Electrospinning of Lignin Nanofibers for Drug Delivery

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Abstract In a biorefinery process, a key component of lignocellulosic biomass, lignin can be recovered at lab-to-pilot scales by using numerous methods. Lignin can be utilized for assorted applications as a renewable and sustainable source and also used as an excellent candidate to substitute and/or eliminate aromatic polymers derived from non-renewable petroleum sources. This chapter focuses on lignin's current state featuring assorted methods, including Kraft, organosolv, alkaline, and dilute acidic, to recover lignin from plant biomass. In addition, lignin types and their derivatives have been discussed and correlated with health and pharmacological activities. This chapter further discusses the lignin-derived carbon nanofibers (CNFs) and processes involving the production of CNFs by using an electrospinning method. The physico-chemical properties of lignin-derived CNFs were characterized using Raman, ^{13}C-^{1}H 2D heteronuclear single quantum coherence (HSQC) NMR, and more. Additionally, a proposed mechanism is presented to produce lignin bio-oils, and the formation of CNFs from this bio-oil is further discussed. The biomedical applications of nanofibers (NFs) and their role in drug delivery are also finally added and discussed. In the future prospective and concluding remarks, NFs derived from biopolymer can be a potential source as a substituent by elimination or substitution of non-renewable fossil feedstocks.

Keywords Electrospinning · Lignin · Nanofibers · Biomedical applications · Drug delivery · Plant biomass · Fossil feedstocks

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1 Introduction

The term electrospinning was conceived in the early sixteenth century by William Gilbert; he observed the formation of a cone-shaped water droplet in the presence of an electric field [1]. Thereafter, several systematic studies were done by Gray [2], Nollet and Stack [3], and Rayleigh [4] to, respectively, observe the electrohydrodynamic atomization, electrospraying experiment to form an aerosol, and charged droplets behavior of water droplets. The coin differences between electrospraying and electrospinning, respectively, lied in the viscoelasticity and viscosity of the liquid used. In 1901, John Cooley and William Morton filed two patents and explained a prototype of setup for electrospinning [5, 6]. The Soviet Union in 1938 first implemented the electrospun nanofibers (NFs) to prepare "Petryanov filters" for capturing the aerosol particles. The strength of electric fields decides the shape of droplets, such as beyond a critical level, the spherical droplets turned to a cone, and is generally referred to as a Taylor cone "Geoffrey Taylor". Electrospinning has been enabled in several areas including catalytic applications, energy harvesting, conversion, and storage materials, and these materials are generally dominated by inorganic NFs. These NFs offered bundles of excellent physical, chemical, thermal, biological, and more substantial properties. Therefore, they are eventually used in various applications including environment and sustainability, air purification, catalysis, energy, photonics, electronics, biomedical, and more [7]. Nowadays, non-renewable fossil feedstocks are mostly applied to synthesize the NFs, in which large amounts of toxic gases are produced in environment, and the utilization of fossil feedstocks are the major threat of global warming through the greenhouse [8].

An alternate solution to save the Earth's atmosphere from Greenhouse gas is to use available renewable and sustainable biomass sources. Biomass is generally categorized into animal and plant-derived biomass. The plant-derived biomass is further categorized into edible and non-edible biomass; the edible biomass competes with food and can be unable to fulfill the market demands. Therefore, the utilization of non-edible plant biomass is the most durable solution for researchers working in the area of biomass utilization. Plant or lignocellulosic biomass is generally composed of three major biopolymer units; cellulose (homopolymer of glucose unit), hemicellulose (heteropolymer of C5 and C6 sugar units), and lignin (heteropolymer of generally, C3/C4/C5 (alkyls) + C6 (aryl)) [9, 10]. Cellulose is a homopolymer of β-linked D-glucose units, whereas C5 and C6 sugars formed the heteropolymer structure of hemicellulose. Covalent lignin–carbohydrate (LC) linkages are eventually present in layered plant cell walls of lignocellulosic biomass [11, 12]. Nowadays, these biopolymers are used widely in both academic and industries, including biofuels synthesis, polymers, materials, and more applications [13–16].

2 Lignin

Lignin is a natural occurring bio-copolymer, that is structured with mainly three phenolic moieties; coniferyl alcohol (G), *p*-coumaryl alcohol (H), and sinapyl alcohol (S) (Fig. 1) [17]. These moieties are present in a lignin structure through several types of linkages that are ether/ester (C–O–C)/ C(O)–O–C, (e.g., α-O-4, 5-O-4, and β-O-4)) and condensed carbon–carbon linkages, including alkyl–alkyl, alkyl–aryl, or aryl–aryl (C–C, (e.g., 5–5, β-β, β-5, and β-1 linkages)) (Figs. 1 and 2). Around 50–70% of these intramolecular linkages are ether bonds, predominantly β-O-4 linkages [18]. Several factors affected the concentrations of these linkages in plant species (e.g., hardwood, softwood, and grasses), including environmental and biological factors (Table 1) [19]. Lignin features are also linked with polysaccharides which are called as lignin–carbohydrates complex (LCC). LCC linkages in plants are linked through phenyl glycoside bonds, benzyl ethers bond, or esters bond [11, 12]. LCC linkages in plant species eventually provide mechanical strength. Lignin works as an antioxidant, antimicrobial, and antifungal agent. It provides more fighting strengths in plant biomass, to prevent the outer and inner damages of plant species from foreign attack, and also works to store the energy in a bundle of layered plant cell walls [17]. Lignin is an up-and-coming candidate to replace and/or eliminate the phenolic chemicals that are currently procured from non-renewable fossil feedstocks. Lignin

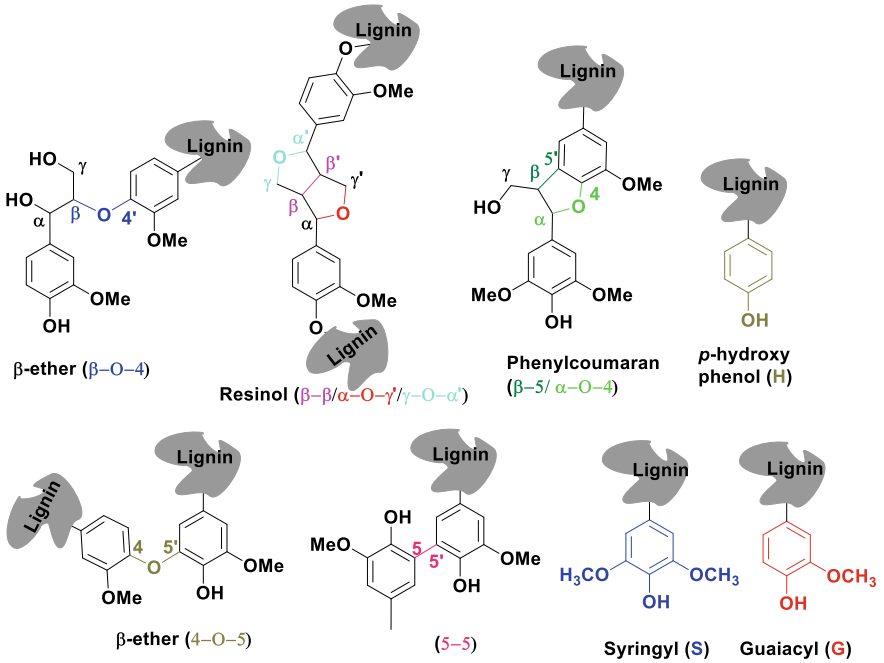

Fig. 1 Linkages (C–O–C/ C–C) present in lignin feature [42]

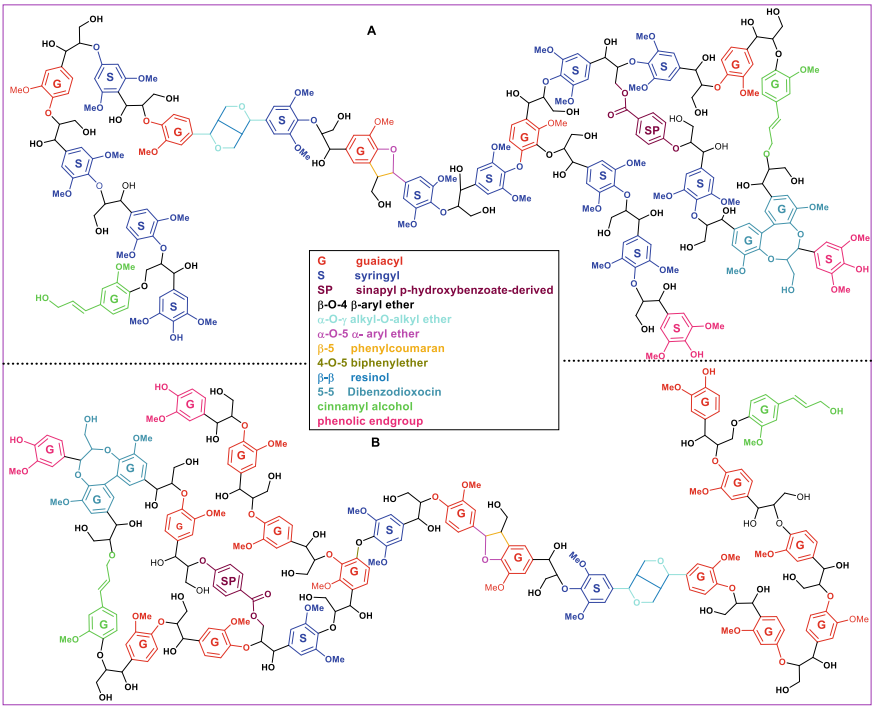

Fig. 2 Lignin copolymer structure for **a** syringyl moiety (hardwood lignin) with 24 units and **b** guaiacyl moiety (softwood lignin) with 24 units, redrawn from reports [30, 43]. For clarity of structure and bonding, see online or use color print for this figure

is produced in large quantities as a side product from pulp and paper industries. It is eventually burned to generate the energy and chemicals as a low-grade application. Lignin is also procured from biorefineries plant as a side product during the biofuel's synthesis from lignocellulosic biomass. Lignin is present in the layered plant cell walls in a native form and can be extracted from plant biomass by applying various treatments, including chemical (acidic, alkali, alkaline, oxidative, and more), solvent fractionation (organosolv fractionation along with small amounts of acids like sulphuric acid, ionic liquids, and more), physical (ball milling and more), and biological processes (enzymatic, fungi, and more) [20–22]. The physico-chemical properties and purity of recovered or technical lignin mainly depend on the isolation methods, degree of purification, fractionation history, plant sources, and measurement [23]. Table 2 shows the methods applied to recover lignin from plant biomass at academic and industrial scales [24–27]. These extraction methods are classified into two sub-categories. During the isolation process in the first sub-category, polysaccharide can be soluble, and lignin remains as a solid (e.g., Klason method and more), and in the second sub-category, lignin is soluble, and polysaccharide remains as an insoluble matter (e.g., organosolv, Kraft method, and more).

Table 1 Various types of linkages, relative abundance, and bond dissociation enthalpy in hardwood- and softwood-derived lignin

Linkage	Relative abundance of linkages in lignin feature (%) [32–34]		Bond dissociation enthalpy (kJ/mol) [35–39]
	Hardwood (Major guaiacyl lignin)	Softwood (Major syringyl lignin)	
Carbon–carbon linkage (30–40%)			
5–5'	4–11	10–25	490
β-β	3–7	2–4	335
β-1	5–7	3–7	270–289
α-1	–	–	360–390
β-5	4–6	9–12	–
Carbon–oxygen–carbon linkage (60–70%)			
β-O-4	46–65	43–50	290–335
α-O-4	4–8	6–8	215–270
4-O-5	3–7	2–5	330
α-O-γ'	–	–	270
– OCH_3	–	–	255–275
others	5–13	–	–
Functional group (per 100 parts unit). References [40, 41]			
Carboxyl	11–13	–	
Carbonyl	3–17	20	
Methoxy	132–146	92–96	
Aliphatic hydroxyl	–	120	
Benzyl hydroxyl	–	16	
Phenolic hydroxyl	9–20	20–28	

Unlike polysaccharides which have well-defined structure, lignin has a highly recalcitrant 3-D structure that provides the mechanical strength to plant cell walls [28]. Lignin composition and amounts within plant biomass depend upon plant species and vary with a set of various factors, including types of plant species, age of plants, location, weather, and more [23, 29]. Lignin contains, at a range of molar masses, various types of functional groups, including hydroxyl, carbonyl, ether, methoxy, phenolic, and more (Table 1) [30]. These functional groups played a crucial role in lignin's utilization for materials, polymers, chemicals, biological, and more applications [31].

Considering the earlier discussion impact of nanofibers, electrospinning, and renewable bioresource lignin, in this chapter, authors centered their attention on lignin features, and how lignin source and synthesis procedures have impacted their effect on healthcare. In addition, the impact of lignin or lignin derivatives over pharmacological activities has also been discussed. The synthesis of carbon nanofibers

Table 2 Various processes applied for lignin recovery [20, 25, 54, 55]

Process	Reaction conditions
Polysaccharides conversion	
Concentrated acid hydrolysis	Concentrated mineral acid (H_2SO_4, HCl, HF), 20–30 °C
Dilute acid hydrolysis	H_2O, H_2SO_4, HCl, HF, H_3PO_4, 170–300 °C,
γ-valerolactone-assisted acid hydrolysis	H_2O, GVL, H_2SO_4, 120–170 °C
Ionic liquid (IL)-assisted acid hydrolysis	IL: H_2O, H_2SO_4, HCl, 100–150 °C
Acid mechanocatalytic pretreatment	RT H_2SO_4, HCl, ball milling, post-hydrolysis, H_2O, 130 °C
Enzymatic hydrolysis	H_2O delignification, hot water, dilute acid, steam explosion, ammonia fiber explosion, deacetylation, and mechanical refining, 30–60 °C
Cellulolytic enzyme	H_2O, pH 4–5 (buffer), cellulolytic enzymes, ball-milled biomass, 40–60 °C
Enzymatic mild acidolysis	2-levels; level 1: cellulolytic enzymes (ball-milled biomass), level 2: mild acidolysis (dioxane/H_2O, HCl, 80–90 °C
Pyrolysis (fast)	Absence of O_2, acidic zeolite, 400–600 °C
Lignin conversion	
Kraft pulping	H_2O, NaOH, Na_2S, 140–170 °C
Sulfite pulping	H_2O, Na, NH_4, Mg or Ca salts of SO_3^{2-} or HSO_3^-, 140–170 °C
Soda pulping	H_2O, NaOH, (anthraquinone; AQ), 160–170 °C
Aqueous alkaline pretreatment	H_2O, NaOH, $Ca(OH)_2$, (AQ), 40–160 °C
Ammonia fiber explosion	H_2O, NH_3, fast decompression, 60–160 °C
Anhydrous ammonia pretreatment	Anhydrous NH_3, dry biomass, 100–130 °C
Ammonia recycle percolation	Aqueous NH_3, 150–210 °C
Flow-through dilute acid pretreatment	H_2O, H_2SO_4, HCl, 120–210 °C
Flow-through hot water pretreatment	H_2O, 160–240 °C
Steam explosion pretreatment + extraction	H_2O, (SO_2), fast decomposition, 100–210 °C
Organosolv pulping	Organic solvent/s H_2O, H_2SO_4, 100–220 °C
Formaldehyde-assisted fractionation	Dioxane, H_2O, formaldehyde, HCl, 80–100 °C
Carbon dioxide explosion	Supercritical carbon dioxide
Co-solvent enhanced lignocellulosic fractionation	THF-H_2O, H_2SO_4, $FeCl_3$, 160–180 °C
Reductive catalytic fractionation	Redox catalyst, H_2 (-donor), organic solvent (+H_2O), 180–250 °C
Wood-degrading microorganisms	Cultured, colonized, 24 °C

(continued)

Table 2 (continued)

Process	Reaction conditions
Fungal pretreatment	10–84 days, 60–75% moisture, 28–30 °C
Ionic liquid (IL) dissolution and ionosolv pulping	IL, H_2O, H_2SO_4, 90–170 °C
Mechanical pretreatment + extraction	Extensive ball milling, RT
Note GVL—gamma-valerolactone; RT—room temperature; THF—tetrahydrofuran	

from lignin and other polymers by using electrospinning is also discussed. Finally, we presented the biomedical applications including drug delivery of CNFs derived from lignin and prospects of NFs productions from assorted types of lignin and their clinical applications, with brief conclusions.

2.1 Lignin Recovery

Pretreatment is an initial step to remove and/ or reduce the inhibitors including lignan, acetate, hemicellulose, lignin, inorganic contents, and more that strike to enzymes and desirable to provide the maximum accessibility for cellulose hydrolysis. It is also believed that pretreatment helped to increase the accessible surface area (i.e., porosity) for enzymatic hydrolysis to maximum amounts of sugar monomers yield [44]. Researchers also believed that the rate of enzymatic hydrolysis is a function of cellulose crystallinity, and crystallinity can be reduced, thereafter the pretreatment of lignocellulosic biomass or pure crystalline cellulose [44]. A series of pretreatment methods are developed, including physical, chemical, thermal, or biological, to recover lignin as a precipitate or solid and carbohydrates-rich pulp or in the solution phase. These methods are ranged from sophisticated to environment friendly and are used in various sets of conditions, including temperature, acids, base, ionic liquids (ILs), organic solvents, ammonia fiber expansion, enzymatic mild acidolysis, and more. Some of the pretreatment methods are briefly discussed below and details are shown in Table 2.

2.2 Kraft Process

Kraft pulping process is the most common chemical pretreatment process that is used to recover lignin from lignocellulosic biomass. It is a well-established industrial technology and currently covered more than 85% pulping of wood to produce delignified pulps. Sodium sulfide and sodium hydroxide as a "White Liquor" are used for the pulping process at elevated temperature and pressure. Lignin binds with

polysaccharides, dissolved in white liquor, and separate as a precipitate by acidifying recovered black liquor [22, 45, 46]. The impact of delignification reaction conditions, including temperature and time in the presence of alkali, has been defined as H-factor [47] and the parameter is defined as below.

$$H = \int_0^t e\left(43.2 - \frac{16117}{T}\right)dt \tag{1}$$

where T(K) is temperature and t (h) is reaction time.

2.3 Dilute Acidic

Dilute acid pretreatment (DAP) is the most widely used deconstruction process of lignocellulosic biomass at a large scale to produce carbohydrates-rich pulp that pulp is mostly free and/or reduce from inhibitors content. DAP helps to cleave the covalent bonds in lignocellulosic biomass. In this process, mineral acids, including sulphuric acid, hydrochloric acid, or nitric acid, are used at a wide range of concentrations ($\leq$4 wt.%) over a range of temperature (170–300 °C). Among all, sulphuric acid is mostly employed due to its economic process and high efficacy for lignin removal as well [48]. The combined severity factor (S) is used to correlate the acidic delignification process under different conditions, and it is defined by using the following equation [49, 50].

$$S = log\left(t\ exp\left(T - \frac{100}{14.75}\right)\right) - pH \tag{2}$$

where t is reaction time, T is temperature, and pH expressed is acid loading.

2.4 Alkaline Process

The alkaline pretreatment process is a widely used chemical pulping for delignification. This process uses several types of bases, including hydroxide of sodium, potassium, calcium, or ammonium over a range of reaction conditions, including time, temperature, and alkali loadings [51]. This process cleaved the ester and glycosidic side chains in layered plant cell walls and resulted in the lignin and hemicellulose solubilization in alkali solution. This process also helped for cellulose intercrystalline swelling. Additionally, the alkali process also removed and/ or reduced the acetate and uronic acid that linked as a hemicellulose substructure and helped to eliminate the inhibitors as well. This process also altered the treated biomass structure in terms

of cellulose swelling that leads to maximum porosity and reduction in crystallinity or degree of polymerization [52]. The swelling of cellulose structure provided the maximum accessibility for enzymatic hydrolysis to produce maximum amounts of sugar monomer that is amenable for further biofuels production.

2.5 Organosolv Process

Organosolv process is used to delignify the lignocellulosic biomass using organic solvents, including aliphatic alcohols (i.e., ethylene glycol, methanol, ethanol, butanol, and more) and aromatic alcohol (i.e., phenol) in the presence or absence of acid catalysts. There are several parameters, including temperature (90–220 °C), time (25–100 min), aqueous organic solvent ratios (ethanol concentration 25–75% v/v), and acid amounts (0.5–2 wt%), involved to impact delignification process [53]. Organosolv lignin has eventually low molar mass and is mostly soluble in water. This lignin is considered as highly pure lignin. However, the amount of lignin recovery is low, and the recycling of organic solvent is another limitation of this process.

3 Types of Lignin and Their Effect on Health

Lignin can be obtained from a range of terrestrial plants and aquatic seaweeds, red algae, and more, by applying various processes (Table 2). Lignin is a remarkable renewable phenolic raw material and currently has limited uses. Although, specific potential applications of biorefinery lignin are in progress using the lignin directly or modified lignin. The pulp and paper industries produce a large quantity of lignin each year. Nearly 98% of recovered lignin is burned at the same factories to generate boiler heat and chemicals [56]. Approximately 2% of lignin, derived from lignosulfonate and Kraft lignin, is commercially exploited for about 1000,000 tons per annum and 100,000 tons per annum, respectively [57]. Nevertheless, commercial applications of biomaterials derived from lignin are promising in the coming years. Plant biomass sources and fractionation conditions of technical lignin must be specified prior to their use in potential applications because their physical, biological, thermal, and chemical properties are extremely variable due to developmental and environmental factors [58]. Similarly, their purity and physico-chemical properties are essential and need to be characterized. Table 3 shows the physico-chemical properties of some academic and industrial scales isolated lignin.

Lignin exhibits a very low level of toxicity. Generally, organic solvent-free lignin including Kraft and lignosulphate lignins has been extensively tested over humans and animals, and laboratory results showed that these lignins are essentially non-toxic for both humans and animals [59]. The LD50 values have been reported as more than 12 g/kg of body weight. Food and Drug Administration, United States of America, has approved both Kraft and lignosulphonate lignins to be used for manufacturing a

Table 3 Impact of various types of methods on physico-chemical properties of extracted lignin

Lignin	$\overline{Mw}$(Da)	PDI	Carbohydrates (*wt%*)	Sulfur (*wt%*)	Ash (*wt%*)	Per phenyl propane unit				References
						Aliphatic –OH	Phenolic –OH	– COOH	– OCH_3	
Kraft	1500–200,000	2.5–7.3	2.3	1.0-3.0	0.5–3.0	~0.4	0.8–1.0	0.2–0.3	~0.6	[60–62]
Lignosulphonate	1000–400,000	6–8	–	3.5-8.0	4.0-8.0	–	0.2–0.3	0.2–0.3	~0.7	[63, 64]
Organosolv	500–17,000	1.7–4.5	1.0–3.0	0	0–2.0	~0.4	~0.4	~0.1	0.9–1.0	[9, 65–67]
Soda	1,000–15,000	2.5–3.5	1.5- 3.0	0	0.7–2.3	~0.4	0.4–0.5	0.2–0.3	1.0–1.2	[23, 61, 63]
Hydrolysis	1,900–10,000	3.0–11.0	15.0 -23.0	0–1.0	1.0–3.0	~0.5	0.2–0.3	~0.1	0.6–0.7	[64, 68, 69]
Ionic liquid	2,000–42,000	1.0–3.0	0.1–15.0	1.5	0.6–2.0	–	–	–	–	[70]

Note $\overline{Mw}$ and $\overline{Mn}$ = weight and number average molar mass; polydispersity index (PDI) = $(\overline{Mw}/\overline{Mn}$

wide range of food-grade applications. As lab study shows lignin is almost present in substantial amounts in all vegetables and whole grains.

3.1 Impact of Lignin or Lignin Derivatives On Pharmacological Activities

Lignin is a heteropolymer structure of phenylpropanoid units. That is structurally linked with aliphatic alcohols and phenolic chains (Figs. 1 and 2). Several studies showed that these structures are associated with good thermal, chemical, physical, and biological properties. These properties of lignin or lignin-derived compounds worked out in different biological activities. These activities included the prevention of tumor growth that is demonstrated in rats [71], reduced serum cholesterol by binding with bile acids in the intestine [72], antioxidant activities, treatment of diabetes, obesity control, antiviral agents and immunomodulators, anticoagulant and anti-emphysema agents, and more (Table 4) [30, 73].

3.2 Lignin Carbon Fibers

Lignin is a low-grade biomaterial that is essentially used as a cement additive, burned to generate energy and chemicals, feed for cattle, and more. It can be a potential renewable, sustainable, and low-cost source to eliminate the synthetic polymers including polyacrylonitrile to produce carbon fibers. The production of carbon fibers from lignin can be improved by the raw material availability, reducing the cost and dependency of petroleum-derived products, and slash and/ or eliminating the greenhouse gas. That can be generated upon the synthesis and utilization of petroleum-derived products. Lignin can be a potential source for carbon fibers in contest of economic and environmental to the petroleum derived carbon fibers. Several factors need to be carefully implemented, including spinning conditions, treatment temperatures, ramping profiles, melt-spinning steps, and more, to obtain carbon fiber of superior strength from lignin [88]. Figure 3 shows the formation of low-cost carbon fibers from lignin (For more details on lignin isolation, see Table 2). The lignin-derived carbon fibers have been substantially applied in a wide range of technical applications, including energy storage (e.g., batteries, supercapacitors, dye-sensitized solar cells) and more [89]. The modified carbon fibers are used in sensing, diagnostics, aerospace, and more [90, 91].

Table 4 Effect of lignin or lignin derivatives on pharmacological activities

Lignin or lignin derivative	Source	Molar mass (Da)	Effect	Mechanism	References
Alkali lignin	*Acacia nilotica*	NA	Antidiabetic	Inhibited glucose movement and α-amylase	[74]
Lignosulfonic acid	NA	~8,000	Antidiabetic	Suppressed blood glucose levels via inhibition of α-glucosidase activity and intestinal glucose absorption	[75]
Lignophenols	*Cryptom-eria Japonica*	~2,000	Obesity control	Suppressed oleate-induced microsomal triglyceride transfer protein (MTTP) mRNA expression and cellular cholesterol	[76]
Lignophenols	Beech	1,500	Obesity control	Suppressed excess oxidative stress, infiltration and activation of macrophages, and glomerular expansion in STZ-induced diabetic kidneys	[77]
Lignosulfonic acid (LA)	NA	~8,000	Viral inhibition	LA inhibited the HIV and herpes simplex virus (HSV-2) replications	[78]
Lignin–carbohydrate Complexes (LCC)	*Pimpinella anisum*	7,000–8,000	Antiviral activities	Virus adsorption showed antiviral activities against HSV-1 and HSV-2, human cytomegalovirus, and measles virus	[79]
Cinnamic Acid-Based Lignins	NA	2,100–16,500	Antiviral activities	Inhibited HSV-1 entry to mammalian cells	[80]

(continued)

Table 4 (continued)

Lignin or lignin derivative	Source	Molar mass (Da)	Effect	Mechanism	References
Sulfated low-molecular-weight lignins	NA	3,300–4,100	Anticoagulants	Inhibited thrombin and factor Xa	[81]
Sulfated low-molecular-weight lignins	NA	3,300–4,100	Anticoagulants	Inhibited coagulation factor XIa and human leukocyte elastase, moderately inhibited cathepsin G	[82]
Sulfated, low-molecular-weight lignins	NA	3,300–4,100	Anticoagulants	Inhibited thrombin and factor Xa	[83]
Sulfated, low-molecular-weight lignins	NA	3,300–4,100	Antithrombin binding	Inhibited the free factor VIIa	[84]
Sulfated β-O-4 lignin	NA	NA	Anticoagulant and antiplatelet	Targeted exosite 2 of thrombin to reduce fibrinogen cleavage through allostery	[85]
Unsulfated or sulfated low-molecular-weight lignins	NA	NA	Anti-emphysema	Elastase, oxidation, and inflammation inhibition	[86]
Functionalized Kraft lignin	NA	NA	Antiproliferative	pH-responsive delivery of anticancer drugs	[87]

Note NA—not available

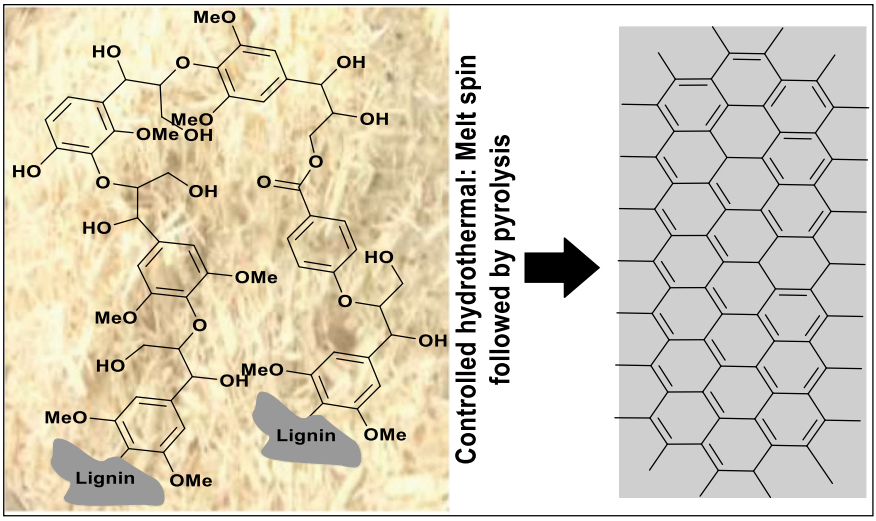

Fig. 3 Depiction of carbon fibers formation from lignin [92]

4 Electrospinning

Electrospinning is a very simple, highly productive, and emerging nanotechnology that is used to produce the thin natural micro- and nanometer scales (0.01–10 μm) fibers. These fibers are associated with substantial advantages that include the extremely lightweight, low manufacturing cost, highly flexible in surface functionality, reduced defects because of small diameter, high molecular orientation, and more. These fibers have been suggested for a wide range of applications due to their high specific surface area, small pore size, high porosity, and more. A "Taylor cone" of fibers is initiated at the tip when a high-voltage electric field is applied over the polymer solution. This method is applied to fabricate a range of NFs of polymers, composites, ceramics, metals, and more. Scaffolds are currently prepared by electrospinning the mixture of nanoparticles and polymers. The electrospinning process does not require any supplementary step including functionalization, heating, cooling, and more. This process requires a suitable solvent that can highly disperse the nanoparticles and could completely dissolve the polymers [93]. Tuning the electrospinning process parameters, including needle type, voltage, feed rate, tip-to-collector distance, and more, greatly affects the physico-chemical properties of electrospun NFs (Table 5) [94]. A capillary tube with pipette or needle with a small diameter, a high-voltage supplier, and a metal collecting screen, whichare the basic three main components, is used for electrospinning of polymers NFs [95].

Table 5 Process parameters for the generation of NFs using electrospinning [94]

Ambient condition	Process condition	Solution properties
• Temperature • Humidity • Environmental pressure • Time required for feeding • Air velocity in the chamber	• Needle diameter • Volume feed rate • Distance between needle and collector • Applied voltage • Motion and size of the target screen	• Elasticity • Surface tension • Electric conductivity • Molar mass of polymer • Polymer concentration • Viscosity • Types of solvent

5 Lignin-Derived Carbon Nanofibers

Lignin is a very low-grade biopolymer and produced in large quantities as a byproduct from pulp and paper industries, and through an integrated biorefinery to produce biofuels as well. Researchers have shown an attractive interest to convert lignin to high value-added commodities including chemicals, [25, 96, 97] materials, [98] polymers [99], and more. Lignin is the most approaching candidate to apply for manufacturing carbon nanofibers (CNFs) due to its meager cost, earth-friendly nature, aromatic and thermoplastics characteristics, and more. Several low-cost precursors have been reported elsewhere for the production of carbon fibers [88, 100]. Table 6 shows the total cost of CFs derived from lignin (US $ 6.3; precursor and production) which is lower as compared to conventional (US $ 34.6), textile-grade (US $ 16.6–38.6), and melt-spun (US $ 23.7) polyacrylonitrile (PAN) carbon fibers (CFs). This comparison study shows that lignin is a cost-effective precursor to produce CFs. There are several advantages including higher modulus, already oxidized, high carbon content, inexpensive and renewable, and more, and disadvantages including disordered and complex structure, diversity, may cross-link during melt spinning, and associated with lignin. Lignin is apparently inexpensive, renewable; therefore, the dependency over the non-renewable petroleum-derived resource could be reduced and/ or eliminated. Lignin is partially oxidized, has high carbon content (≥55%), and associated with more fruitful properties categorize that lignin is a good-to-excellent

Table 6 Various sources of carbon fibers and their precursor and production costs [114–116]

Entry	Source	Precursor cost (per kg US $)	Production cost (per kg US $)	Total cost (per kg US $)
1	Lignin	1.1 (including spinning)	5.2	6.3
2	Conventional PAN	10.2	24.4	34.6
3	Textile-grade PAN	4.4–13.2	12.2–25.4	16.6–38.6
4	Melt-spun PAN	6.3	17.4	23.7
5	Polyolefin	1.57–2.36	NA	NA

Note PAN—polyacrylonitrile; NA—not available

candidate for producing low-cost CFs from manufacturing prospects by using a melt-spun and energy-efficient method [101]. Moreover, the generation of toxic gases including hydrogen cyanide (HCN), nitrous gases, and more can be avoided by using lignin as a precursor that occurred during the carbonization of petroleum-based precursors.

Two methods including vapor growth and electrospinning were eventually applied to produce CNFs. Additionally, few other methods, including template synthesis, phase separation, drawing, and self-assembly have been reported elsewhere [102, 103]. Lallave et al. reported the filled and hollow CNFs at room temperature and without polymer binders by applying co-axial electrospinning of Alcell lignin in ethanol [104]. Lignin nanofibers (L-NFs) were produced from the lignin/ethanol/platinum acetyl acetonate and lignin/ethanol solutions using electrospinning [105]. Lignin phosphoric acid mixtures were fabricated via electrospinning to obtain L-NFs [106]. To check the role of the metal complex with lignin and phosphoric reaction mixtures, platinum acetyl acetonate was used to get L-NFs via the electrospinning route [107]. Seven different types of softwood lignins were reported to produce lignin-derived beaded fibers in the varying concentration of DMF and water solution [108]. However, the production of uniform CNFs from recovered lignin is rarely seen, except the work done by Lallave et al. by using Alcell lignin and ethanol (1:1) solution [104, 105], and other work done by Dallmeyer et al. by using purified softwood Kraft lignin [109]. The low electrospinning ability of pure lignin occurred due to several points including low molar mass, nonlinear structure, and the formation of anion charge in solution [110]. The high contents of graphite and diamond-like carbons were obtained using electrospinning lignin/PAN solutions in the presence of catalysts including $Fe(NO_3)_3{\cdot}9H_2O$ or $PdCl_2$ [111]. The different sets of noble monometallic and bimetallic nanoparticles, including Pd, Pt, Au, Pd/Pt, Pd/Au, or Pt/Au, were applied to produce LCNFs mats by using the electrospun and thermostabilized routes [112]. An extension of the ice-segregation-induced self-assembly methodology was applied to make the LCNFs. In this method, a rapid freezing of aqueous lignin solution was done, and subsequent sublimation of resultant freeze dryer material was performed to obtain L-NFs at −15 °C,100 millitorr. Stabilization and carbonization processes were then performed under similar conditions reported elsewhere to get LCNFs [113].

Dalton et al. developed biobased CNFs that are derived from a mixture of PAN and lignin in different ratios (up to 70%). The impact of lignin addition is characterized regardless of the reduced diameter of CNFs from 450 to 250 nm, enhanced sample flexibility, and more [117]. Raman spectra of lignin-derived CNFs were done and provided two crystalline bands at 1350 cm^{-1} and 1580 cm^{-1} for D-band and G-band, respectively (Fig. 4) [118]. The electrical conductivity of biobased CNFs was determined and high amounts of lignin contents (i.e., 70%) resulted in higher electrical conductivity. This phenomenon was explained based on maximum inter-fiber fusion achieved with high lignin loadings in biobased CNFs. Table 7 shows the different lignin types and their respective fraction with PAN used to synthesize the biobased CNs. It was noted that the impact of lignin loading in between 50–70% was good to produce excellent NFs morphology.

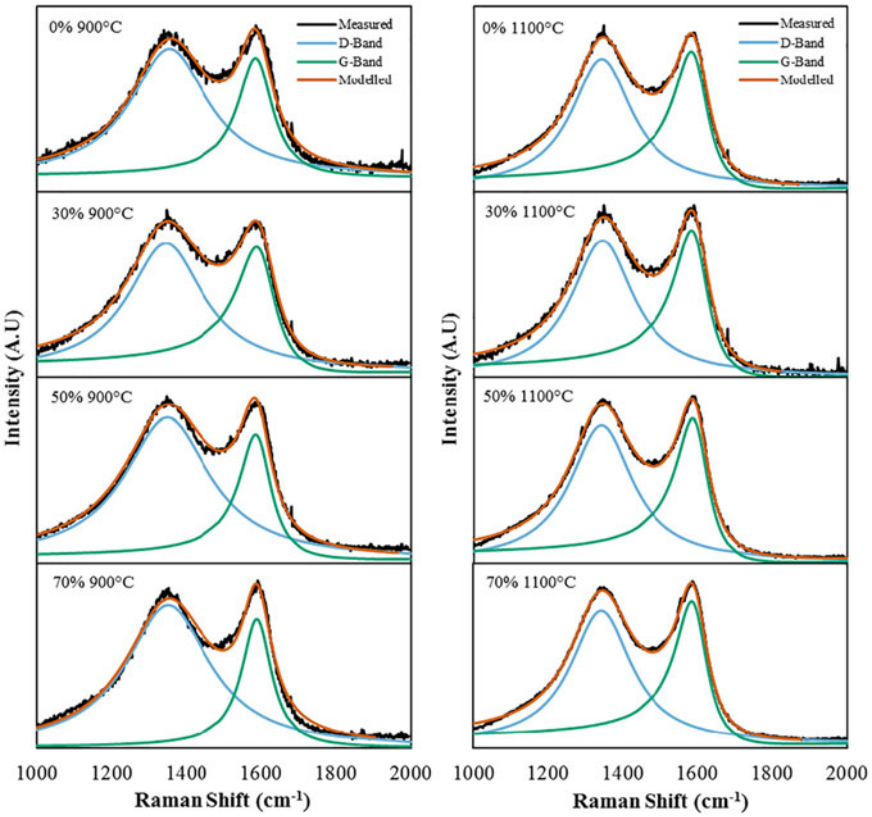

Fig. 4 Deconvoluted Raman spectra of biobased CNFs with different ratios of lignin. Figure adapted from Ref. [117] with Elsevier permission

Table 7 Types of lignin and their ratio with auxiliary polymer for lignin-based NFs synthesis

Entry	Type of lignin	Auxiliary polymer	Solution concentration (wt%)	Polymer-to-lignin ratio (wt%)	References
1	Kraft lignin	PAN	30	50:50	[119]
2	Kraft lignin	PAN	12	50:50	[120]
	Kraft lignin	PAN	18	80:20 and 50:50	[121]
3	Alkali lignin	PAN	20	50:50	[122]
4	Alkali lignin	PAN	15	50:50	[111]
5	Hardwood lignin	PAN	18	50:50	[123]
6	Lignin powder	PAN	25	70:30	[124]
7	Corn straw lignin	PAN	10	90:10	[125]
8	Enzymatic hydrolyzed lignin	PAN	10	60:40	[126]
9	Lignin bio-oil	PAN	20	15:85	[127]

Note PAN—polyacrylonitrile

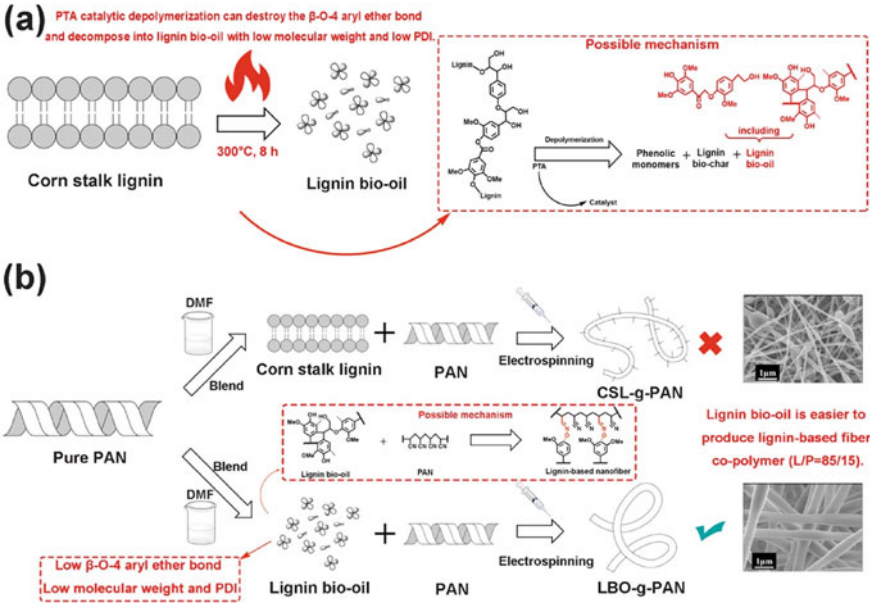

Fig. 5 Proposed mechanism for **a** lignin conversion to bio-oil and **b** lignin-based nanofibers. Figure adapted from Ref. [127] with Elsevier Permission

Figure 5 shows a possible mechanism for the formation of lignin or bio-oil-based CNFs. Corn stalk lignin was initially depolymerized to aromatic bio-oil that contained various types of functional groups, including hydroxyl, aldehyde, ester, acid, and more. These functional groups are highly susceptible to the formation of linkages with PNA. SEM images of lignin-derived CNFs and bio-oils-based CNFs were analyzed and average diameters of bio-oil-based CNFs were hanging between pure PAN and lignin-derived CNFs.

The ^{13}C-^{1}H 2D heteronuclear single quantum coherence (HSQC) NMR was recorded for PAN, lignin, and biobased CNFs, and the obtained spectra are shown in Fig. 6. New cross-signals were characterized in both lignin and biobased CNFs samples, besides the cross-signals presented in PAN (δ_H/δ_C 6.51/151.37 ppm). This study confirmed the formation of linkage between the PAN and lignin or bio-oils.

Alkali lignin was used to prepare the electrospun CNFs. The properties correlation suggested that lignin-derived CNFs have 10-times high absorption capacity, six-times high permeability, and two-time faster absorption kinetics relative to conventional CNFs [128]. These properties of lignin-derived CNFs relative to conventional CNFs were explained based on the high specific surface area, larger average pore diameter and high pore volume [128]. Kraft lignin is produced in maximum amounts by pulp and paper industries and used to prepare the CNFs. Acrylonitrile (AN), α,α′-azobisisobutyronitrile, and Kraft lignin were mixed to synthesize a copolymer, and the synthesized copolymer was transformed for electrospinning to prepare CNFs [129].

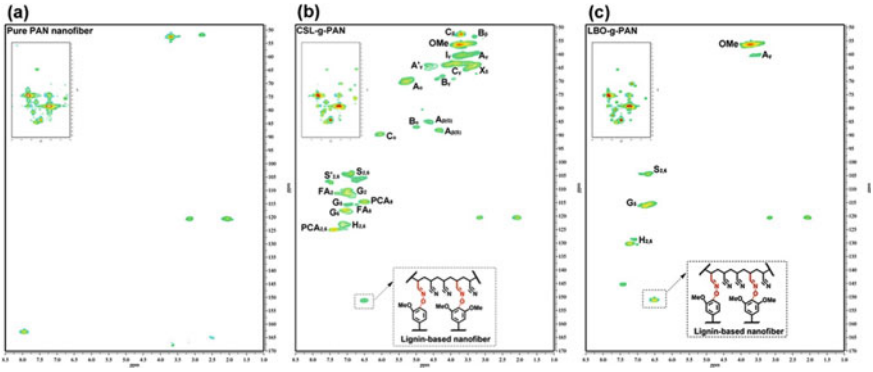

Fig. 6 2D ^{13}C-^{1}H HSQC NMR spectra of **a** pure PAN, **b** corn stalk lignin-g-PAN nanofiber, and **c** lignin-derived bio-oil-g-PAN nanofiber. Figure adapted from Ref. [127] with Elsevier Permission

6 Biomedical Application of Electrospun Nanofibers

In the field of biomedical applications, the advantages of using nanomaterials can be explored by using the NFs that are designed from a variety of polymers, either biocompatible or non-biodegradable. Due to the versatile and unique physical, chemical, thermal, mechanical, and biological properties of NFs, they have been used in a wide range of biomedical communities for their applications including drug delivery [130], gene delivery [131], skin tissue engineering [132], bone tissue engineering [133], cartilage tissue engineering [134], skeletal muscle tissue engineering [135], and more. For drug delivery applications, most of the drugs are introduced in the body by applying conventional methods, including oral tablets and/or intravenous injections. There are encounter problems and side effects including poor solubility, tissue damage during extravasation, cytotoxicity, undesirable biodistribution, and more. Considering these issues, advanced drug delivery systems can be implemented that aim to minimize toxicity, targeted drug release, extended drug release picture, enhanced bioavailability, and more. The CNFs scaffolds, fabricated by electrospinning, are the most attractive and modern competent drug delivery carriers. They are the transfigure agent in the nanomedicines field due to their structure and properties, including large surface area, diameters, porosity, and improved drug loading capacities, that enhance the drug permeation and retention effects and more [7].

6.1 Drug Delivery

The drug delivery system offers numerous selective forthcoming properties, including improving the therapeutic efficiency of several existing drugs. Several factors need to be considered prior to design an efficient drug delivery system (Fig. 7). The use of NFs for drug delivery systems is enormously developing in

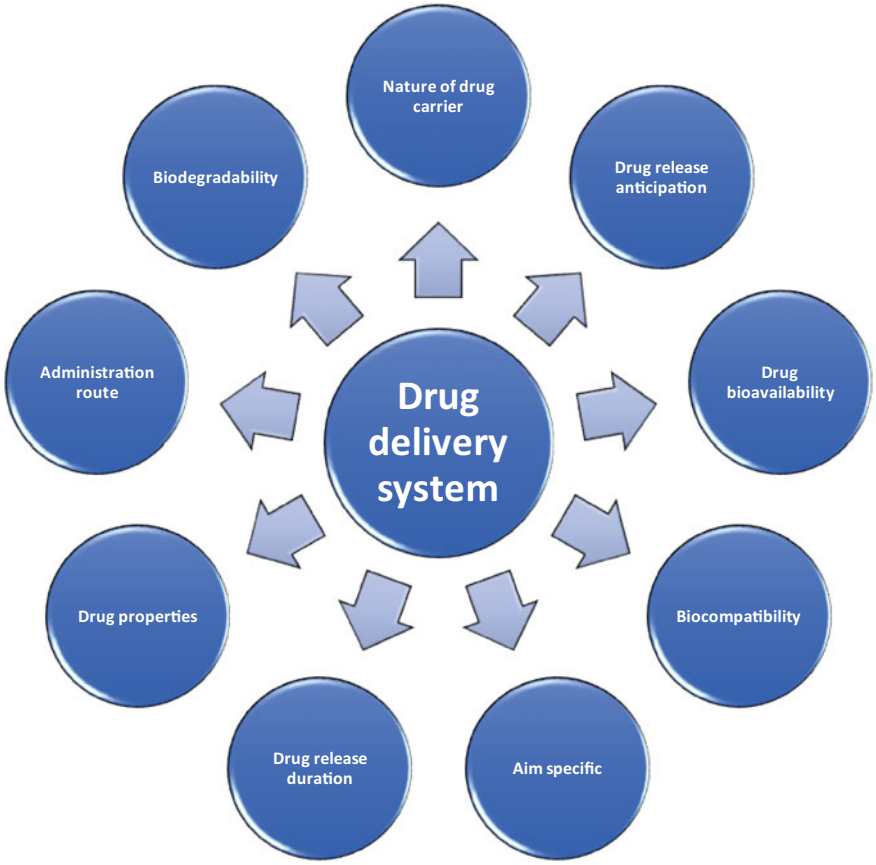

Fig. 7 Factors need to be considered before designing an efficient drug delivery system [137, 138]

various applications including anticancer therapeutics, surgical implants, antibacterial sheets, wound dressings, tissue scaffolds, and more [136]. A various set of drug loading methods, including coating, embedding, encapsulating (co-axial and emulsion electrospinning), and more, are reported elsewhere [130]. These methods have been utilized to release the kinetics of drugs in a controlled manner. Over the past few decades, control drug delivery systems have found a lot of academic and industrial attention regarding biomedical applications for drug release. Both academic and industrial attention occurred because of various advantages offered compared to a conventional dosage form including a reduction in toxicity by delivering the drug at the targeted site of the body and controlled rate, improved therapeutic efficacy, and more.

Several types of NFs fabricated by electrospinning, that are derived from biocompatible or non-biodegradable materials, are used for a wide range of biomedical applications [139]. Similarly, lignin and lignin-derived biomaterials nanoparticles have

also been applied in drug release, tissue engineering, and more applications [140, 141]. Kai et al. have synthesized a range of different concentrations of alkylated lignin (10–50%) with biodegradable poly(lactic acid) (PLA). These PLA-lignin copolymers further blended with PLA and proceeded to form the NFs composites by electrospinning. These NFs were evaluated for antioxidant activity over three different types of cells, including PC12, human dermal fibroblasts, and human mesenchymal stem cells [142]. Lignin was blended with other polymers, including poly(ε-caprolactone-co-lactide), polystyrene, and poly(ethylene glycol), and proceeded then for electrospinning to obtain NFs. These lignin-polymers-derived NFs were evaluated for various biomedical and/or healthcare applications [143, 144]. A highly stretchable lignin-based electrospun biomaterial was synthesized by using poly(methyl methacrylate) (PMMA) and poly(e-caprolactone) (PCL). Synthesized lignin-derived CNFs were processed for cell culture study. It was characterized that the synthesized biomaterial is biocompatible and showed human dermal fibroblasts interaction [145]. Electrospun poly (ε-caprolactone) (PCL)-grafted lignin (PCL-g-lignin) copolymer CNFs showed excellent antioxidant, anti-inflammatory, and low cytotoxicity properties. PCL-g-lignin NFs inhibited the reactive oxygen species generation and activated the antioxidant enzyme activity by an autophagic mechanism. The nanofibrous membrane of PCL-lignin can be implanted for arthroscopic and that provides an effective Osteoarthritis therapy [146]. Arginine-derived lignin NF was prepared by using an electrospun technique and obtained NF showed suitable viscosity that can be used for the spreadability for topical application. In *vivo*, the wound-healing assay was demonstrated in rats. The Arginine-based lignin NF accelerated wound healing and substantially increased re-epithelialization, collagen deposition, and angiogenesis relative to lignin NFs and arginine [147]. In another study, lignin copolymer was synthesized by using β-butyrolactone and/or ε-caprolactone. The synthesized lignin copolymer was further incorporated with poly(3-hydroxybutyrate) (PHB) to prepare PHB/lignin NFs by using electrospinning techniques. The obtained PHB/lignin NFs characterized using various techniques and results showed that the tensile strength and elongation of materials increased. The obtained materials were also screened for biodegradation and biocompatibility test and results showed that synthesized materials can be used for biomedical applications [148]. Lignin-polycaprolactone (PCL) copolymer was synthesized by ring-opening polymerization (ROP) in the presence of a tin (II) 2-ethylhexanoate catalyst. The obtained copolymer was further electrospunned with different PCL ratios (5:95, 10:90, and 15:85 wt/wt). The PCL/lignin-PCL nanofibers were cultured with Schwann cells and dorsal root ganglion (DRG) neurons to access nerve generation potential. The resulted cultures were characterized, and data suggested that lignin NFs promoted the cell proliferation of bone marrow mesenchymal stem cells and Schwann cells. The synthesized NFs also enhanced the myelin basic protein expressions of Schwann cells [149]. Poly(3-hydroxybutyrate) (PHB)-derived lignin copolymer was synthesized by the ROP mechanism. This copolymer was further reacted with PHB to produce composite NFs by using an electrospinning technique. The synthesized PHB/lignin NFs were demonstrated for an antioxidant activity to allow the excess free radicals neutralization. The nonirritating and biocompatible nature of PHB/lignin NFs was reported over

the animal studies [150]. Cellulose-derived CNFs have also been studied for drug released kinetics for four drugs; naproxen (NAP), indomethacin (IND), ibuprofen (IBU), and sulindac (SUL). The liberation of these drugs from NFs was evaluated in solvent cast films, and the films followed the trend as NAP > IBU > IND > SUL, due to their higher interaction [151].

6.2 Electrospun Lignin-Based Nanocomposites for Drug Delivery

In the past few decades, nanocomposite scaffolds, derived from biopolymers, have received more attentions in a wide range of area, including tissue engineering, drug delivery, and more, from academia and industries [152]. A large number of nanocomposite interest can be defined due to its excellent physical, chemical, thermal, and biological properties, including, pore sizes, pore volumes, and more, that allow more readily cells differentiation and vascularization. These properties can be used for the substitution of bone and skin tissues [152]. Lignin and polycaprolactone (PCL) were used to synthesize a nanocomposite by using an electrospinning technique. A wide range of lignin concentration (i.e., 0, 5, 10, and 15 wt%) was mixed with PCL, and obtained lignin-PCL nanocomposite with 10 wt% of lignin showed the good properties, including porosity, fiber diameter, tensile strength, and Young's modulus, relative to pure PCL. These nanocomposites were tested for cell cytotoxicity, and characterized results showed that the 10 wt% lignin composite has been selected for the cell test [153].

7 Conclusions and Prospects

Nanofibers are unique and versatile class of nanomaterials with their excellent physical, -chemical, thermal, and biological properties. Moreover, their functional properties can be tuned as per need. NFs have attracted increasing attention in the past few decades and gained novel applications in assorted biomedical disciplines. Rapid and substantial advances in biology, chemistry, material science, and medical, micro-, and nanotechnologies have enabled us to produce renewable and sustainable sophisticated and biomimetic NFs for biomedical, drug delivery systems, and more applications. However, the clinical applications of renewable lignin-derived NFs are lesser relative to conventional non-renewable petroleum-derived NFs. Biomedical applications of L-NFs are still at their very early stage. This chapter offers a plethora of opportunities to design, synthesize, and study NFs from assorted lignins for biomedical applications.

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