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Amrutha TA
PhD Scholar, Dept. of Dairy Microbiology, VKIDFT, Mannuthy, Kerala, India

AK Beena
Professor and Head, Dept. of Dairy Microbiology, VKIDFT, Mannuthy, Kerala, India

Correspondence:
Amrutha TA
PhD Scholar, Dept. of Dairy Microbiology, VKIDFT, Mannuthy, Kerala, India
Email: amutha.ayyappankutty15@gmail.com

Microbial Exopolysaccharides: A Promising Health Booster

Amrutha TA, AK Beena

ABSTRACT

Microbial exopolysaccharides (EPS) are long-chain polysaccharides that are synthesized and secreted by microorganisms into the external matrix. In bacteria, EPS can either be associated with the cell surface in the form of capsules or be secreted into the environment. The yield of EPS is influenced by various factors, including the growth conditions and composition of the growth media. EPSs are high molecular-weight carbohydrates that consist of a backbone of repeated subunits of monosaccharides in varying ratios. Recently, there has been an increasing interest in EPS-producing microbes with Generally Recognized as Safe (GRAS) status. These food-grade organisms have the potential to produce polymers that can control the rheological and functional properties of food systems. EPSs have also been reported to have prebiotic and immune-modulating functions like anticancer, antidiabetic, antiviral, etc. The increasing recognition of the association between EPS and health benefits suggests the potential of EPS-producing starters with functional characteristics in the production of value-added functional products. Such products align with consumer demand for natural and healthy alternatives with fewer additives. The exploration of functional means of EPS in Pharmacology will provide an opportunity to identify novel and robust microbial resources producing unique EPSs.

Keywords: Microorganism, Exopolysaccharides, Immunomodulation.

INTRODUCTION

Exopolysaccharides (EPS) are the organic macromolecule, synthesized during the fermentation process by various microbes using different carbon sources and are secreted outside the cell wall or as slime or into the extracellular medium as jelly-like material. In 1972, I.W. Sutherland coined the term "exopolysaccharides" to typify the polysaccharides extracted from bacteria [1]. EPSs are one of the potential bioactive functional molecules produced by microorganisms. During their biosynthesis, the polymerization of simple or identical building blocks will take place, which may be arranged as repeating units within the polymer molecules. The exopolysaccharides are classified mainly into homo-exopolysaccharide and hetero-exopolysaccharides. Homoexopolysaccharides are consisting of a single type of monosaccharide such as glucans, fructans, and galactins. In the case of hetero-exopolysaccharides, they are formed by the polymerization of different types of monosaccharides and their derivatives. The functional attributes of microbial EPS are not confined to a particular field but spread over different niches like Medicine, food, cosmetology, textiles, and many others. These polysaccharides may contribute to human health, by their anti-tumoral, antiulcer, immune modulating, or cholesterol-lowering activity. Therefore, EPS has the potential to be used for development and exploitation as functional food ingredients with both health and economic benefits. The production and approval of dextran from *Leuconostoc mesenteroides* in 1947 and the approval of food-grade xanthan from *Xanthomonas campestris* in 1969 by the United States Food and Drug Administration (FDA) are important milestones that paved the way for large-scale application of microbial EPS [2,3]. Some of the microbial EPS that are commonly used and the organisms from which they are obtained are given in Table 1 and the application of EPS in various industries is illustrated in Figure 1.

Health Aspects of Microbial Exopolysaccharides

Anticancer

Although the idea of bacterial cancer therapy has been around for more than a century, it is still in its infancy. The complexity of tumor biology makes many passive treatments difficult to use, however, microbes have special properties that can circumvent these limitations. Microbial metabolism, motility, and sensitivity can lead to site-specific therapy that is harmless to adjacent tissues while being highly tumor-targeted. Extracellular polysaccharides have been studied for their potential anticancer activities, and their effects are thought to be mediated by various mechanisms. While the specific mechanisms may

vary depending on the type of EPS and the cancer cell line studied, they include some common modes of action:

1. Cell cycle regulation: exopolysaccharides are reported for their regulating effect in the cell cycle progression of cancer cells. They can induce cell cycle arrest at specific phases such as G0/G1, S, or G2/M (Cell cycle phases), thereby arresting the cancer cell cycles.

2. Inhibition of proliferation: The suppression or reduction in the proliferation of cancer cells by EPS molecules can be achieved by interference with their growth signals or by inhibiting essential signaling pathways like PI3K/AKT and CDK4/CDK6-RB.

3. Induction of apoptosis: EPS can promote apoptosis (programmed cell death), in cancer cells. They can activate apoptotic pathways, increase the expression of pro-apoptotic proteins, specifically cysteine proteases (caspases), Bax protein, Fas/FasL, etc., and production of white blood cells

4. Modulation of the immune system: strengthening of the body's natural defense mechanism can be mediated by EPS against cancer cells attributed to the stimulation of the activity of immune cells such as natural killer (NK) cells, macrophages, or T cells. Also, EPS increases the production of cytokines or chemokines involved in immune response and tumor regression [4,5,6,7,8].

It is important to note that the anticancer activity of EPS may vary depending on their specific structure, source, and type of cancer studied. EPS from *H. stenophila* have been reported to block the growth of human T-lymphocyte tumors. Also, the EPS from *Halomonas spp.* was testified for their ability to remove mutagens like polycyclic aromatic hydrocarbons, naphthalene, pyrene and fluoranthene [9]. Antitumor activity of produced by *Lactococcus lactis ssp. cremoris* strains have been reported in various studies due to the presence of potent B-cell and T-cell-dependent mitogenic substances [10]. Viili is a fermented milk product with a fibrous and gelatinous consistency, produced by strains of lactic acid bacteria that produce EPS. Viilian is the important polysaccharide produced by *Lactococcus lactis ssp. Cremoris* in viili contains phosphate-containing heteropolysaccharides, which contain about 10 to 40% protein and 20 to 80% carbohydrates. Recent studies have shown that Viili polysaccharides were able to induce the cancer antigen MAGEA10 gene, which delivers a higher opportunity for immunotherapy because the overexpression of the cancer antigen will increase the ability of CTL to destroy cancer cells. An increase in cancer antigen expression and presentation is possible for increasing the possibilities of CTL-mediated cytotoxicity against cancer cells [11].

Anti-ulcer

The ulcer is one of the most common, but major chronic diseases faced by the current generation, characterized by pain developed on the lining of the esophagus, stomach, or intestines. The formation of ulcers is the result of an imbalance between our defense mechanisms and threatening factors on internal surfaces. Stimulants for ulcers may include a high prevalence of pathogens such as *Helicobacter pylori* on long-term use of NSAIDs, and cigarette smoking [12]. Ulcers are often caused by an imbalance between aggressive factors (such as stomach acid and *Helicobacter pylori* bacteria) and protective factors (such as the stomach's mucosal barrier). While research on EPS and its antiulcer effects is still evolving, several mechanisms have been proposed. EPS may improve the integrity and function of the gastric mucosal barrier, which protects tissues from damage. They can help strengthen the mucus layer, increase the production of protective mucus, and promote the excretion of bicarbonate, which can neutralize stomach acid. The anti-inflammatory properties of EPS may help reduce inflammation associated with ulcers. Inflammation is a key factor in the development and progression of ulcers, and EPS can inhibit the release of pro-inflammatory cytokines and modulate immune responses, thereby reducing inflammation in the gastric mucosa [13]. The anti-ulcer effect of *Bifidobacterium* species and their polysaccharide fractions (PSF) through increasing gastric tissue production by the immunomodulation of epidermal and basic fibroblast growth factors as well as improved production of 6-keto prostaglandin F1 alpha macrophages has been reported by Nagaoka *et al*. [14]. Ulcer healing related to oxidative stress may be limited by EPS activity. *Helicobacter pylori*, is a bacterium commonly associated with stomach ulcers. EPS-producing microbes may exhibit an additional competitive effect by with interfering the adhesion of *H. pylori* to the gastric mucosa and inhibiting its growth [15,16].

Antiviral

Polymers of exopolysaccharide have shown potent antiviral effects; however, concerns have been raised about their acceptability due to the presence of compounds with relatively large molecular weight, which block virus attachment. *L. brevis* KB290, a lactic acid bacterium with known immunomodulatory properties showed potent antiviral effects against the influenza virus in experimental mice models. The augmentation of influenza virus-specific immunoglobulin-A production and long-lasting enhancement of interferon production, suggests that KB290 might have exopolysaccharide-like components responsible for this antiviral effect [17,18]. An exopolysaccharide isolated from a probiotic strain *L. bulgaricus* OLL1073R-1 showed a potent immunostimulatory effect with augmented NK cell activity [19]. Sulfated polysaccharides including pentosan, polysulfate, sulfated cyclodextrins, xylofuranan sulphate, ribofuranan sulphate and mannan sulphate have also been found to exhibit inhibition of the viral replication process for herpes simplex virus, human cytomegalovirus, and human immunodeficiency virus [20,21]. Novel exopolysaccharides (EPSs) produced by *Bacillus licheniformis* strain B3-15 *Geobacillus thermodenitrificans* strain B3-72 and *B. licheniformis* strain T14 have been reported with antiviral and immunomodulatory activity. EPSs treatment induced high amounts of Th1 cytokines (IFN-γ, IFN-α, TNF-α, IL-12 and IL-18), leading to a restriction of viral replication via the induction of antiviral state in neighbouring cells (i.e., IFNs) or the destruction of virus-infected cells (i.e., TNF-α and IL-18) [22].

Antidiabetic

Diabetes is caused by a defect in insulin secretion or insulin action. Insulin is the main hormone regulating glucose uptake from blood into muscles and fat cells. Subclinical inflammation contributes to β-cell dysfunction and insulin resistance, which is driven by cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interlukin-6 (IL-6), and High-Sensitivity C-Reactive Protein (hs-CRP). Growing evidence suggests that gut microbiota plays an important role in the development of systemic inflammation and metabolic disorders such as obesity and diabetes mellitus [23,24]. Microbial exopolysaccharides have shown potential in the management of diabetes and its associated complications. EPS can modulate glucose metabolism by inhibiting enzymes involved in carbohydrate digestion, such as alpha-amylase and alpha-glucosidase. By reducing the breakdown of complex carbohydrates into glucose, EPS can help regulate postprandial blood

glucose levels. Some microbial EPS have been found to stimulate insulin secretion from pancreatic beta cells [1,9]. They may also enhance insulin sensitivity by promoting glucose uptake in peripheral tissues, such as skeletal muscle and adipose tissue. Improved insulin secretion and sensitivity contribute to better glucose control in individuals with diabetes. reducing oxidative damage, EPS may protect pancreatic beta cells and prevent the progression of diabetic complications. By mitigating inflammation, production of pro-inflammatory cytokines and reduction in the activation of inflammatory pathways, EPS may improve insulin sensitivity and protect against diabetes-related complications. A balanced gut microbiota has been associated with improved glucose metabolism and reduced risk of diabetes. An improper balance of bacteria in the gastrointestinal tract leads to several metabolic disorders like diabetes. Inulin, which is a common EPS has a great potential in glycemic control. Beta –glucans on the other hand, which is also an EPS, reduces blood glucose level by acting of PI3K/Akt pathway . PI3K/Akt pathway is a critical signal pathway which regulate many cellular functions such as apoptosis, cell growth, and glucose transporter 4 (GLUT4). Activation of PI3K also leads to glycogen synthesis in the liver to reduce blood glucose levels [25].

Cholesterol regulation

The primary regulation of cholesterol homeostasis is carried out by interdependent reactions of the liver and gut. Synthesis of cholesterol and bile salts, secretion of VLDL, and modulation of the expression of the LDL receptors are mainly carried out by the liver. Microbial exopolysaccharides have shown potential in the management of hypercholesterolemia and the reduction of cholesterol levels [26]. EPS can also interfere with the absorption of dietary cholesterol in the gastrointestinal tract. They may form complexes with cholesterol, preventing its uptake into the bloodstream. An imbalance in the bile acid also has a considerable effect on cholesterol homeostasis and also, enhances the excretion of cholesterol in the feces. EPS can bind to bile acids, promoting their excretion in feces. This leads to increased bile acid synthesis in the liver, utilizing cholesterol as a precursor and reducing the hepatic pool of cholesterol. As a result, the hepatic LDL gets increased as a compensatory action and finally clearance of LDL from the blood. They may increase the solubility of cholesterol in the gut, facilitating its elimination. EPS can influence lipid metabolism in the liver and peripheral tissues thereby reducing cholesterol and triglycerides synthesis by the inhibition of key enzymes involved in these reactions [27,28]. Additionally, microbial EPS may promote the breakdown of triglycerides by enhancing lipoprotein lipase activity. Chronic inflammation and oxidative mechanisms are also a part of contributing factors to cholesterol. The antioxidant and anti-inflammatory properties of EPS can help to reduce oxidative stress and inflammation in blood vessels. The ability of EPSs like Levan and dextrans to improve cholesterol metabolism is similar to soluble fiber. Levan might increase the viscosity of the digesta and increase the thickness of the unstirred layer in the small intestine, thereby possibly inhibiting the uptake of cholesterol and bile acids and increasing fecal excretions of total sterol and lipids. Being an excellent substrate for fermentation by the microorganisms in the cecum and colon, which enhances the production of short-chain fatty acids and these SCFAs reduces hepatic cholesterol synthesis. The increase in the total amount of SCFA produced by the fermentation of EPS may decrease intracolonic pH and at low pH values, the bile salts are protonated and precipitated. Thus, the increase in the production of the SCFA contributed to the occurrence of the co-precipitation of cholesterol with deconjugated bile salts. Furthermore, the decrease in intracolonic pH could favor an increase in the production of the BSH enzyme by the bacteria, which would consequently lead to an increase in the excretion of cholesterol by the host [22,26,28]. Genetic activation has also been observed within the domain of EPS-cholesterol regulation, manifesting as an elevation in mRNA levels of UCP, which engages in energy expenditure through thermogenesis. Increased expression of UCPs would increase energy expenditure and contribute to the suppression of body fat accumulation [29,30].

Anti-oxidation

Numerous major disorders, such as Parkinson's disease, atherosclerosis, cancer, and rheumatoid arthritis, are caused by reactive oxygen species (ROS), such as hydroxyl (OH), superoxide (O2), nitric oxide (NO), etc. EPSs have been proven to have antioxidant and free radical scavenging properties [31]. The EPS of *W.cibaria* DMA18 demonstrated potential antioxidant properties including *in vitro* 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity [32]. Lee *et al.* [33] demonstrated that ginseng seeds fermented with species of *Lactobacillus* and *Pediococcus* exhibited remarkably higher antioxidant activities than non-fermented seeds as measured by 2,2’ –azino –bis(ethylbenzothiazoline-6-sulphonic acid) and superoxide dismutase enzyme activity.

Infant health

Pregnancy to early life is the golden time for the establishment of the infant microbiota, which is affected by both environmental and genetic factors [34]. Microbial components polysaccharide A(PSA), HBP (d-glycero-β-d-mannoheptose-1,7-bisphosphate), and peptides contribute mainly to host immunity. PSA can enter the circulatory system through the host’s intestinal epithelial cells (IECs) and inhibit inflammation by connecting with dendritic cells and T cells via MHC (major histocompatibility complex) and T-cell receptors. As in adults, normal microbiota has a positive impact on the health of infants also. While disturbance of the gut microbial balance can increase the chances of metabolic disorders [35]. EPS extracted from *Streptococcus spp* showed the same trisaccharide sequence b-D-GlcpNAc-(1-3)-b-D-Galp (1-4)-b-D-Glcp as two trioses of oligosaccharides present in the in the human milk , that had a stimulating effect in the gut microbiome [36] .

Heavy metal biotransformation

Heavy metals are defined as metals and metalloids having densities greater than > 5g cm^{-3}. Heavy metals are found naturally and have vital importance in human physiology [37]. Living organisms require varying amounts of heavy metals like Iron, cobalt, copper, manganese, molybdenum, and zinc for their daily life mechanism. However, surpassing a specific threshold could potentially add to the ambiguity. Elements like mercury, Lead, cadmium, and plutonium are also included in this group, which are well-known toxins. The excessive accumulation of heavy metals disrupts the function of vital parts of the body and also, acts as a barrier to the functioning of key nutritional factors. There are many ways by which these toxins can be introduced into the body such as consumption of food, soil, water, and even through the inhaled air. The brain is the target organ for mercury, which may lead to the impairment and malfunctioning of any organ and glands. The replacement of important bivalent (Ca^{2+} and Mg^{2+}) and monovalent (Na^{+}) cations in the cell by the lead ions may result in the complete destabilization of biological metabolism [38].

Conventionally physicochemical methods are used for the reduction of bioavailability of heavy metals. The high cost and complications motivate the researcher's interest in environment-friendly, cost-effective, and gentle biological methods. One of the important biological systems used for heavy metal detoxification is the use of microbial systems. Which utilizes various mechanisms including active and passive uptake of metal ions depending upon the interaction. These interactions biologically transform them either into less toxic or less available (less utilizable) form or immobilize them to prevent their breach into bio-systems. The constitutive nonspecific mechanism involves the exopolysaccharides. Metal binding properties of bacterial EPS can be used as a control measure for heavy metal discrepancies. Biosorption is a surface phenomenon, mediated by the interaction of positively charged metal ions and negatively charged EPS andit is an important role in the present era. Several literatures reported the ability of heavy metal biotransformation by EPS-producing microorganisms such as *Rhizobium radiobacter* (zinc), *Enterobacter cloaceae*-(cadmium) *Methyobacter organophyllum* (lead and copper), *Bacillus firmus* (lead) [39,40, 41].

Skin protection

Skin aging is a multifactorial sum up of two diverse and independent reactions i.e., intrinsic and extrinsic aging. Water content is important to maintain the cherished young skin with appropriate turgor, pliability, and resilience. Hyaluronic acid (HA) is the key molecule involved in skin moisture retention [42]. HA is a linear polymer composed of repeating units of b-1, 3-N-acetyl glucosamine, and b-1, 4-glucuronic acid. In addition to water retention, HA is well known for its viscoelasticity and biocompatibility, this makes HA find applications in different fields like medicine, foods, cosmetics, pharmaceuticals, and nutraceuticals. Shiseido pioneered the industrial manufacturing of microbial HA in the 1980s. *Streptococcus zooepidemicus* was used to make the first microbial HA for commercial use, and it is still the most widely used strain in HA production. But, the use of *Streptococcus zooepidemicus* for the production of HA makes concerns due to their pathogenicity. In this scenario, the use of recombinant strains attracted wide interest in HA production on an industrial scale. Bacterial strains with GRAS status including *Bacillus sp, E. coli, L. lactis,* and *Agrobacterium sp.* were used as hosts [43, 44]. Also, Lee *et al.* [45] studied the skin-protecting effect of EPS from *L. plantarum* HY7714 against UVB-induced photoaging in human dermal cells and skin diseases, and they found that HY7714 EPS can act as a functional molecule in skin–gut axis communication.

Table 1: Commonly using microbial exopolysaccharides [46, 47]

Microbial EPS	Microbial Source	Monomeric units
Dextran	*Leuconostoc ssp*	Glucose
Levan	*Halomonas smyrnensis , Zymomonas mobilis, B.subtilis*	Fructose
Pullulan	*Aureobasidium pullulans*	Glucose
Xanthan	*Xanthamonas* sp	Glucose, Mannan and glucuronate
Inulin	*Lb. johnsonii . Streptococcus mutans*	Fructose and glucose

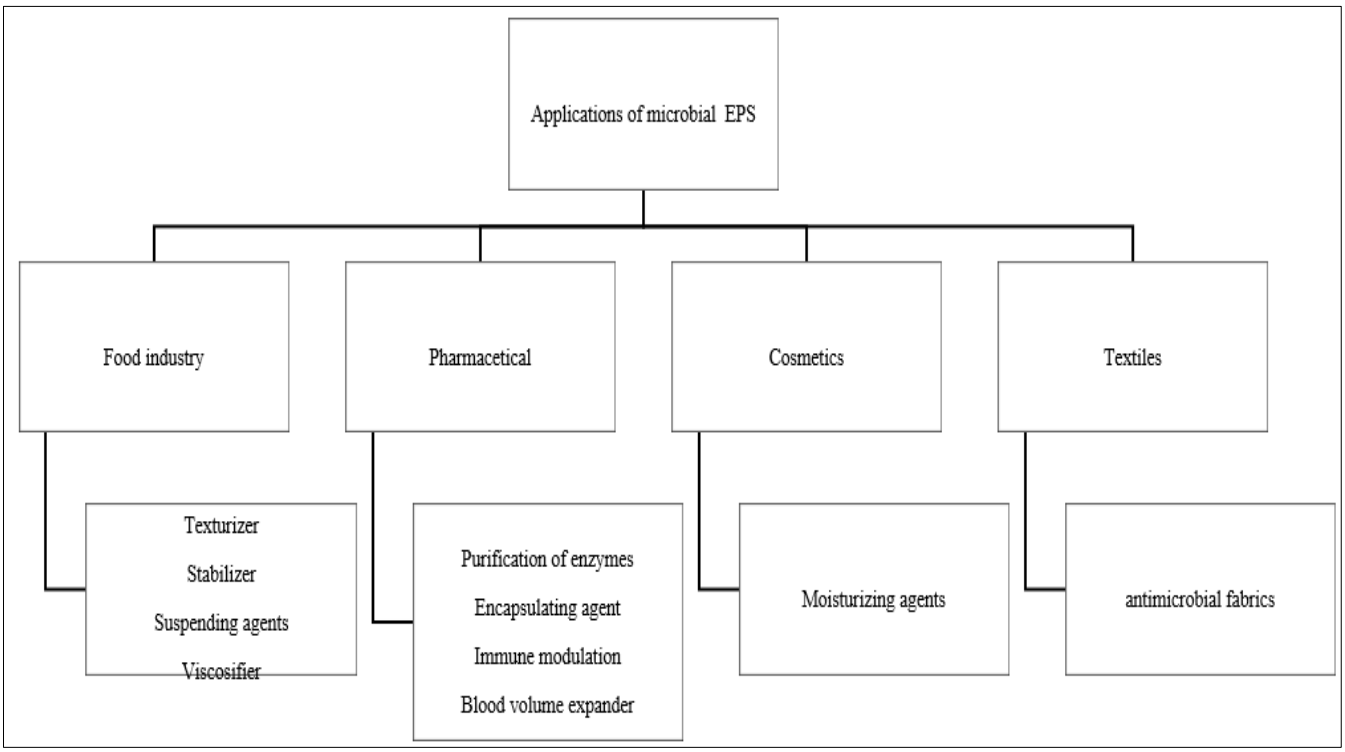

Figure 1: Applications of microbial exopolysaccharides (EPS) in various industries [48, 49,50]

CONCLUSION

Microbial exopolysaccharides are the well-known functional bioactive metabolites of microorganisms but are still in the emerging phase of use. The enormous structural and functional diversity of EPS makes it in use with a broad range of applications in various field. If the therapeutic values of microbial EPS have been explored in an effective way by the researchers, there will be a revolution in the medical field.

Conflict of Interest

None declared.

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REFERENCES

1. Poli A, Di Donato P, Abbamondi GR, Nicolaus B. Synthesis, production, and biotechnological applications of exopolysaccharides and polyhydroxyalkanoates by Archaea. Archaea . 2011 ;2011:1–13. Available from: https://doi.org/10.1155/2011/693253
2. Ateş Ö. Systems Biology of Microbial exopolysaccharides production. Frontiers in Bioengineering and Biotechnology . 2015;3. Available from: https://doi.org/10.3389/fbioe.2015.00200
3. Bajpai VK, Rather IA, Majumder R, Shukla S, Aeron A, Kim KM, *et al*. Exopolysaccharide and lactic acid bacteria: Perception, functionality and prospects. Bangladesh Journal of Pharmacology . 2015 ;11(1):1. Available from: https://doi.org/10.3329/bjp.v11i1.23819
4. Wu J, Zhang Y, Ye L, Wang C. The anti-cancer effects and mechanisms of lactic acid bacteria exopolysaccharides in vitro: A review. Carbohydrate Polymers . 2021 ;253:117308. Available from: https://doi.org/10.1016/j.carbpol.2020.117308
5. El-Deeb NM, Yassin AM, Al-Madboly LA, El-Hawiet A. A novel purified *Lactobacillus acidophilus* 20079 exopolysaccharide, LA-EPS-20079, molecularly regulates both apoptotic and NF-κB inflammatory pathways in human colon cancer. Microbial Cell Factories . 2018 ;17(1). Available from: https://doi.org/10.1186/s12934-018-0877-z
6. Asker MS, Sayed OH, Mahmoud MG, Yahya SMM, Mohamed SS, Selim MS, *et al*. Production of exopolysaccharides from novel marine bacteria and anticancer activity against hepatocellular carcinoma cells (HepG2). Bulletin of the National Research Centre . 2018 ;42(1). Available from: https://doi.org/10.1186/s42269-018-0032-3
7. Ma L, Xu GB, Tang X, Zhang C, Zhao W, Wang J, *et al*. Anti-cancer potential of polysaccharide extracted from hawthorn (Crataegus.) on human colon cancer cell line HCT116 via cell cycle arrest and apoptosis. Journal of Functional Foods . 2020;64:103677. Available from: https://doi.org/10.1016/j.jff.2019.103677
8. Chen YT, Yuan Q, Shan L, Lin M, Cheng D, Li C. Antitumor activity of bacterial exopolysaccharides from the endophyte *Bacillus amyloliquefaciens sp.* isolated from Ophiopogon japonicus. Oncology Letters. 2013 ;5(6):1787–92. Available from: https://doi.org/10.3892/ol.2013.1284
9. Biswas J, Ak P. Diversity and production of extracellular polysaccharide by halophilic microorganisms. Biodiversity International Journal . 2017 ;1(2). Available from: https://doi.org/10.15406/bij.2017.01.00006
10. Patel A, Prajapat J. Food and Health Applications of Exopolysaccharides produced by Lactic acid Bacteria. Advances in Dairy Research . 2013 ;01(02). Available from: https://doi.org/10.4172/2329-888x.1000107
11. Luo C, Deng S. Viili as Fermented Food in Health and Disease Prevention: A review study. Journal of Agricultural Science and Food Technology. 206;2: 105-113. Available from: https://www.researchgate.net/publication/307475948_
12. Khoder G, Al-Menhali AA, Al-Yassir F, Karam SM. Potential role of probiotics in the management of gastric ulcer. Experimental and Therapeutic Medicine . 2016 ;12(1):3–17. Available from: https://doi.org/10.3892/etm.2016.3293
13. Lee MG, Joeng H, Shin J, Kim S, Lee C, Song Y, Lee BH, Park HG, Lee TH, Jiang HH, *et al*. Potential Probiotic Properties of Exopolysaccharide-Producing *Lacticaseibacillus paracasei* EPS DA-BACS and Prebiotic Activity of Its Exopolysaccharide. Microorganisms. 2022; 10(12):2431. https://doi.org/10.3390/microorganisms10122431
14. Nagaoka M, Hashimoto S, Watanabe T, Yokokura T, Mori Y. Anti-ulcer effects of lactic acid bacteria and their cell wall polysaccharides. Biological & Pharmaceutical Bulletin . 1994 ;17(8):1012–7. Available from: https://doi.org/10.1248/bpb.17.1012
15. Yang S, Xu X, Peng Q, Ma L, Qiao Y, Shi B. Exopolysaccharides from lactic acid bacteria, as an alternative to antibiotics, on regulation of intestinal health and the immune system. Animal Nutrition . 2023;13:78–89. Available from: https://doi.org/10.1016/j.aninu.2023.02.004
16. Abdalla A, Ayyash M, Olaimat AN, Osaili TM, Al-Nabulsi AA, Shah NP, *et al*. Exopolysaccharides as Antimicrobial agents: Mechanism and spectrum of activity. Frontiers in Microbiology . 2021;12. Available from: https://doi.org/10.3389/fmicb.2021.664395
17. Satomi S, Khanum S, Miller P, Suzuki S, Suganuma H, Heiser A, Gupta SK. Short Communication: Oral Administration of Heat-killed *Lactobacillus brevis* KB290 in Combination with Retinoic Acid Provides Protection against Influenza Virus Infection in Mice. Nutrients. 2020 ;12(10):2925. doi: 10.3390/nu12102925. PMID: 32987850; PMCID: PMC7600661.
18. Waki N, Yajima N, Suganuma H, Buddle BM, Luo D, Heiser A, *et al*. Oral administration of *Lactobacillus brevis* KB290 to mice alleviates clinical symptoms following influenza virus infection. Letters in Applied Microbiology . 2013 ;58(1):87–93. Available from: https://doi.org/10.1111/lam.12160
19. Makino S, Ikegami S, Akinori K, Horiuchi H, Sasaki H, Orii N. Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with *Lactobacillus delbrueckii ssp. bulgaricus* OLL1073R-1. British Journal of Nutrition . 2010 ;104(7):998–1006. Available from: https://doi.org/10.1017/s000711451000173x
20. Lee JB, Hayashi K, Hayashi T, Sankawa U, Maeda M. Antiviral Activities against HSV-1, HCMV, and HIV-1 of Rhamnan Sulfate fromMonostroma latissimum. Planta Medica . 1999 ;65(05):439–41. Available from: https://doi.org/10.1055/s-2006-960804
21. Baba M, Snoeck R, Pauwels R, De Clercq E. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus. Antimicrobial Agents and

Chemotherapy . 1988;32(11):1742–5. Available from: https://doi.org/10.1128/aac.32.11.1742
22. Gugliandolo C, Spanò A, Maugeri TL, Poli A, Arena A, Nicolaus B. Role of bacterial exopolysaccharides as agents in counteracting immune disorders induced by herpes virus. Microorganisms . 2015 ;3(3):464–83. Available from: https://doi.org/10.3390/microorganisms3030464
23. Li W, Stirling K, Yang J, Zhang L. Gut microbiota and diabetes: From correlation to causality and mechanism. World Journal of Diabetes . 2020;11(7):293–308. Available from: https://doi.org/10.4239/wjd.v11.i7.293
24. Dehghan P, Gargari BP, Jafarabadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. International Journal of Food Sciences and Nutrition 2013;65(1):117–23. Available from: https://doi.org/10.3109/09637486.2013.836738
25. Chen J, Raymond K. Beta-glucans in the treatment of diabetes and associated cardiovascular risks. Vascular Health and Risk Management . 2008 ; 4:1265–72. Available from: https://doi.org/10.2147/vhrm.s3803
26. Tok E, Aslim B. Cholesterol removal by some lactic acid bacteria that can be used as probiotic. Microbiology and Immunology . 2010; Available from: https://doi.org/10.1111/j.1348-0421.2010.00219.x
27. Daba GM, Elnahas MO, Elkhateeb WA. Contributions of exopolysaccharides from lactic acid bacteria as biotechnological tools in food, pharmaceutical, and medical applications. International Journal of Biological Macromolecules . 2021 ;173:79–89. Available from: https://doi.org/10.1016/j.ijbiomac.2021.01.110
28. Reis SAD, Da Conceição LL, Rosa DD, Siqueira NP, Peluzio MCG. Mechanisms responsible for the hypocholesterolaemic effect of regular consumption of probiotics. Nutrition Research Reviews. 2016 ;30(1):36–49. Available from: https://doi.org/10.1017/s0954422416000226
29. Kang SA, Hong K, Jang K h., Choue R. Anti-obesity and hypolipidemic effects of dietary levan in high fat diet-induced obese rats. Journal of Microbiology and Biotechnology .2004;14(4);796-804.
30. Dave SR, Vaishnav AM, Upadhyay KH, Tipre DR. Microbial Exopolysaccharide - An Inevitable Product for Living Beings and Environment. Journal of Bacteriology & Mycology. 2016;2(4):109-111. Available from: https://doi.org/10.15406/jbmoa.2016.02.00034
31. Madhuri KV, Prabhakar K. Microbial exopolysaccharides: biosynthesis and potential applications. Oriental Journal of Chemistry . 2014 Sep 26;30(3):1401–10. Available from: https://doi.org/10.13005/ojc/300362
32. Amrutha TA, Beena AK, Aparna SV, Rejeesh R, Archana C, Vinod V. Antioxidant property of Weissella cibaria DMA 18 isolated from tender coconut water. The Pharma Innovation. 2019;8(9):01-06.
33. Lee MH, Lee YC, Kim SS, Hong HD, Kim KT. Quality and antioxidant activity of ginseng seed processed by fermentation strains. Journal of Ginseng Research . 2015;39(2):178–82. Available from: https://doi.org/10.1016/j.jgr.2014.10.007
34. Yao Y, Cai X, Ye Y, Wang F, Chen F, Zheng C. The role of microbiota in infant health: From early life to adulthood. Frontiers in Immunology . 2021 ;12. Available from: https://doi.org/10.3389/fimmu.2021.708472
35. Yang I, Corwin EJ, Brennan PA, Jordan S, Murphy JR, Dunlop A. The Infant Microbiome: Implications for Infant Health and Neurocognitive Development. Nurs Res. 2016 Jan-Feb;65(1):76-88. doi: 10.1097/NNR.0000000000000133.
36. Vincent SJF, Faber EJ, Neeser JR, Stingele F, Kamerling JP. Structure and properties of the exopolysaccharide produced by *Streptococcus macedonicus* Sc136. Glycobiology . 2001 ;11(2):131–9. Available from: https://doi.org/10.1093/glycob/11.2.131
37. Oves M, M SK. Heavy Metals: Biological importance and detoxification strategies. Journal of Bioremediation and Biodegradation . 2016 ;07(02). Available from: https://doi.org/10.4172/2155-6199.1000334
38. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. Interdisciplinary Toxicology. 2014 ;7(2):60-72. doi: 10.2478/intox-2014-0009. Epub 2014 Nov 15. PMID: 26109881; PMCID: PMC4427717.
39. Mathivanan K, Chandirika JU, Mathimani T, Rajendran R, Annadurai G, Yin H. Production and functionality of exopolysaccharides in bacteria exposed to a toxic metal environment. Ecotoxicology and Environmental Safety . 2021 ;208:111567. Available from: https://doi.org/10.1016/j.ecoenv.2020.111567
40. Concórdio-Reis P, Reis M a. M, Freitas F. Biosorption of heavy metals by the bacterial exopolysaccharide FuCOPOL. Applied Sciences . 2020;10(19):6708. Available from: https://doi.org/10.3390/app10196708
41. Gupta P, Diwan B. Bacterial Exopolysaccharide mediated heavy metal removal: A Review on biosynthesis, mechanism and remediation strategies. Biotechnology Reports . 2017 ;13:58–71. Available from: https://doi.org/10.1016/j.btre.2016.12.006
42. Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: A key molecule in skin aging. Dermato-endocrinology . 2012;4(3):253–8. Available from: https://doi.org/10.4161/derm.21923
43. Yu H, Stephanopoulos G. Metabolic engineering of *Escherichia coli* for biosynthesis of hyaluronic acid. Metabolic Engineering . 2008 ;10(1):24–32. Available from: https://doi.org/10.1016/j.ymben.2007.09.00
44. Liu L, Liu Y, Li J, Du G, Chen J. Microbial production of hyaluronic acid: current state, challenges, and perspectives. Microbial Cell Factories . 2011 ;10(1). Available from: https://doi.org/10.1186/1475-2859-10-99
45. Lee K, Kim HJ, Kim SA, Park SD, Shim JJ, Lee JL. Exopolysaccharide from *Lactobacillus plantarum* HY7714 Protects against Skin Aging through Skin-Gut Axis Communication. Molecules. 2021 ;26(6):1651. doi: 10.3390/molecules26061651. PMID: 33809637; PMCID: PMC8002305.
46. Rodríguez-Carmona E, Villaverde A. Nanostructured bacterial materials for innovative medicines. Trends in Microbiology . 2010 ;18(9):423–30. Available from: https://doi.org/10.1016/j.tim.2010.06.007
47. Osemwegie OO, Adetunji CO, Ayeni EA, Adejobi OI, Arise RO, Nwonuma CO, Oghenekaro AO. Exopolysaccharides from bacteria and fungi: current status and perspectives in Africa. Heliyon. 2020 ;6(6):e04205. doi: 10.1016/j.heliyon.2020.e04205. PMID: 32577572; PMCID: PMC7303563.
48. Ahuja V, Bhatt AK, Banu JR, Kumar V, Kumar G, Yang YH, *et al*. Microbial exopolysaccharide Composites in Biomedicine and

Healthcare: Trends and Advances. Polymers. 2023 ;15(7):1801. Available from: https://doi.org/10.3390/polym15071801
49. Salimi F, Farrokh P. Recent advances in the biological activities of microbial exopolysaccharides. World Journal of Microbiology & Biotechnology. 2023 ;39(8). Available from: https://doi.org/10.1007/s11274-023-03660-x
50. Yildiz H, Karatas N. Microbial exopolysaccharides: Resources and bioactive properties. Process Biochemistry. 2018 ;72:41–6. Available from: https://doi.org/10.1016/j.procbio.2018.06.009

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