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ANTIMICROBIAL ACTIVITY OF NATURAL CARBOHYDRATE POLYMERS AND THEIR MECHANISM OF ACTION - A REVIEW

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Abstract

Microbial infections represent a concerning health issue, and antibiotic-resistant pathogens represent a priority all over the world, having a negative impact on life quality and the economy. Therefore, there is an increase in focus on natural and renewable resources capable to inhibit microbial proliferation and their adherence on the surfaces. The mechanism involved in antimicrobial action and plant polysaccharides is still not clear. In this study, the plant polysaccharides extracted from different organs of plants, extraction methods, antibacterial and antiviral spectra and their mechanisms were reviewed. This review aims to provide a screening that could enhance the application of polysaccharides extracted from plants as antimicrobial agents related to the urgent need for natural alternative approaches to combat antimicrobial drug resistance (AMR).

Key words*: AMR, antioxidants, pathogens, plants green polymers, polysaccharides.*

INTRODUCTION

With the increasing incidence of antibiotic-resistant microorganisms and with the existence of a few viable remedies, potential preventive techniques, and a limited number of antibiotics, there is a necessity for the discovery of innovative medicinal approaches and natural antimicrobial therapies, to fight the emerging antimicrobial-resistant threat. Microbial biofilms make infection control more complex; the horizontal gene transmission of resistance is facilitated by extracellular DNA present in the biofilm matrix. In humans, approximately 80% of all microbial infections are a direct result of biofilms (Singer et al., 2016, Asghar et al., 2021, Uddin et al., 2021, Irfan et al., 2022). WHO 2021 mentioned that Antimicrobial Resistance (AMR) represent one of the top ten global public health threats facing humanity and published a list in 2017 with priority pathogens for which are needed new antibiotics (the first and critical priority is: *A. baumannii, P. aeruginosa, and Enterobacteriaceae*; the second and critical priority are: *E. faecium, S. aureus, H. pylori*, *Campylobacter* spp., *Salmonellae, N. gonorrhoeae* and on the third and medium priority are: *S. pneumoniae, H. influenza and Shigella* spp.), and antivirals including antiretroviral (ARV) drugs.

In the soil were also found antibiotic-resistant microorganisms. The microbiota of the soil is very important for life on our planet, having a role in the cycling of carbon, nitrogen and other essential nutrients (Armalytė et al., 2019). The usage of conventional agricides influences the microbial activities in soils and contributes to the increase in incidences of co-resistance. There are a lot of reports on the effect of biocide impacting the development of cross-to-co-resistance in pathogenic bacteria and also the agricultural usage of antibiotics and its impact on soil microbiome that can lead to antibiotic resistance (Paul et al., 2019; Udiković-Kolić et al., 2014). Resistant microorganism as *Pseudomonas* spp., *Stenotrophomonas* spp., *Sphingobacterium* spp., and *Chryseobacterium* spp. were found in the soil, their resistance being dependent on the efflux mechanisms and on specific transporters (Armalytė et al., 2019).

Publications related to natural polysaccharides are increasing year by year (Figure 1), polysaccharides received more and more attention, having been explored from natural resources due to their multifaceted properties like antimicrobial, antioxidant, antidiabetic (having hypoglycemic action), anti-inflammatory, anti-angiogenesis, immunomodulatory (can modulate innate immunity), anticancer, anti-angiogenesis, anticoagulant, antihyperlipidemic, antihepatotoxic, anti-ageing, prebiotic, probiotic and symbiotic action, regulating intestinal microbiota. Polysaccharides are biomolecules that act as a major role in the formulation of pharmaceuticals (drug delivery applications due to their solubility, permeability, and diffusivity), foods (natural excipients in the form of thickening, binding, gelling, suspending, emulsifying, stabilizing, film forming, matrix-forming, and disintegrating agent), health products (tissue engineering, abrasion curing, drug distribution, biosensors), fabric, dyes/paints, paper, gums/binding agents (Miteluț et al., 2015, Friedman, 2016, Rahimi et al., 2020, Ghosh et al., 2021, Misaki et al., 2021; Otu et al., 2021, Sindhu et al., 2021, Albuquerque et al., 2022, Bai et al., 2022; Pan et al., 2022, Sharma et al, 2022, Sun et al., 2022, Ray et al., 2023). A potential use of polysaccharides obtained from fungi (especially those that have immunomodulatory and antioxidant activities) is for vaccine production due to their low-cost source (Barbosa & Carvalho, 2020).

Polysaccharides are not only vital biomacromolecules but also environmentally safe products which have in their structure homo or hetero monosaccharides chains and uronic acids connected with glycosidic bonds, their configuration being influenced by their source (Otut et al., 2021). The green synthesis of plant carbohydrate polymers is preferred for the following aspects: improving biocompatibility, avoiding the utilization of toxic organic chemicals, and reducing the cost (Asghar et al., 2021). The most common polysaccharides and their sources are as follows: bacteria (exopolysaccharides, capsular polysaccharides, lipopolysaccharides, peptidoglycans, teichoic acids); algae (sulfated polysaccharides: laminarans, fucoidans, carrageenans, ulvans agar, sodium alginate), fungi and yeast (exopolysaccharides, chitin, glucans, galactomannans), mushrooms (β-glucans polysaccharides, α-glucuronoxylomannans, mannogalactan), lichens (galactoglucomannan, sulfated polysaccharides), plants (inulin, pectin, gums, cellulose, hemicelluloses, arabinans, xylans and starch), insects (chitin and its derivatives) and animals (glycogen, hyaluronic acid, glycosaminoglycans, heteropolysaccharides, sulfated glycosaminoglycans, keratin sulfate, heparan sulfate, dermatan sulfate, and chondroitin sulfate) (Friedman, 2016; Ullah et al., 2019; Barbosa & Carvalho 2020; Liu et al., 2020b; Valasques Junior et al., 2020; Sindhu et al., 2021; de la Harpe et al., 2021; Bai et al., 2022; Ray et al., 2023).

Figure 1 presents the number of papers listed by Science Direct since 2000 using "polysaccharides, plant polysaccharides and antimicrobial plant polysaccharides" as search terms.

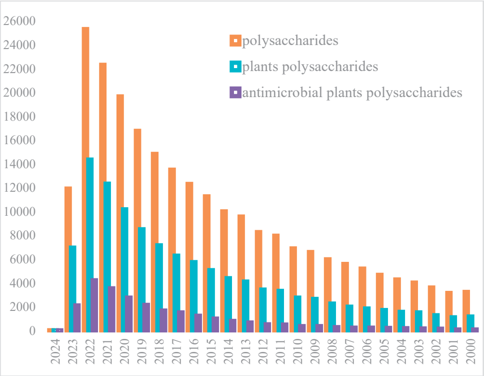

Figure 1. The evolution of the articles from 2000-2024 related to polysaccharides from Science Direct

The activities of plant polysaccharides are influenced by the number of branches that they contain, a greater number of branches or side chains in fucose, galactose, and/or mannose are associated with a high immunostimulatory activity that is in close connection with antimicrobial activity, according with Zhou et al., 2022.

Polysaccharides' molecular weights are related to their antimicrobial, immunostimulatory, antioxidant activities and phenolic acids content, (1→4)-d-mannans exhibit high immunostimulatory activity compared to low molecular weight (1→4)-d-mannans, acidic polysaccharides with high molecular weights are more active than those with lower molecular weights, instead for carrageenans, low molecular weight fractions are associated to higher immunostimulating properties (Bai et al., 2022).

Table 1. Antimicrobial activity of plants and polysaccharides

Plant name	**Family**	**Antimicrobial activity**	**References**
Daucus carota peel by-product (water-soluble polysaccharides)	Apiaceae	*E. coli*, *S. enterica*, *Enterobacter* sp., *S. aureus* and *Micrococcus luteus*	Ghazala et al., 2015, Albuquerque et al 2022
Periploca laevigata- root barks	Apocynaceae	*E. coli*, *P. aeruginosa*, *L. monocytogenes*, *S. aureus*, *M. luteus*, B. cereus	Hajji et al., 2019, Zhou et al., 2022
Ilex paraguariensis- leaves and stems	Aquifoliaceae	*E. coli*, *E. cloacae*, *S. enteritidis*, *S. typhimurium*, *B. cereus*, *M. flavus*, *S. aureus*, *L. monocytogenes*	Kungel et al., 2018, Li et al., 2022, Zhou et al., 2022
Panax ginseng- roots *(*polysaccharides PG-F2 (12 kDa) and PG-HMW (80 kDa)	Araliaceae	*S. aureus*, *B. pumilus*, *B. subtilis*, *H. pylori;P. gingivalis* and *A.actinomycetemcomitans* adhesion	Lim et al., 2002, Zhao et al., 2019, Zhou et al., 2022
Carthamus tinctorius-bee pollen (PBC-II)	Asteraceae	*E. coli* and *S. aureus*	Wu et al., 2021, El-Ghoul et al., 2021
Tridax procumbens	Asteraceae	*Vibrio alginolyticus* and *Vibrio harveyi*	Naqash &Nazeer., 2011, Zhou et al., 2022
Saussurea controversa- leaves (polysaccharides of 5.5 kDa) *Tamarindus indica*- seeds	Asteraceae Leguminosae (Fabaceae)	*S. aureus*	Khlusov et al., 2019, Albuquerque et al 2022, Zhou et al., 2022
Epimedium acuminatum- leaves	Berberidaceae	*E. coli*, *B. subtilis*	Cheng et al.,2013, Zhou et al., 2022
Cordia myxa- fruits	Boraginaceae	*E. coli*, *P. aeruginosa*, *B. cereus*, *S. aureus*	Hoijati & Beirami-Serizkani, 2020, Zhou et al., 2022
Lepidium sativum -seeds	Brassicaceae	*E. coli*, *S. aureus*	Alkahtani et al., 2020, Zhou et al., 2022
Pea pod- Byproducts	Fabaceae	*P.aeruginosa*, *B.subtilis*, *B. thuringiensis*, *M. luteus*	Belghith-Fendri et al., 2018, Zhou et al., 2022
Trigonella foenum-graecum- seeds- Senegrain Water-Soluble Polysaccharide (SWSP)	Fabaceae	*B. subtilis*, *S. enterica*, *M. luteus*	Ktari et al., 2020, Zhou et al., 2022
Hypericum perforatum- leaves	Hypericaceae	*S. dysenteriae*, *S. typhimurium*, *E. coli*	Heydarian et al., 2017, Zhou et al., 2022
Aloe barbadensis (leaf gel)	Liliaceae	*E. coli* and *E. faecalis*	Salah et al., 2017, Sindhu et al.., 2021
Lilium davidii var. unicolorCotton- bulbs	Liliaceae	*P. putida*, *K. pneumoniae*, *B. cereus*, *M. luteus*	Hui et al., 2019, Zhou et al., 2022
Althaea officinalis-roots (polysaccharides- 4.87 × 104 Da)	Malvaceae	*E. coli*, *S. enterica*, *S. aureus*, *B. circulans*	Abbaspour et al., 2022, Zhou et al., 2022
Durio zibethinu- fruit rind, peel	Malvaceae	*A.actinomycetemcomitans*, *S.mutans*, *Vibrio harveyi S.aureus* , *B. subtilis*, *B.aeruginosus*, *E.coli*, *S.typhi*, *P.aeruginosa*, *C. albicans*	Wu et al.,2010, Thunyakipisal et al., 2010, Sutanto et al.,2022, Zhou et al., 2022
Malva aegyptiaca- leaves (precipitation with cetylpyridinium chloride, precipitation with ethanol)	Malvaceae	*E. coli*, *K. pneumoniae*, *S. enterica, S. typhi*, *M. luteus*, *S. aureus*, *B. cereus*	Fakhfakh et al., 2017, Zhou et al., 2022
Forsythia suspensa- fruit	Oleaceae	*E. cloacae*	Liu et al., 2020 a, Zhou et al., 2022
Olea europea - leaves	Oleaceae	*S. enterica*, *M.luteus*	Khemakhem et al., 2018, Zhou et al., 2022
Zizyphus jujuba (galacturonic acid 242 kDa)	Rhamnaceae	*E. coli, B. subtilis, S. mutans*, *P. gingivalis*	Feng et al., 2021, Xu et al., 2022 b
Crataegus azarolus var. aronia- pulps,seeds	Rosaceae	*E. coli*, *K. pneumoniae*, *S. typhimurium*, *B. cereus*, *L. monocytogenes*, *S. aureus*, *E. faecalis*, *P. aeruginosa*, *Listeria monocytogenes*, *B. cereus*	Rjeibi et al., 2020, Albuquerque et al 2022, Zhou et al., 2022
Camellia sinensis- leaves, *Tetrastigma hemsleyanum* Diels et Gilg's (TDG)	Theaceae Vitaceae	*E. coli*	Chen et al., 2019, Zhu et al., 2020, Zhou et al., 2020, Zhou et al., 2022
Polygonatum cyrtonema Hua- rhizome, *Allium cepa*- bulbs, *Broussonetia papyrifera-leaves* *Peony*- seed dreg	Asparagaceae Liliaceae Moraceae Paeoniaceae	*E. coli*, *S.typhimurium*, *S. aureus*, *B. subtilis*, *P. aeruginosa*	Han et al.,2016, Li et al., 2018, Li et al., 2018 b., Ma et al., 2018, Xu et al., 2022 a, Zhou et al., 2022
Taraxacum officinale- shoots *Salicornia arabica*- leaves, *Cucurbita moschata*- seeds (Polysaccharides- 21,000 g/mol) *Cyclocarya paliurus*- leaves, *Phyllostachys pubescens*- leaves (5.77 × 103 Da),	Asteraceae Chenopodiaceae Cucurbitaceae Juglandaceae Poaceae	*E. coli*, *B. subtilis*, *S. aureus*, *C. albicans*, *F. phyllophilum* and *F. oxysporum*	Qian, 2014, Hammami et al., 2018, Xiao et al., 2020, Xie et al., 2012, Albuquerque et al 2022, Li et al., 2022, Zhou et al., 2022,

Low molecular weight (3.105×10^4 Da) polysaccharides produced by *Chaetomium globosum*, had higher inhibitory effects against *E. coli* and *S. aureus* than high molecular weight (5.340×10^4 Da) (Zhang et al., 2021). Álvarez-Viñas 2021, and co-workers found that sulfated polysaccharides have a weak ability to tissue-penetrating, making it almost impossible to pass away the cell membranes, making them suitable for external use. The monosaccharide composition could also influence antimicrobial activity (Albuquerque et al., 2022). Because of their ability to enter in the cells due to reduced molecular weight, low viscosity, and high solubility at neutral pH, oligosaccharides may have stronger antiviral effects (Álvarez-Viñas et al., 2021). Ketones or aldehydes with many hydroxyl groups make up monosaccharides (Barriga & Fields 2023). 11-hydroxy-16-hentriacontanone, isolated from leaf cuticular wax of *Annona squamosa*, has antibacterial and antifungal activity on both Gram-positive and Gram-negative bacterial strains (Shanker et al., 2007). Hellewell and Bhakta 2020 describe in their study how the chemical classes of ketones, chalcones and stilbenes have the potential to help in the fight against antimicrobial resistance of *E. coli*, *B. subtilis*, *M. smegmatis, M. aurum* and *M. bovis* BCG, being novel efflux pumps and biofilm inhibitors. Different polysaccharides derived from plants such as aloe vera, okra fruit, ginseng, liquorice root, and blackcurrant have been demonstrated to prevent adherence of *Helicobacter pylori* onto the mucin and gastric cells in vitro (Ray et al., 2023). Extracted polysaccharides from *Broussonetia papyrifera* fruits were further purified to obtain three different fractions of the polysaccharides with antimicrobial activities: BPP-1 (314.4 kDa), BPP-2 (284.2 kDa), and BPP-3 (235.4 kDa). Bamboo leaves polysaccharides, with 60.23% xylose content showed the best antimicrobial activity. Purified fraction of *Epimedium acuminatum* Franch. polysaccharides with major monosaccharides glucose and galactose showed the best antimicrobial activity (Otu et al., 2021) The therapeutic efficiency in some disorders can be increased by controlling the particle size that range between 10-500 nm (Zhao et al., 2019).

As a result, these polysaccharides-based nanomaterials can be effectively employed as a carrier to transport antibiotics, genes, or immunotherapeutic antigens, acting as a nano-vaccine. (Ahmad et al., 2022). Guar gum hydrogels as an injectable pharmaceutical form, can exhibit rapid self-healing, and antibacterial properties towards: *E. coli*, *P aeruginosa*, *S.aureus* thereby confirming new and optimistic prediction for injectable hydrogels (Talodthaisong et al., 2020).

EXTRACTION METHODS

According to Otu et al. (2021), extraction solvents has been found to play a mechanistic role in antimicrobial activity. Polysaccharides from both natural and modified sources were found to be insoluble in organic extraction solvents, due to their hydrophilic property. Therefore, water is the most common solvent and the base solvent for extraction methods, including acid and alkali extraction, and enzymolysis methods (Albuquerque et al., 2022).

The use of **acidic solutions** with temperature, time, and pH-controlled has the main advantage of a high extraction rate and short extraction time. Similar to the acid extraction method mentioned above, the alkaline extraction method may also remove polysaccharides from plants by destroying their cell walls (Talodthaisong et al., 2020). The main disadvantages are modifications in the polysaccharide structure, organic solvents mainly alcohols can selectively precipitate some target carbohydrates whilst other components remain dissolved in the extraction mixture. The high viscosity of the extract obtained can compromises filtration steps, and also its flavor, affecting also the quality and color of the polysaccharides (Albuquerque et al., 2022; Otu et al., 2021).

The disadvantages of **enzymolysis** extractions are related to the price of the enzymes, and the limiting factors (enzyme mass concentration, temperature, pH) associated with a large-scale application (Albuquerque et al., 2022).

Enzymatic hydrolysis of polysaccharides and transglycosylation can be the focus of a new research field that aims to increase efficiency and decrease the production costs of functional oligosaccharides (Martins et al., 2023)

Ultrasonic extraction has the advantages of high extraction efficiency, short time, and low energy consumption, while the main disadvantage is the difficulty to reach the best frequency, solid-liquid ratio, and temperature conditions. Other extraction methods have occasionally been applied in scientific researches as: high voltage pulsed electric field, ultrahigh pressure, microwave, liquid phase pulse discharge, supercritical carbon dioxide and subcritical water extraction methods according to Albuquerque et al., 2022.

Cellulose is an inexhaustible raw material that exists as the most abundant polysaccharides present primarily in lignocellulosic material (Ma et al., 2021). As a biomaterial, cellulose offers numerous advantages such as nontoxicity, high availability, renewability, low cost, biodegradability and other quintessential physical and chemical properties (de la Harpe et al., 2021; Mayer et al., 2021). Cellulose is low soluble in most organic solvents, in water being insoluble, these properties represent the most important and difficult step in extraction. This is due to its stiff molecules (high degree of polymerization ranging from 10,000 glucopyranose units and numerous intra- and intermolecular hydrogen bonds (Taokaew et al., 2022). Physical toughness is also enhanced by hemicellulose, which is responsible for binding cellulosic fibres to lignin (Przypis et al., 2023). Wu et al. (2023) developed a new method for cellulose **derivatization using amino acid hydrochloride** ([AA]Cl) because it can efficiently catalyze esterification reactions and can break the hydrogen bond network, to synthesize cellulose amino acid. The synthesized products demonstrated bacteriostatic activity on *E. coli* and *S. aureus*. Mayer et al., 2021, in their study, mentioned that using **selective cleavage of the C2 single bond and C3 bond by periodate oxidation**, leads to the formation of a very important cellulose derivative, 2,3-dialdehyde cellulose. These aldehyde groups are sensitive to Schiff base reactions, having antimicrobial activity on *E. coli* and *S. aureus*. Different derivatives of cellulose such as oxidized regenerated cellulose, hydroxyethyl cellulose and cellulose nanofibrils, are ideal candidates for new, innovative sutures (de la Harpe, 2021). Ahmad et al., 2022, revealed that to produce cellulose nanofibers with antimicrobial activity, the most suitable method is **hydrolysis through acid**. Cellulose nanofibers obtained throught hydrolysis, enhance gut health by increasing good bacteria from *Lactobacillaceae* while decreasing *Streptococcaceae* in mice. *Streptococcaceae*, has been associated with obesity, diabetes, as well as colon cancer. Ilangovan et al., 2018, extracted cellulose fibres from *Curcuma longa* L. leaves and stalks, with alkali solutions and demonstrated that these natural cellulose fibers have inhibition activity on *S. aureus*, *E. coli* and *B. cereus*. However, the poor solubility of cellulose in water and other common solvents has prevented its full utilization in the biomedical and related fields, new cellulose production techniques are emerging, such as dissolution and functionalization in ionic liquids known as green extraction methods (Taokaew et al., 2022).

Hemicellulose is composed of two or more different monosaccharide units, hexoses (β-D-glucose, β-D-mannose, and β-D-galactose), pentoses (β-D-xylose and α-L-arabinose), fructose, rhamnose in lower quantities and uronic acids, β-(1→3, 1→4)-glucans receiving little consideration (Zhang et al., 2021b).

The antimicrobial activities of hemicellulose are less studied as against cellulose and lignin. Hemicellulose films can inhibit the growth of the bacteria *S. aureus*, *E. coli*, and *P. aeruginosa*. Hemicellulose extracted from almond gum, have proven higher inhibitory activity against *B. thuringiensis*, *S. enterica*, and *P. aeruginosa* and moderated inhibition against *Sal. thyphimirium*, *Actinomyces sp.*, *K. pneumonia*, *L. monocytogenes*, and *B. subtilis* (Lobo et al., 2021).

Lignin is composed of C_6-C_3 phenylpropane units including sinapyl, coniferyl and p-coumaryl alcohols, or syringyl, guaiacyl and *p*-hydroxyphenyl units, the unit ratio in lignin varies according to biomass species in terms of the number of methoxy groups (Lu et al., 2022). The polyphenolic structure of lignin in addition to the presence of O-containing functional groups (including phenolic hydroxyl, carbonyl, carboxyl, and methoxy groups) is potentially responsible for antimicrobial activities (Greco et al., 2019). For lignin was used extraction methods such as:

- **Kraft lignin** (it is used a solution of NaOH and NaHS, at a temperature between 150 to 170°C);
- **Hydrolysis lignin** and **organosolv lignin**, use organic solvents (acetic acid, ketone, and ester), the organosolv lignin being highly pure and sulphuric-free;
- **Ionic liquids extraction**, which uses green solvents has high thermal stability and present low toxicity. On enzymatic hydrolyzed lignin from corn stalk, it was observed that in the first extraction showed higher antibacterial activity against all the bacteria *E. coli*, *B. subtilis*, *Sal. enterica* and *S. aureus*, Gram-positive microorganisms being more sensitive to the lignin extract than the Gram-negative bacteria. In this context, the materials produced with lignin can be considered for different areas of application, as a natural antimicrobial agent (Lobo et al., 2021). Salem et al., in 2014 showed that lignin extracts show antimicrobial activity against *Listeria innocua* and *Bacillus sp.* than against *Klebsiella sp.* The antimicrobial mechanism is given by sugar content of the lignin that might cause and/or support the adhesion to the bacterial membrane. The activity against *S. aureus* can be increased by the interaction between peptidoglycan layer of bacterial cell walls and sugar molecules. Lignin films present activity on Gram-positive bacteria more than Gram-negative bacteria. Films containing organosolv lignins presented higher antimicrobial activity on *S. aureus*, than kraft lignins. For *E. coli*, the kraft lignin films presented no activity at low concentration. These findings that polysaccharides actions are more efficient against Gram-positive bacteria than Gram-negative ones could be related to the presence of an external phospholipid membrane in Gram-negative bacteria, limiting the diffusion of hydrophobic compounds through its lipopolysaccharide cover, and acting as a barrier against hyper acidification, according to Albuquerque et al., 2022.

Pectin it is a naturally occurring complex heteropoly saccharide with a cytocompatible mechanism, consisting of galacturonic acid and low amount of neutral sugars in the side chains, being considered one of the most complex macromolecules in nature (Ciriminna et al., 2020; Lisitsyn et al., 2021). Pectin has a large broad-spectrum antimicrobial capable to kill Gram-negative bacteria, yeasts and non-filamentous fungi. Its mechanism of action involves the binding action of the carboxylic acid groups in the main backbone of the biopolymer, enhances mechanical properties and decreasing the solubility of water. Pectin being a good source for the development of nanoparticles. Optimal antibacterial activity was observed at acid pH (around pH 5-6) (Ciriminna et al., 2020; Lisitsyn et al., 2021; Albuquerque et al., 2022).

Processes such as **microwave hydro diffusion and gravity and hydrodynamic cavitation carried out with ultrasounds** applied to the wet peels of different fruits (apple, citrus, *Opuntia-ficus indica* etc.) using water as solvent, followed by freeze-drying, allow pectins embedding polyphenols, flavonoids, terpenes and phenolic acids. The pectin obtains through the methods described above, shows high antibacterial activity against both Gram-positive and negative bacterial strains *S. aureus*, *P. aeruginosa*, *S. epidermidis*, *H. pylori*, *E. coli*. 1% pectin solution killed within the first 15 min. of contact more than 90% of the Gram-negative bacteria (*S. vulgaris*, *S. typhi*, *S. paratyphi*, *S. typhimurium*, *K. aerogenes, E. coli*, *P. vulgaris*, *B. bronchiseptica* and *P. aeruginosa*). Pectin's **green extraction** methods represent a new and highly promising area of research in the life sciences and medicine (Ciriminna et al., 2020, Lisitsyn et al., 2021). Lin et al., 2023, obtained high molecular weight polysaccharides (>84.7 kDa) from citrus peel pectin from aqueous extract of 9 different citrus species through enzymatic methods. Those citrus peel pectin oligosaccharides presented antimicrobial activity on: *S.epidermidis*, *B.subtilis*, *S.aureus*, *K. pneumoniae*. Another mechanism of pectin action on pathogen microorganisms is through prebiotic activity, reducing pathogens' growth in favor of friendly microorganisms (Albuquerque et al., 2022). Instead Lisitsyn et al., 2021, found that bioactive packaging films made from pectin have very weak antimicrobial properties.

Another extraction for polysaccharides is the one that uses **dilute alkali** solutions. Onion polysaccharides extracted in this way had the highest antibacterial activity against both Gram-positive and Gram-negative bacteria.

From *Lilium davidii* var. unicolor were extracted two heteropoly saccharides, BHP-1 and BHP-2. C**etylpyridinium chloride was used to precipitate polysaccharide** in order to obtain BHP-1, and BHP-2 was obtained by **precipitating ethanol**. The inhibitory zone of BHP-1 was larger, which may be related to the high sugar content and high number of sulfate groups (Zhou et al., 2022).

Methanol, ethanol and hydroalcoholic solvents are very good to separate ketoses from non bioactive aldoses. To confirm the mechanistic role of organic solvent (alcohol), a study on ethanol extract of *Phellodendron amurense* bark showed better antimicrobial activity than the aqueous extract.

Anisophyllea laurina pulp and seed powder were extracted by sonication over an ice bed with methanol/water 80:20 (v/v), ethanol/ water 80:20 (v/v), ethyl acetate/water 1:5 (w/v), and finally with water for 15 mins. The ethanol and methanol extracts recorded the highest phenolics, flavonoids, tannin, and monomeric anthocyanin content. Ethanol and methanol seed extract showed best antimicrobial activity on both gram negative and gram-positive bacteria, ethyl acetate seed extract showed moderate antibacterial effect and water extract doesn't have antibacterial effect. This result displayed the importance of plant bioactive compounds solubility in an extraction solvent and its strong correlation with antimicrobial activity (Otu et al., 2021). Darmohray et al, 2021 observed also that 20% aqueous extract of *Galega orientalis* has a slight antimicrobial effect on Gram-negative and Gram-positive bacteria and yeast.

Generally, it is difficult to obtain pure polysaccharides by performing only one method, thus combined techniques have been employed to improve purification and achieve good yields Albuquerque et al., 2022.

ANTIMICROBIAL MECHANISMS

Until now, the mechanism of polysaccharide antimicrobial activity was not been fully elucidated (Otu et al., 2021; Lin et al., 2023). However, the degree of polymerization, alteration, solubility and monosaccharide composition is likely to influence this mechanism while no consensus mechanism has been accepted by researchers (Lin et al., 2023). To withstand environmental and other drastic conditions, most of the pathogenic microbes create an exopolysaccharide biofilm around all growing populations, which protects the pathogenic microbes from many bacteriophages, biocides, and immune cells from the host (El-Batal et al., 2020).

Bacterial cell membrane permeability

Gram negative bacteria *S. typhi* without the peptidoglycan wall may hydrolyze available polysaccharides in order to produce monosaccharides as source of nutrition. This property of the bacteria it is confirmed by *Capparis spinosa* leaf polysaccharides. A higher concentration led to a reduction in inhibition zone. Aqueous extract of *Syzgium aromaticum* seeds applied on *E. coli*, *P. aeruginosa*, and *S. aureus* lead to an increase in malondialdehyde which may cause peroxidation of the lipid bilayer of the bacterial cell membrane and subsequently led to the release of nucleic acid content. The lipophilic character of polyphenolic compounds favors the interaction with the cell membrane which enhances their antimicrobial activity. Their interactions with cell membranes may induce irreversible damage to the cytoplasmic membrane and coagulation of the cell content and even lead to the inhibition of intracellular enzymes (Otu et al., 2021).

Aqueous polysaccharides extract from *Trachyspermum ammi* presented more mannose than glucose, and showed better antimicrobial activity than *Dolichos biflorus* which had more glucose than mannose. This observation suggested the presence of mannose receptor in the targeted microorganism membrane and therefore aided in the higher absorption of polysaccharides (Otu et al., 2021)

Albuquerque et al., 2022, suggested that the polysaccharides could induce the disruption of the cell wall of bacteria and increase ion permeability and the antimicrobial activity could be related to their total sugar contents.

The plant polysaccharides may interact with the cell membrane through **hydrophobic action and electrostatic adsorption, or glycoprotein receptors**. There is hydrophobic–hydrophobic interaction between the hydrophobic substrates and lipid bilayers of bacterial membranes.

The protein or polyphenols in some plant polysaccharides confer **hydrophobic characteristics** to these polysaccharides, as apple pomace polysaccharides that can diffuse passively through the lipids of cytoplasmic membrane bilayer into the bacterial cytosol, leading to the escape of intracellular components and alteration of the bacterial enzyme system.

Electrostatic adsorption

Plant polysaccharides display antibacterial activity by increasing membrane permeability via electrostatic adsorption, which can lead to a rapid increase in the amount of water-soluble proteins in cells, protein dissolution, DNA degradation, leakage of essential molecules, and cell death

Inhibition of the adsorption of nutrients

Plant polysaccharides can block the absorption of nutrients by bacteria and affect energy metabolism, leading to the inhibition of bacterial growth. Polysaccharides extracted from *Tetrastigma hemsleyanum* can block glycolysis and gluconeogenesis of *E. coli*. In this way, deprives bacteria in obtaining adenosine triphosphate and nicotinamide adenine dinucleotide necessary for energy metabolism (Zhou et al., 2022). Sulphated polysaccharides extracted from *Malva aegyptiaca* can also inhibit cell growth (Barriga & Fields, 2023). The antibacterial activity of polysaccharides might stem from the fact that they act as a barrier preventing the entry of nutrients. The mechanism of **metal toxicity** is metal species-specific. Some metals can cause protein dysfunction, lead to the production of reactive oxygen species (ROS) and depletion of antioxidants, impair membrane function, interfere with nutrient assimilation, and be genotoxic. Iron is an essential element for bacterial growth usually needed in a range of 0.4-4 μM.

Metals and bacterial cells

Yerba mate polysaccharides show antibacterial activity against various strains except *for E. coli*. The antibacterial activity of polysaccharides can be their ability to inhibit the absorption of iron by bacteria. *E. coli* can secrete enterobacteria, which has a high affinity for iron; consequently, the absorption of iron by bacteria is inhibited after the addition of plant polysaccharides (Kungel et al., 2018). According to hard-soft acid-base theory, soft acids such as Hg, Cu, Ag and Cadmium and borderline acids such Co, Ni, Cu and Zn do associate tightly with soft bases, such as sulfhydryl groups found in proteins. The antibacterial activity of these metals is therefore dependent on their affinity to sulfhydryl group (Otu et al., 2021).

Aqueous extract of *Tilia* leaves was used to reduce copper ions in sulfate pentahydrate solution (4:1 v/v) to form Cu nanoparticles. To reduce zinc ions (Zn^{2+}) to zinc oxide nanoparticles was used extract from *Brassica oleraceae* leaves. The use of chemical and biological techniques has shown that metal ions such as Cr (VI) As (III), and Te (IV), but especially Fe (II) and Cu (II) do increase ROS which leads to DNA damage and the inhibition of enzymes activity essential for cell growth.

The phenolic acids present in the carbohydrate polymers also can act as secondary anti-oxidants by inducing the activity of antioxidant enzymes such as peroxidase, catalase, superoxide dismutase, ascorbate peroxidase, glutathione reductase and glutathione S-transferase (Ghosh et al., 2021).

Plant polysaccharides can also **prevent the adhesion of pathogenic** bacteria to host cells. The *Panax ginseng* polysaccharides are not able to inhibit the adhesion of bacteria and cells such as *Lactobacillus acidophilus* and *E. coli*, suggesting that they have selective anti-adhesion activity (Ghosh et al., 2021).

Bacteria spores formed can protect and make organisms indestructible to anti-bacterial action. However, water-soluble polysaccharides of cabbage remarkably displayed great antimicrobial effect against a spore-formed gram-positive *Bacillus* spp. Curcumin extracted from rhizomes of *Curcuma longa* demonstrated the ability to inhibit *Clostridium difficile* formed spore. The anticlostridial properties of curcumin can be related to its phenolic content (Otu et al., 2021).

Liu et al. (2020 b) presented **antiviral activities** of several polysaccharides anti HSV from *Acanthopanax sciadophylloides*, *Adenanthera pavonina*, *Avena sativa*, *Azadirachta indica*, *Caesalpinia ferrea*, *Cedrela tubiflora*, *Echinacea purpurea*, *Portulaca oleracea*, *Prunella*, *Stevia rebaudiana*, having the following antiviral mechanisms: inhibits adsorption and penetration, virucidal effects, inhibits viral DNA and protein synthesis.

Cydonia oblonga, *Glycyrrhiza glabra*, *Nigella sativa*, *Tinospora cordifolia*, and *Zizyphus jujube* against COVID-19 because of their proven antiviral it has been suggested that sulfated polysaccharides can be used to bind the virus proteins, consequently blocking cell entry. An important member of the glycose amino glycans is heparin, which represents a key binding factor for SARS-CoV-2 and Ebola virus. Most physiological and pathophysiological activities of heparin sulfate are due to electrostatic interactions with various proteins. In investigations on the SARS-CoV-2 virus, heparin and its derivatives, such as enoxaparin, 6-O-desulfated UFH, and 6-O-desulfated enoxaparin, have shown encouraging results (Barriga & Fields, 2023) and on HSV-1, HSV-2, HPV-16 and RSV infections (Lu et al., 2021).

Glycosaminoglycans are proteins heavily decorated with sulfated polysaccharides. These proteins are cellular receptors for the binding of viruses like herpes simplex, HIV, dengue virus and many others (Barriga & Fields, 2023).

Ferula sinkiangensis polysaccharide, *Morus nigra* polysaccharide and their sulfated modifiers had the best antiviral effect on the anti-Newcastle disease virus. Polysaccharide from the *Adenanthera pavonina* seeds have antiviral action on poliovirus type 1. *Sophora tomentosa* root polysaccharide and its sulfate, significantly inhibited the protein translation and RNA synthesis of duck hepatitis A virus-1. The sulfate derivative of *Cyathula officinalis* polysaccharide showed significant antiviral effects by interfering with the HSV-2 adsorption process. Sulfated derivatives of Angelica polysaccharides showed effect on murine leukemia virus in vivo. Sulfated modification of *Polygonum taipaishanease* polysaccharide can notably increase the activity on: transmissible gastroenteritis virus, *Shigella* and *E. coli*. The crystal-like arrangement of the nano assemblies with a higher level of sulfation exerted stronger antiviral activity, indicating the polysaccharide configuration may be important in the development of antiviral agents (Lu et al., 2021).

CONCLUSIONS

In recent years, there has been shown an increase in researches about the extraction, characterization, and biological functions of plant polysaccharides.

The most used methods to obtain polysaccharides from plants were those by hot water extraction and alcohol precipitation. Microwave hydro diffusion and gravity and hydrodynamic cavitation carried out with ultrasounds are green extraction methods representing new and highly promising extraction methods, but the purification yield of plant polysaccharides can represent a limiting factor for large-scale commercial use.

Moreover, investigations of the shelf life of possible formulations based on polysaccharides will be very important and the investigations of their biocompatibility to highlight possible adverse effects. Thus, it is expected that in the future, after adequate testing in vivo these carbohydrates can be used in formulations with therapeutic and preventive solutions.

We hope that this review could promote the application of plant polysaccharides in antimicrobial formulations in the future.

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