis/ zooepidemicus; Bacillus subtilis*	Chronic, difficult wound healing; osteoarthritis treatment (intraarticular injection); eye surgery (vitreous substitution/ replacement)	[18, 51–53]

illustrates other potential health-promoting functions of EPS [80]. Free radical production in the body has a major negative impact on health. Free radicals harm proteins, RNA, and DNA. Since some of the procedures employed to stop it are artificial, there have been concerns about potential negative repercussions. It is crucial to use natural antioxidants like EPS to stop free radicals because of this. In the past, it was discovered that *Lactobacillus plantarum* JLAU103 could make EPSs and that the EPSs it produced had antioxidant activity from hurood cheese, a fermented food made in China [81,65]. EPSs production by probiotic bacteria also has several effects on probiotic action, such as colonization, immune modulation, and protection under harsh conditions in the gut [18,82,83].

Consumers' recent preferences are pushing the food sector to create functional foods with functional ingredients. One of these essential components with intriguing functional roles is EPSs created by LAB. A vast variety of EPSs are produced by LAB, and these EPSs' health-promoting properties are somehow connected to their fundamental structure [13,76,82]. Table 3 shows exopolysaccharides LAB producers and their corresponding applications. Therefore, more research is needed to find more EPSs structures in LAB and investigate their health-promoting properties, including immune modulation, antiviral, and antioxidant effects [13,61,64,65,80,81,67,68–70,84].

Phellinus linteus, Fusarium sp., *Ganoderma lucidium, Pleurotus* sp., and *Inonotus obliquus* are some examples of fungi that have been used extraction of exopolysaccharides [61,85,73]. Fungi, such as *Aspergillus niger* and *Penicillium* sp., create extracellular photopolymers of glucose that are used in the food and cosmetic industries [86]. Some fungi glucans have linkage β (1,3; 1,6) and β (1,3) which makes them useful in anti-inflammatory, anti-tumor, and immunomodulation activities [59]. Dextran is a vector molecule that is made by the bacteria *Streptococcus, Lactobacillus, Leuconostoc mesenteroides, Gluconobacter,* and *Xanthomonas campestris* [21,87]. It helps to deliver drugs to the specific target for the action [17,88]. Exopolysaccharides are also observed to be used as a blood flow tonic, blood plasma extender, and anticholecterolics [22]. A placebo and nasal formulations are administered using gellan made from *Pseudomonas elodea* and *Sphingomonas paucimobilis*. Exopolysaccharides from *Lactobacillus helveticus, Rhodotorula glutinins, Alteromonas infernus,* and *Leuconostoc paracasei* have also been discovered to possess strong anticancer, antioxidant, antiviral, and anticoagulant effects [22]. Additionally, it has been discovered that exopolysaccharides can promote cell growth, operate as an anti-tumor agent, and cause favourable physiological reactions. EPS generated by *Cordyceps sinensis* Cs-HK1 also aids in immunomodulatory activities. From the *Schizophyllum commune,* schizophrillian contains anti-tumour and immune-stimulating properties. The schizophyllan that has been sulphur-modified has better potential as an anti-retroviral treatment for the Human Immunodeficiency Virus because the macromolecule strengthens the immune system's defence against malignant cells [89]. In addition to being incredibly helpful in wound dressings for patients with burns and persistent skin ulcers, *Acetobacter xylinum's* EPS (BioFill) is employed as an implantable material in plastic surgery [90,91].

The use of EPSs in a variety of biomedical applications, including drug delivery systems, scaffolds, and coating materials for medical and surgical sealants, is encouraged by their biocompatibility and functional qualities. EPSs may be employed in their natural form, cross-linked, or modified with different bioactive substances. EPSs have demonstrated strong biocompatibility, biodegradability, and mechanical strength as natural-based materials, which are advantageous for the development of biological scaffolds. For bone tissue creation, gellan hydrogels customized with hydroxyapatite have been created [92]. Hydroxyapatite was heated and combined with a low-acyl gellan solution. The gel was created, cooled to room temperature, and then freeze-dried to produce a spongy construct [93].

The gelatinous substance known as alginate is taken from the cell walls of bacteria or brown algae. There has been research on the viability of encapsulated human stem cells in alginate-chitosan hydrogels. The ability of an ALG-based hydrogel to stimulate the regeneration of the retinal pigment epithelium (RPE) was revealed in a study. Taurine, a neurotransmitter found in retinal tissue, was added to the scaffold to support RPE cell immune defense. In vitro, tests of the taurine-loaded ALG hydrogel on RPE cell migration and proliferation were encouraging. When implanted in naked mice, the scaffold also demonstrated good biocompatibility and biodegradability [94].

3.1. EPS and composites in drug delivery systems

EPSs also offer qualities that make them useful for the biomedical sector. They are very hydrophilic and typically form pseudo plastic solutions in water, in addition to having biocompatible and biodegradable qualities. Due to their favourable rheological properties, they are suitable for industries like food and cosmetics where viscosity can be crucial [95]. The potential of exopolysaccharides for Medical and healthcare applications has been examined in several articles. Alginate blend has been cross-linked with various divalent cations to create hydrogels that can be used to make scaffolds and deliver medicines in the form of beads. The molecules, chains, etc. that make up a gel are linked together in a fluid medium by electrostatic interactions, crosslinking, or macroscopic entanglements. The term "hydrogel" refers to three-dimensional polymeric networks that have enormous water or biological fluid absorption capacities [31]. Cross linkers and the provision of experimental conditions for the generation of physical chain entanglements are two ways to create gels. Alginate, a copolymer made up of -*d*-mannuronic and -*l*-guluronic acids, is derived from the bacterium *Azotobacter vinelandii* and has a molecular weight range of (0.5–1.5) 106 Da. Because of their comparable structures, alginate from bacteria and alginate from Seawood has similar qualities. Due to an increase in its G-length chain, microbial alginate is a stiffer polymer, which is the primary distinction [43]. Alginate has a variety of uses, including wound dressing, encapsulating substances, and boosting water solubility. Alginate beads have been widely employed for many applications because of their gelation, which is caused by crosslinking with divalent cations (Ca^{2+} or Ba^{2+}) [96]. Exopolysaccharide-Coated Nanoparticles Nanomaterials have a high surface area to volume ratio, making them more reactive and useful in all applications than other types of materials. Using a DDS in nanoparticle form, disease therapy is one of the key applications of nanotechnology. Typically, nanoparticles for DDSs are made up of an outside "shell" material made of EPS and an inner "core" material with active chemicals (Fig. 5). These can be categorized

based on the material used for the core or shell (e.g. organic-inorganic, inorganic-inorganic, etc.) or based on the characteristics of the shell or core [97]. However, there are situations when the medicine adheres to the carrier's surface using electrostatic charges. co-valent bonds or interactions. Surface engineering tests must be carried out in this situation. formerly to alter the polymer's functional groups and enable an effective drug attachment [96].

3.2. Use of EPSs in cosmetics

EPSs produced by microorganisms are biocompatible and non-toxic, which expands their use in the beauty sector. The hydrophilic EPSs have a great capacity to hold water, which aids in keeping skin compositions moist [98]. Dextran is a well-known EPSs made from glucose polymer. *Leuconostoc mesenteriodes* and *Streptococcus mutans* are two examples of the Leuconostocaceae family of microorganisms from which dextran is derived [99]. Dextran is used in the cosmetics industry as a skin brightening and smoothing agent because it helps to improve skin firmness, encourages brightness, and minimizes wrinkles. Dextran are utilized as an anti-inflammatory because it increases blood flow and increases the production of nitric oxide (NO) in human epidermal keratinocyte cells [38,98].

Alginate EPS, which can hold onto water, was discovered to be produced by *Azotobacter vinelandii* and *Pseudomonas aeruginosa* [100]. Alginate is used in skin and cosmetic formulations as a thickening agent, gelling agent, and excipient. The complex heteropolymer EPS xanthan is produced by *Xanthomonas campestris* [101]. Xanthan is utilized in skin formulations to aid in skin-smoothing and moisturizing since it also has thickening qualities and helps in gelling. Additionally, it has been discovered to help reduce *trans*-epidermal water loss in keratinocyte cells. It is also helpful in skin formulations as an emulsifier and foaming agent [102]. A glycosaminoglycan (GAG) called hyaluronic acid (HA) is made up of the amino acids -4-glucuronic acid (GlcUA) and -3-N-acetyl-glucosamine (GlcNAc) [98]. In skin lotions, serums, and cosmetic surgery, HA is utilized as a dermal filler. Because of its ability to retain moisture, sodium hyaluronate is used as an active ingredient in these products, which also helps to improve skin firmness and elasticity [50]. The skin's melanin pigment provides its colour and serves to shield it from UV light's damaging effects as well as to stop the development of cancer. Hyperpigmentation, or the darkening of the skin, is caused by melanocyte overproduction. As people age, melanocyte management, control, and distribution become erratic, giving the skin the appearance of dark, discoloured areas [103]. Tyrosinase is a crucial enzyme in the production of melanin, and by decreasing it, hyperpigmentation can be effectively minimized. Phlorotannin and 7-phloroeckol, two chemicals produced by the marine brown seaweed *Ecklonia cava*, can block the action of tyrosinase, hence lowering melanogenesis and being employed as a potential skin-lightning agent [104]. Astaxanthin, which belongs to the carotenoid family and is produced by *Haematococcus pluvialis*, has been reported to have similar effects [105].

3.3. Use of EPSs in the food industry

Whether it is in its natural state or has been processed, food has always been a vital component of human existence. In the

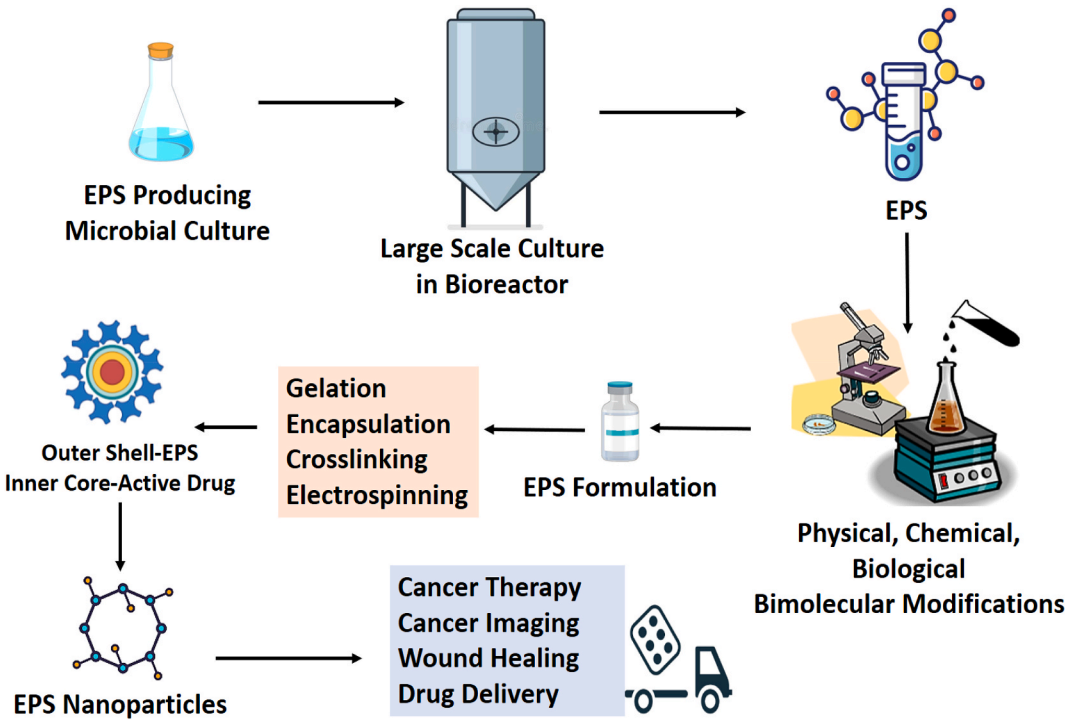


Fig. 5. Use of EPSs in nanoparticle mediated drug delivery system.

manufacturing, processing, and preservation of food, EPSs are helpful. In dairy products and fermented foods like milk, curd, sour cream, yoghurt, cheese, and buttermilk, EPSs from lactic acid bacteria like *Lactococcus lactis, Leuconostoc mesenteroides, Streptococcus thermophilus, Bifidobacterium bifidum,* and *Pediococcus acidilactici* is helpful. It is also used to improve the flavor, taste, texture, and shelf life of fermented foods [36,22]. Dextran enhances viscosity and speeds up the crystallization of sugar in confections, whereas xanthan and emulsan (*Pseudomonas fluorescens)* are used in different food sectors as stabilizers, emulsifiers, suspensors, and thickening agents, respectively. The fungus *Aureobasidium pullulans* produce pullulan, which is utilized in the food industry as a viscosity stabilizer and thickening [90]. Most of the uses of EPSs in the food sector are summarized in Fig. 1. EPSs are utilized, in particular, to improve the rheology of foods that have undergone fermentation. EPSs are regarded as a natural texturizer and a superior substitute for various synthetic or novel biopolymers used in food as a gelling agent, as well as for thickening and suspending food [106]. The primary microbial exopolysaccharides, including dextran, pullulan, xanthan, gellan, scleroglucan, and curdlan, have enormous industrial uses for food preparation. The study talks about the unique physical characteristics of EPSs that primarily define their use in the food industry and the health advantages of EPSs [1,10,60]. For several years, bakeries can use the EPS produced. Dextran was formerly added to sourdough because of its ability to thicken. Nowadays, EPS is used more frequently in the bakery sector, particularly when making gluten-free goods. The only method of treatment for celiac disease is a gluten-free diet. With a hereditary predisposition, the chronic autoimmune condition known as celiac disease largely causes small intestinal inflammation and malabsorption [107]. The sole remedy is a gluten-free diet. It is quite difficult to make bread gluten-free because gluten is a fundamental component of bread's structure and quality. Low water absorption, altered crumb properties, lower bread volume, and poor stability characterize gluten-free products [108–110].

The advantageous impact of bread's EPSs can connect to other dough ingredients to build networks that hold water together. Because of the enhanced structure, volume, and rheology of wheat bread, crumb softness has increased, staling rates have decreased, and shelf life has increased [111]. The dextran produced by *Weissella confusa* is said to enhance the quality of whole-grain pearl millet bread dough by boosting bread-specific volume, lowering the staling rate and moisture loss, enhancing crumb firmness, and reducing crumb hardness [112]. Additionally, it was shown that *Weissella confusa* Ck15's dextran increased the viscosity of chickpea sourdough [113]. The meat products' quality attributes were altered by the EPSs created in labs, which also increased the spreadability of the uncooked sausages with less fat. It has been noted that EPSs are employed in a variety of meat matrices, including cooked ham, rebuilt ham, raw fermented sausages, and raw fermented sausages with reduced fat. The texture of meat products is improved by the EPSs created [114]. Exopolysaccharides produced by lactic acid bacteria are found in beverages that resemble yogurt made from plants [22, 115]. The demand for diet-free alternatives has surged due to people's growing interest in veganism. Making products with consumer-acceptable taste and texture is thus a significant task. As the EPSs enhance the texture and taste qualities and lengthen the shelf life of the plant-derived goods, they are utilized to produce fermented foods made from plants, such as yogurt-like beverages and cheese substitutes [70,116,117]. *Weissella confusa*, a producer of EPSs, and a *Lactiplantibacillus plantarum* strain have been reported to produce fermented beverages using quinoa. A viable method for substituting additional hydrocolloids in plant-based yogurt substitutes is fermentation with EPSs [29,108,118]. Yogurt made from EPS starter culture has higher sensory qualities, a high apparent viscosity, and a low amount of syneresis. Dextran is used in the production of ice cream as a stabilizer and viscosifier. Ice cream's physical, chemical, and rheological characteristics were shown to have improved [22,90,119].

4. Conclusion

Microbial exopolysaccharides (EPSs) have been extensively investigated for their potential biomedical and pharmaceutical applications due to their unique physicochemical and biological properties. EPSs are high molecular weight polysaccharides produced by microorganisms that are secreted into the extracellular environment. Exopolysaccharides are a varied group of biodegradable polysaccharides with diverse biological and biochemical properties. They are compatible with the environment, biomes, and humans. It is good knowing that these polysaccharides are formed under stress by bacteria, algae, fungi, mammals, and plants. It has been observed that these bio-polysaccharides derived from different biogenetic resources are of great usage for living beings and thus these variable bioactive, inexpensive bio surfactants, bio emulsifiers, and exopolysaccharides are industrially produced for biotechnological, pharmacological, industrial and medical applications. These EPSs are effective against osmotic stress, desiccation, phagocytosis, cell recognition, phage attack, hazardous substances, and antibiotics. The industries of cosmetics, pharmaceuticals, and food can all benefit from the use of EPSs. Thus, it can be concluded that EPSs are observed as non-toxic and natural products, and also their different activities are useful for further research can be done to extract more and more useful exopolysaccharides from microbes. Advances in fermentation technology and genetic engineering are expected to increase EPSs production and reduce costs, making them more accessible for biomedical and pharmaceutical applications. The future of microbial EPSs in the biomedical and pharmaceutical industries looks promising, with the potential for the development of new therapies and treatments that can improve human health. EPSs have shown potential in cancer therapy due to their ability to stimulate the immune system, inhibit tumor growth, and enhance the efficacy of chemotherapy drugs. They can be used as delivery vehicles for gene therapy due to their ability to encapsulate and protect DNA from degradation. EPSs have been shown to have antibacterial properties and can potentially be used as alternative antibacterial agents to combat antibiotic resistance. EPSs have anti-inflammatory properties and can potentially be used as a natural alternative to synthetic anti-inflammatory drugs. Apart from these they also can be used in treating neurological disorders such as Alzheimer's and Parkinson's disease due to their ability to cross the blood-brain barrier and reduce neuroinflammation. Overall, the future uses of microbial EPSs in medicines look promising, with significant potential for developing new therapies and treatments that can improve human health.

Author contribution statement

Ashwini A. Waoo: Conceived and designed the study; wrote the paper.
Sukhendra Singh: Analyzed and interpreted the data.
Ashutosh Pandey: Conceived and designed the study; wrote the paper.
Gaurav Kant: Analyzed and interpreted the data.
Kamlesh Choure: Performed data collection; wrote the paper.
Kassian T. T. Amesho: Analyzed and interpreted the data; wrote the paper.
Sameer Srivastava: Analysis tools and data collection; wrote the paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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