BIOLOGICAL AND PHARMACEUTICAL APPLICATIONS OF LIGNIN AND ITS DERIVATIVES: A MINI-REVIEW

IULIANA SPIRIDON

"Petru Poni" Institute of Macromolecular Chemistry, 41A, Grigore Ghica Voda Alley, 700487 Iasi, Romania
✉ *Corresponding author: iulianaspiridon@yahoo.com*

Dedicated to Acad. Bogdan C. Simionescu on the occasion of his 70th anniversary

The use of natural substances is currently considered as a promising alternative to conventional therapy. Recent researches have demonstrated the bioactivities of natural polymers, which lead to their application in the treatment of different diseases. Also, natural compounds and bioinspired materials require more investigations to understand the structure–property relationships and interactions with cellular environment.
As with other biological macromolecules, the interest in lignin has increased due to its potential applications. Lignin is the second component, after cellulose and provides higher plants with rigidity and strength. It assures the transport of water and nutrient transport in plant tissues, as well as the resistance to microbial attack.
In this mini-review, some aspects related to the applications of lignin have been summarized, including some pharmacological applications, such as anti-tumor, anti-virus, antioxidant and antimicrobial activities.

Keywords: lignin, biological activities, applications

INTRODUCTION

Lignin is the second most abundant biopolymer of lignocellulosic biomass, after cellulose.[1] Due to its hydrophobic nature, it makes the cell wall impermeable to water and ensures a well-organized water and nutrition transport in the cells. Its chemical structure has not been completely established, although most of the functional groups and units that make up the molecule have been identified. Thus, lignin is an amorphous biomacromolecule, consisting of phenylpropanoid units, namely *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol (Fig. 1).[2-3] Phenylpropane units are crosslinked to each other by various chemical bonds, such as β-*O*-4-aryl ether linkages, α-*O*-4-aryl ether, 4-*O*-5-diaryl ether, β-5-phenylcoumaran, 5-5-biphenyl, β-1-(1,2-diarylpropane) and β-β-(resinol).

Lignin is strongly linked with cellulose and hemicellulose by non-covalent forces or covalent bonds to form carbohydrate complexes. The differences in the properties and structure of lignin depend on the separation method, as well as on the biomass source.

The main separation method of lignin from lignocellulose is Kraft pulping, which accounts for about 85% of the produced lignin.[4] The differences in chemical delignification methods result in a variety of lignin fragments.

Sulphite pulping dominated the pulp industry at the beginning of the 20th century, but has gradually been replaced by the Kraft process, which gives stronger fibers and allows a more efficient recovery of chemicals. During kraft pulping, about 90-95% of the lignin is chemically degraded to fractions that are soluble in aqueous alkali.[5] Kraft lignin has low water solubility, presents high phenolic contents, while lignosulfonates are soluble in water and contain low phenolic contents.

New approaches, such as steam explosion, enable the recovery of the lignin fraction, while leaving the cellulose structure intact and therefore purer. Meanwhile, organosolv processes use an organic solvent and water, with or without the addition of acid or base as a catalyst.[6-7]

Organosolv lignins are free of sulfur and hemicellulose, and are soluble in organic solvents.

The ratio between the most relevant functional groups, including carbonyl groups, phenolic hydroxyl, methoxyl, benzyl alcohol, aliphatic hydroxyl and noncyclic benzyl ether, have great significance for lignin reactivity.

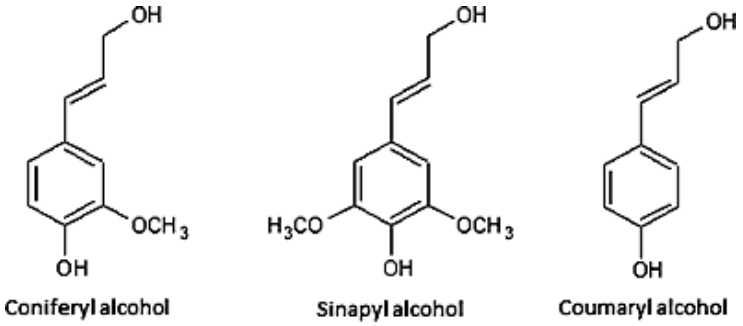
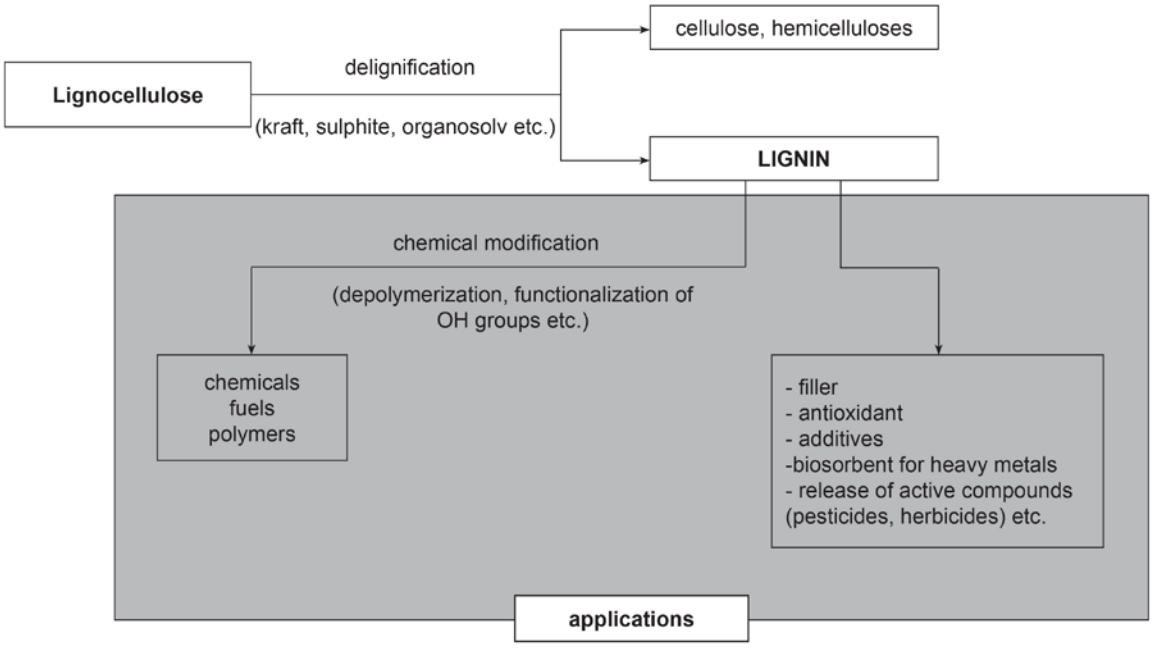


Figure 1: Phenylpropanoid units of lignin

The glass transition temperature (Tg) of woody lignin ranges from 102 to 175 °C, while the Tg of annual plants varies from 119 to 175 °C.[8-10] Lignin is more resistant to chemical and biological attacks, as compared to other components of the cell wall.[11] However, the recalcitrance of different linkages in the structure of lignin represents a major barrier to its efficient utilization.[12]

Lignin is mostly burned to produce heat and electricity, but it has gained extensive attention in the framework of biorefinery for converting it into valuable chemicals.[13] Its valorization is a key factor in achieving economically viable second generation biorefineries. Thus, having in mind the increasing demand of green materials, lignin reactivity, its low cost and eco-friendly properties, lignin could be exploited in applications such as dyes, binders, emulsifiers, synthetic flooring, dispersal agents, paints, for the production of polymer building blocks, chemicals such as aromatic monomers, including benzene, toluene and xylene, phenol, and vanillin or for bio-fuels and energy production (Scheme 1). Also, high-performance composites based on lignin could be obtained.[14-18]



Scheme 1: The main applications of lignin

Lignin has diverse pharmacological activities, such as anti-tumor, antimicrobial, anti-HIV and antioxidant activities;[19-22] however, in contrast to polysaccharide-based materials,[23-30] lignin has not yet been exploited significantly in the biomedical field.

BIOMEDICAL APPLICATIONS OF LIGNIN

Anti-tumor activity

Cancer is a disease with the highest incidence and mortality worldwide. The biodegradability, biocompatibility and chemical stability of lignin, as well as the possibility to obtain it as nanoparticles, make lignin a potential candidate for applications in cancer therapy.

In 1998, Lu *et al*. reported that lignin could play a role in protecting against colon cancer.[31] Podophyllotoxin is a lignan known as the most active cytotoxic natural product, being used as starting compound for the synthesis of anticancer drugs etoposide and teniposide. A recent study related to the *in vivo* effect of deoxypodophyllotoxin on gastric cancer cells in a xenograft model evidenced its inhibitory effect.[32]

Two carbohydrate–lignin metabolites with anti-tumor activities were separated from a hot-water extract of *Inonotus obliquus*. Cytotoxicity tests showed that these lignin compounds induced cell apoptosis and inhibited the activation of the nuclear transcription factor NF-κB in cancer cells.[33]

The cytotoxic effect of different lignins was studied using the cell membrane of human keratinocyte HaCaT and murine fibroblast 3T3 cells.[34] The report revealed that lignins presented good antioxidant properties at low concentrations and cytotoxic effects at high concentrations.

Pancreatic lipase has an important role in the efficient digestion of triglycerides, being responsible for the hydrolysis of 50-70% total dietary fats. Serum pancreatic lipase is associated with many kinds of diseases. The inhibitory effect of lignin on pancreatic lipase, through the disruption of substrate emulsification in a heterogeneous reaction system was demonstrated, as well as its direct activation effect through the formation of a lignin–pancreatic lipase complex in a homogeneous aqueous reaction system.[35] The positive effect of lignosulfonic acid for the treatment of inflammation-induced intestinal barrier dysfunction observed in inflammatory bowel disease was reported.[36] It enhanced the tight junction barrier function and ameliorated the intestinal barrier disruption induced by the inflammatory cytokines TNF-α and IFN-γ.

Antiviral activity

It was found that an alkaline hydrolysate of lignin strongly inhibited the entry of hepatitis C virus into cultured cells.[37] Recently, some authors[38] evaluated the kraft lignin in modulating immune responses and antiviral functions against yellow head virus and its toxicity in black tiger shrimp. They concluded that it is possible to control and reduce the risk of infection by this virus through the early transfer of affected shrimp and the administration of kraft lignin as feed at a final concentration of 1-20 mg/L.

Lee *et al*.[39] demonstrated that lignin–carbohydrate–protein complexes from *Pimpinella anisum* (family Apiaceae) presented antiviral activities against HSV 1 and 2 by inducing nitric oxide (NO) production and mRNA expression of IL-1β.

Also, a high molecular weight lignin-related fraction extracted from cones of *Pinus parviflora Siebold et Zucc* suppresses the multiplication of influenza viruses by preventing viral RNA synthesis.[40]

H. Nakashima *et al*.[41] demonstrated the anti-HIV activity of lignin fractions, which was higher compared to that of hydrolysable (mono, di, tri, tetrameric) and condensed tannins. Another study[42] reported that the lignin used as immobilization matrix was able to maintain the secondary α-helix structure of the peptide, which is essential for molecular recognition. The specific human immune deficiency virus antibodies are adsorbed on this lignin–peptides immunosensor, which represents a real advantage with respect to known HIV immunosensors, in which the antigenic peptides have to be protected into liposomes.

Antidiabetic effect

Lignophenols could attenuate vascular oxidative stress and/or inflammation *via* inhibition of nicotinamide adenine dinucleotide (phosphate) oxidase. This may lead to an improvement in the vascular impairment of diabetes.[43] Y. Chen *et al*.[44] have compared the inhibition ability of lignin and acarbose toward α-glucosidase and found that lignin has an extremely strong inhibition effect on the enzyme. It was evidenced that the lignin was linked through hydrophobic interaction and hydrogen

bonding to α-glucosidase, and formed a 1:1 complex. The microenvironment of tryptophan residue was changed and induced a conformational transformation of the enzyme.

Antioxidant and antimicrobial effects

Many efforts have been devoted to the study of lignin from various natural sources as antioxidant and microbicidal agent.[45-48] Regarding the applications[49] of sugarcane bagasse lignin, which was chemically modified by acetylation, epoxidation and hydroxymethylation reactions, it has been evidenced that unmodified lignin and hydroxymethyl lignin presented higher antioxidant activity, as compared to acetylated and epoxy lignin, while epoxy lignin was the most effective among the unmodified and modified lignins against *Bacillus* sp. and *Klebsiella* sp. The authors concluded that the phenolic OH groups and the methoxyl groups have important roles in the antioxidant activity, whereas the methoxyl and epoxy groups were found to be responsible for the antibacterial activity. Lignin separated from corn stover residue[50] exhibited high antioxidant activity, as well as minimal estrogenic impact when tested using the MCF-7 cell proliferation.

According to M. B. Marulasiddeshwara *et al.*,[51] lignin capped silver nanoparticles showed antibacterial and antifungal activity against human pathogens *S. aureus*, *E. coli* and *A. niger*, as well as antioxidant activity. Also, they did not lyse the RBC membrane when the hemolytic activity was assayed, suggesting its non-toxic nature.

Cellulose–lignin beads were prepared using pretreated dissolving grade pulp and extracted from birch wood hydrotropic lignin as starting materials. Antibacterial studies showed a great potential for antibacterial applications against *S. aureus*.[52]

A greater stability to lysozyme degradation, antimicrobial activity and biocompatibility with human cells were evidenced when lignosulfonates were added into chitosan nanoparticles.[53] Other studies[54] confirmed that the presence of lignin nanoparticles in a polyvinyl alcohol/chitosan hydrogel was effective against Gram-negative bacteria (*E. coli*), when compared to Gram-positive (*S. aureus* and *S. epidermidis*) strains.

Some experiments, consisting in the addition of lignin to simple and silver-doped hydroxyapatite thin films,[55] resulted in composites that exhibited low cytotoxicity toward human mesenchymal stem cells, being therefore promising candidates for fabricating implantable biomaterials.

Different kraft lignin/silica Ag NPs nanocomposites have been developed and their behavior towards various Gram-positive bacteria was investigated.[56] The study revealed that higher concentration of silver nanoparticles increased the inhibition of bacterial growth.

Applications in tissue engineering

Hydrogels considered as scaffolds for tissue engineering applications should respond to many issues of extracellular matrices related to surface properties, mechanical strength, biodegradability and electroactivity. S. Quraishi *et al.*[57] obtained a hydrogel as a result of exposure of alginate and lignin aqueous alkali solution containing calcium carbonate to CO_2 at 4.5 MPa. Carbon dioxide acted as an acidifier to liberate Ca^{2+} ions for the crosslinking of the alginate–lignin mixture. It was supposed that the OH groups of lignin may participate in the formation of egg-box junctions, but only to a certain extent. *In vitro* cytotoxicity screening has demonstrated that lignin does not influence cell viability. Also, it has been proved that the alginate–lignin aerogels are non-cytotoxic and feature good cell adhesion, which makes them attractive candidates for a wide range of applications, including bone tissue engineering and regenerative medicine.

A lignin–agarose hydrogel was prepared by the use of epichlorohydrin as crosslinking agent.[58] It presented the desired moment fracturability, ideal hardness and springiness, properties that suggest that it can have tissue engineering applications, in biomedical, biodegradability and medication conveyance.

New hydrogels based on hyaluronan and glycinated kraft lignin crosslinked with carbodiimide were developed. It was found that the incorporation of lignin into the hyaluronan hydrogels does not negatively influence the cytotoxicity of the final product, which is suitable for tissue engineering or other biomedical applications.[59] Kraft lignin has been reinforced with hydroxyapatite and beta-tricalcium phosphate to obtain a composite material for bone tissue engineering. The occurrence of pores with dimensions between 50 and 100 μm upon sintering at 900 °C was explained by lignin degradation.[60]

Surface modification of lignin nanofibers with arginine molecules led to developing a new gel, which was able to promote wound closure, re-

epithelialization, collagen deposition and angiogenesis.[61] Based on its properties, this material can be considered as an effective nanofiber-based option, with its gel-forming ingredients, in hydrocolloid wound dressings for the treatment of acute and chronic wounds. Due to the antioxidant and antimicrobial properties of lignin, which can minimize bacterial contamination in wounds, the arginine surface-modified lignin nanofiber gel (Arg-Lig-NF gel) was investigated for the future development of effective hydrocolloid wound dressings. The wound closure, re-epithelialization, collagen deposition and angiogenesis effects of the gel have been evidenced through *in vivo* wound-healing studies. These effects can be explained by the structural similarity of lignin nanofibers and natural extracellular matrix proteins, as well as by the wound-healing effects of arginine molecules.

Other authors[62] evidenced that lignin model dehydrogenate polymer in alginate hydrogel was active against some Gram-positive and Gram-negative bacterial strains, with the strongest activity against *L. monocytogenes*, *P. aeruginosa*, *S. typhimurium* and *S. aureus*. The activity of this material against wild bacterial strains isolated from patients with chronic wounds recommends its applications as a wound-healing agent or as an adjunct substance for wound treatments.

LignoBoost and Organosolv lignin microparticles were homogeneously incorporated into a PLA matrix by the melt blending process. The mechanical performance declined after immersion in simulated body fluid, but the properties of the biomaterials remained sufficiently high for the perspective of their use in medical applications. *In vitro* biocompatibility studies evidenced that the addition of lignin to a poly(lactic acid) matrix can allow tailoring the final properties of the composites without inducing any significant change in cell metabolic activity (compared to poly(lactic acid) itself).[63]

D. Kai *et al.*[64] have prepared some PLLA/PLA-lignin composites *via* the ring-opening polymerization of lactide onto selectively alkylated lignin. Three different cell types, such as PC12 (rat phaeochromocytoma), human mesenchymal stem cells and human dermal fibroblasts, were cultured. The oxidative stress induced by the polyester itself resulted in low metabolic activities on neat PLLA nanofibers for all the cells, while the presence of lignin determined higher cell proliferation values, which suggests that the antioxidant activities may enhance the viability of the cells.

Lignin-polycaprolactone (PCL) copolymers were prepared *via* solvent-free ring-opening polymerization. These lignin-PCL copolymers were incorporated with PCL and engineered into nanofibrous scaffolds. It was found that the nanofibers with lignin copolymers promoted cell proliferation of both BMSCs and Schwann cells, enhanced myelin basic protein expressions of Schwann cells and stimulated neurite outgrowth of dorsal root ganglion neurons.[65]

Lignin in drug delivery

Considerable effort is aimed at the synthesis of nanoparticles for the transport of drugs. Thus, lignin nanotubes synthesized from the aromatic plant cell wall polymer lignin in a sacrificial alumina membrane template have potential application as vehicles for gene delivery into human cells.[66]

Moreover, pH-responsive lignin-based nanocapsules for the controlled release of hydrophobic molecules were synthetized.[67] Lignosulfonate was first grafted with allyl groups through etherification and the modified lignosulfonate was further dispersed in an oil-in-water miniemulsion using sonication.

Alkali lignin was quaternized and further self-assembled into lignin-based complex micelles with sodium dodecyl benzenesulfonate in an ethanol/water mixture. The pH-responsive lignin-based complex micelles have potential application in the controlled delivery of hydrophobic oral drugs, such as indomethacin, nifedipine, aspirin.[68] Some lignin/complexed-lignin nanoparticles[69] were synthesized and investigated for potential biomedical applications. Thus, the Fe_3O_4-lignin nanoparticle complex showed superparamagnetic behavior, which makes it promising for magnetic targeting and magnetic resonance imaging applications. Also, a mixture containing 50:50 w/w of lignin solution and oleic acid coated Fe3O4 NPs in THF was prepared and dialyzed against MilliQ water; it was found to present potential for applications in cancer therapy and diagnosis.[70] Y. Uraki *et al.*[71] prepared ethylene glycol diglycidyl ether cross linked hydroxypropyl cellulose-lignin gel, which, at body temperature, shrinks and releases the content outside the gel network, because the lower critical solution temperature of the gel is 38.1 °C.

Sinapyl alcohol, a lignin precursor, exhibits anti-inflammatory and antinociceptive properties. It also performs the inhibition of lipopolysaccharide-induced nitric oxide, PGE2 (prostaglandin) and TNF-α production by macrophages; and reduces the expression of inducible NO synthase and cyclooxygenase (COX)-2 in a concentration-dependent manner.[72] Ferulic acid, 4-hydroxy-3-methoxy-cinnamic acid, is found as a component of lignin, and has some physiological functional properties, such as antimicrobial, anticancer, antioxidant and anti-thrombosis activities.[73]

The potential of polyphenols (including their derivatives and analogues) against ischaemic heart disease by reducing myocardial oxygen consumption and/or increasing oxygen supply was evidenced.[74] Other authors[75] reported that the biological functions of polyphenols are exhaustive, but more studies investigating the real importance of polyphenols to prevent some human diseases are needed.

A julolidine derivative has been shown to decrease amiloid-β concentration and reduce senile plaques *in vivo*, disassembling mature α-synuclein and amyloid-β fibrils into smaller nontoxic protein aggregates.[76] The amiloid-β self-assembly could represent a promising initial therapeutic strategy for Alzheimer's disease.

The anticancer activity of polyphenols derived from seed coat of *A. pedunculata* Pall was demonstrated using *in-vitro* assays with HepG2 cells.[77] The main polyphenol compounds identified (apigenin 7-O-glucoside, kaempferol, rutin, cyanidin 3-rutinoside, cyanidin 3-O-galactoside and quercetin) also exhibited anticonvulsant, anti-inflammatory and antioxidant properties.

Penta-galloylglucose has demonstrated its efficiency in the prevention and cure of some diseases, such as diabetes, sarcoma, prostate, breast and lung cancer.[78-79]

Chitosan nanoparticles loaded with phenolic compounds were used against bacterial gastrointestinal pathogens,[80] while a collagen hydrogel with layer-by-layer self-assembled films, comprising tannic acid and lignin, exhibited an antibacterial effect against Gram-positive and negative bacteria, and endured higher compression stress than collagen hydrogel.[81] Some plant extracts containing bioflavonoids and polyphenols, such as quercetin and resveratrol exhibited protection against diabetic complications.[82] Some authors synthesized Pt-polyphenol nanoparticles and demonstrated their potential antidiabetic applications, leading to a significant decrease in plasma glucose levels after injecting the nanoparticles into streptozotocin-induced diabetic rats.[83]

CONCLUSION

During the last years, research focused on the integrated utilization of lignin and its derivatives to produce various products with biomedical and pharmaceutical applications has flourished. Due to lack of clinical trials, the use of lignin in different bioapplications is limited. To overcome the obstacles between the research and applications of the sustainable valorization of these natural compounds, more investigations need to be carried out in the near future in order to elucidate their structures, reaction mechanisms and interactions with possible pathogens.

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