Fruit pomace-lignin as a sustainable biopolymer for biomedical applications

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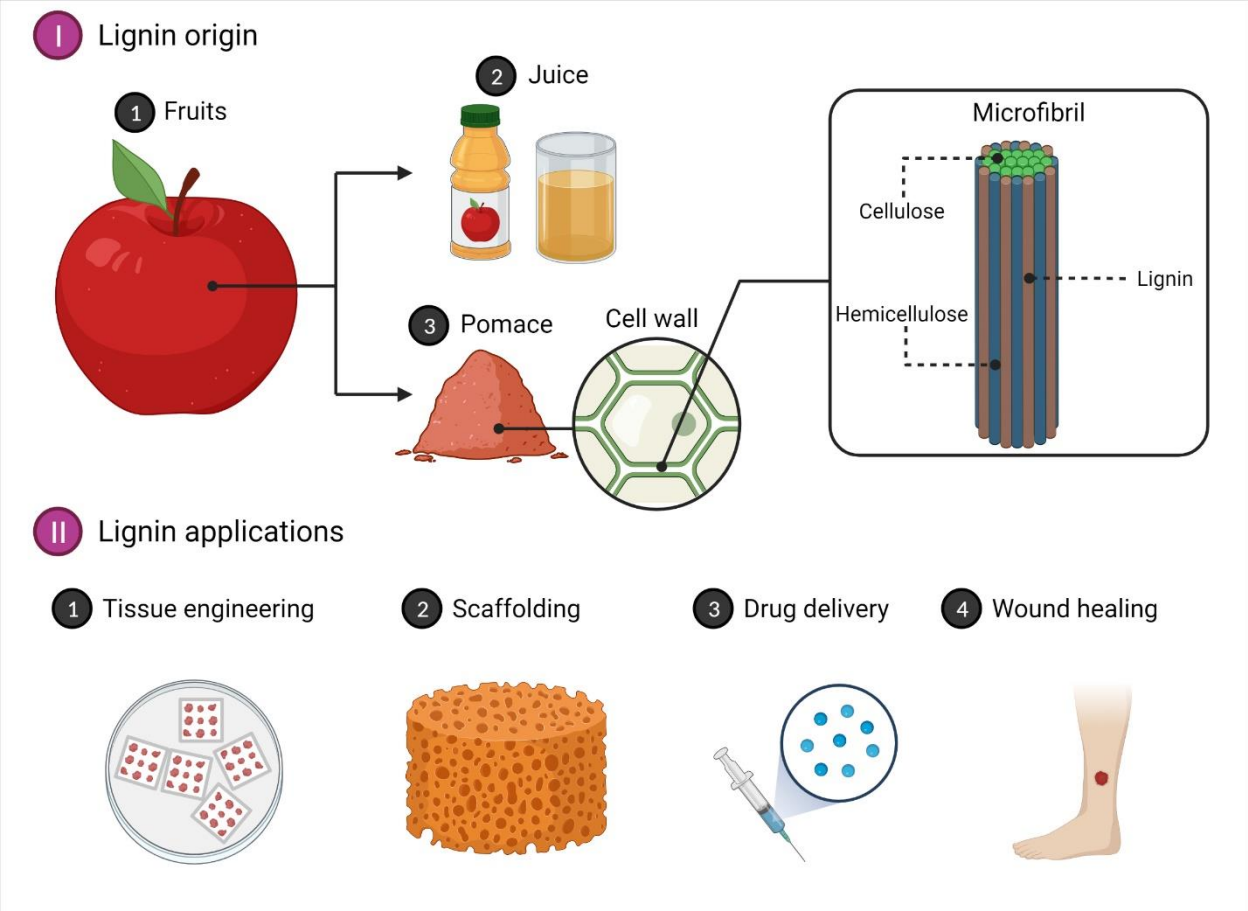

Graphical abstract

Highlights

- The current status of pomace waste generation was discussed
- Limitations of pomace valorization strategies were discussed
- Misconceptions regarding lignin valorization were discussed
- Anticipated breakthroughs on the use of pomace-lignin discussed

Abstract

Previous studies have explored the potential of pomace valorization, with an emphasis on the transformation of polysaccharide biopolymers of pomace-cellulose and hemicellulose to produce high-value bioproducts such as microcrystalline cellulose. Notably, opportunities for the exploration of the biopolymer of pomace-lignin for its employment in biomedical applications such as tissue engineering have not been comprehensively explored. There is, therefore, a need for an intervention to highlight the potential of utilizing pomace-lignin as a high-value biomass resource. This review explores potential biomedical applications of pomace-lignin and highlights some of the factors that hinder the industrial utilization of pomace-lignin. In addition, the present review covers lignin chemistry, extraction methods, depolymerization approaches, and prospects of lignin utilization in biomedical applications. It is anticipated that this review will aid future decisions regarding the preferred approaches for the valorization of pomace-lignin.

Keywords: waste pomace; biomedical applications; valorization; lignin

1 Introduction

Agro/food industries generate significant masses of waste streams, which are largely untreated and underutilized (Aschemann-Witzel & Peschel, 2019; Okoro et al., 2017b) with the waste streams typically disposed of via burning/combustion and dumping in landfills. These approaches lead to several environmental issues due to greenhouse gas (GHG) emissions, waste combustion, uncontrolled degradation, and additional pollution challenges due to the generation of unpleasant odors and soil contamination via leachates (Ferronato & Torretta, 2019; Plazzotta et al., 2017). Additional consideration of the food and agro-industries shows that the fruit processing industry is the major culprit responsible for the generation of a significant amount of post-production waste, also referred to as pomace (Van Dyk et al., 2013). Waste pomace (WP) is generated as a consequence of the processing of fruits for juice extraction (Kosseva, 2013; Kruczek et al., 2016). At the global scale, the overall mass of WP generation is quite substantial, with 25-50 wt. % of the mass of the whole-fruit is typically converted into WP (Carunchia et al., 2015; Kruczek et

al., 2016). For example, apple processing alone generates nearly 10 million tons of pomace each year from the apple juice industry (Alongi et al., 2019). The associated waste pollution potential of the pomace generated from apple pomace will be exacerbated when other pomace generating fruits such as pear, cherry, etc., are considered. WP is generated as 'press-cake' after juicing the fruit, via a series of steps which may include milling; primary mash enzymation (liquefaction); primary juice extraction; leaching, heating, secondary liquefaction, and secondary juice extraction (Carunchia et al., 2015; Kennedy et al., 1999). The composition of the WP may, however, vary since its properties are largely a function of the morphology of the fruit and the juice extraction technique employed (Kennedy et al., 1999). The previously reported compositions of common waste pomaces are presented in **Table 1**. **Table 1** shows that the WPs from different fruits are characterized by high moisture content and are composed of mainly insoluble carbohydrates of cellulose, hemicellulose, and lignin, which is a polymer of phenyl propane derivatives. Briefly, the cellulose component exists as a linear syndiotactic (alternate spatial arrangement of side-chain) polymer of hexoses of glucose molecules that are linked via ß-l,4-glycosidic bonds (Achyuthan et al., 2010; Tayyab et al., 2017). Cellulose has a three-dimensional matrix responsible for its favorable tensile properties and crystalline form (Curvello et al., 2019; Jovic et al., 2019; Ullah et al., 2018). The macromolecule of hemicellulose, on the other hand, consists of the complex network of branched heteropolymers that form hydrogen interactions with cellulose and covalent bonds with lignin via mainly α-benzyl ether linkages (Bian et al., 2012). Hemicellulose can also form ester linkages with acetyl units and hydroxycinnamic acids (Bian et al., 2012). These linkages tend to restrict the liberation of hemicellulosic polymers from the cell wall matrix (Bian et al., 2012). Lignin is a highly cross-linked macromolecule that presents as a three-dimensional structure and is composed of the substituted phenols of coniferyl, sinapyl, and p-coumaryl alcohols or monolignols (Kakroodi & Sain, 2016; Kim & Choi, 2018). These phenols are typically substituted by enzymatic polymerization and are capable of generating a large number of linkages (Watkins et al., 2015). The monolignols are also capable of undergoing combinatorial oxidative coupling under varying degrees of

Table 1: Composition of common fruit pomaces

Component	Pear pomace (%)	Carrot pomace (%)	Tomato pomace (%)	Apple pomace (%)	Chokeberry pomace (%)	Cherry pomace (%)	Black current pomace (%)	Olive pomace (%)	Grape Pomace (%)	References
Dry matter	-	13.10	6.03	17.84	54.9	30	40.18	35	27.8	(Azman et al.; Cequier et al., 2019; Greiby et al., 2014; Moldes et al., 2007; Reißner et al., 2019; Szymańska-Chargot et al., 2017)
Pectin (dry mass basis)	13.40	3.88	-	19.60	7.85	1.51	2.73	-		(Azman et al.; Nawirska & Kwaśniewska, 2005)
Cellulose (dry mass basis)	34.50	51.60	38.01	17.70	34.60	18.40	12.00	17.00	18.20	(Azman et al.; Kheiralla et al., 2018; Moldes et al., 2007; Nawirska & Kwaśniewska, 2005) (Cequier et al., 2019) (Ma et al., 2019)
Hemicellulose (dry mass basis)	18.60	12.30	31.42	10.90	33.50	10.70	25.30	6.80	8.00	(Azman et al.; Cequier et al., 2019; Kheiralla et al., 2018; Ma et al., 2019; Moldes et al., 2007; Nawirska & Kwaśniewska, 2005)
Extractives (i.e. triglycerides and waxes)	-	-	-	24.5	-	-	-	17.00		(Cequier et al., 2019; Ma et al., 2019)
Lignin (dry mass basis)	**35.50**	**32.10**	**6.87**	**15.40**	**24.10**	**69.40**	**59.30**	**39.00**	**56.70**	(Azman et al.; Cequier et al., 2019; Kheiralla et al., 2018; Ma et al., 2019; Moldes et al., 2007; Nawirska & Kwaśniewska, 2005)
Protein	-	-	16.6	-	-	-	-	-	-	(Kheiralla et al., 2018)
Lipid			4.1	-	-	-	-	-	-	(Kheiralla et al., 2018)
Ash (dry mass basis)	-	-	3.0	1.90	-	-	-	4.50	-	(Cequier et al., 2019; Kheiralla et al., 2018; Ma et al., 2019)

Notably, for all pomace types considered in **Table 1**, polysaccharides were shown to constitute a dominant component, ranging from 23.8 wt. % (in olive pomace) to 69.4 wt.% (in tomato pomace). Similarly, some pomaces were characterized by high lignin contents with as much as 69.4 wt. %, with residual lignin fraction shown to range from 6.87 wt. % (in tomato pomace) to 69.4 wt.% (in cherry pomace). **Table 1** also shows that pomaces of pear, apple, chokeberry, cherry, and blackcurrant also contain the important component of pectin with apple pomace having the highest pectin content of 19.6 wt.%. Pectin is a structural acidic heteropolysaccharide which is the methylated ester of polygalacturonic acid and is composed of methoxy esterified α, d-1,4-galacturonic acid units (Flutto, 2003; Lochhead, 2017). Interestingly, the availability of macromolecules (i.e. cellulose, hemicellulose, lignin, etc.) suggests that the WP may constitute a viable material for the production of bio-based value-added products (Tripathi et al., 2019; Weiss et al., 2012). This reclassification of WP as a possible raw material or natural resource will facilitate the circumvention of their associated negative impacts leading to improved environmental outcomes. These negative impacts associated with the improper management of WP are highlighted in the subsequent section, which also discusses the current WP management approaches reported in the literature.

2 Current strategies for management of waste pomace

The high moisture content and biodegradable organic load, demonstrated by high biochemical oxygen demand and chemical oxygen demand values, of WPs, are indicative of possible unwanted pollution consequences when improperly managed (Gassara et al., 2011; Okoro & Shavandi, 2021). A review of the literature has identified several traditional approaches which have been employed in the management of pomace including its use as a low-cost animal feed, fertilizer, a substrate for enzyme production, and as a carbon source (i.e. solid fuel) in power stations (Cliffe & Patumsawad, 2001; Gassara et al., 2011; Haddadin et al., 2009). Several issues characterize the management of WP via the aforementioned utilization strategies. For instance, the considerations of WP as a cheap animal feed may constitute an impractical long-term strategy given that pomaces are characterized by low nutritional values due to their poor protein and vitamin/nutrient content, as well as low pH values (Okoro et al., 2021). Additionally, the presence of anti-nutritional factors like phenolic components will inhibit ruminal symbionts, thus further discouraging its use for feeding purposes (de Paula et al., 2016). Alternatively, the disposal of waste pomace on agricultural lands cannot constitute a management approach for favorable environmental outcomes given that the low pH values of pomace (ranging from ~3-5) may hinder the functionality of its use as a soil additive (Dedenaro et al., 2016; Gouw et al.,

2017; Okoro & Shavandi, 2021; Shalini & Gupta, 2010). Furthermore, the alternative WP management approach of WP disposal in landfill are now well recognized as unsustainable and environmental unfavorable due to their associated impacts of global warming (Bjerg et al., 2003). This is due to the uncontrolled generation of GHG emissions (i.e CH_4 generation) from the degradation of the WP in the landfill (Bjerg et al., 2003). There is also an enhanced risk of the pollution of underground waters from pomace leachates (Bjerg et al., 2003). Recognizing the significant risk posed by landfill disposal, current European Union (EU) legislation stipulates that no more than 10% of waste can be disposed of in landfills by the year 2035 (EU, 2020). Furthermore, apart from pH concerns, the utilization of waste pomace as a soil additive to improve soil properties may be hindered by its possible phenolic content which may limit a plant's access to nutrients and may inhibit the germination properties in fertilizers respectively (Kruczek et al., 2017; Okoro & Faloye, 2020). Notably, the introduction of WP characterized by such low pH values will also enhance the risk of aluminum toxicity since, under such acidic conditions, the phytotoxic form (Al^{3+}) of aluminum predominates in the soil (Okoro & Sun, 2020). Additionally, when WP is employed in agricultural soils, its high moisture content enhances its susceptibility to microbial decomposition, leading to uncontrolled fermentation and associated environmental pollution issues (Lyu et al., 2020). Other commonly employed organic waste management approaches such as incineration and composting, are limited by the emission of GHG and the preliminary requirement for high-energy moisture reduction operations (drying) due to the high moisture content of WP as shown in **Table 1** (40–94 wt.%) (Gassara et al., 2011).

2.1 State of value extraction from waste pomace.

Based on the WP management concerns presented above, several researchers have investigated enhanced value extraction opportunities by exploring the biorefinery concept (Ferreira, 2017; Okoro et al., 2019). Such an approach facilitates the integration of biomass conversion technologies to improve or enhance the production of valuable products (Ferreira, 2017). This is because the application of the biorefinery concept, not only enables an efficient waste management approach but also facilitates the achievement of a net-zero emission target which is now recognized as a corollary to a truly sustainable system (Okoro et al., 2017b). This enhanced interest in the application of the concept is also consistent with the current drive by the EU to promote resource recovery from renewable sources to attain sustainable growth based on bioeconomy (Kardung et al., 2021; Romaní et al., 2018). An example of the aforementioned approach for value extraction from WP

is highlighted in the work of Hijosa-Valsero et al. (2017) where the production of the valuable product of butanol was experimentally investigated. In this study, WP obtained from apple fruit was subjected to several physicochemical pretreatments to facilitate the degradation of lignin for the release of a sugar liquor or hydrosylate. The hydrosylate was then subjected to a fermentation operation under the action of *Clostridium beijerinckii*, for butanol, acetone, and ethanol production with yields of 9.11 g/L, 3.55 g/L, and 0.26 g/L achieved, respectively (Hijosa-Valsero et al., 2017). In another study, the valorization of apple pomace for lactic acid production was explored via the use of hydrolytic enzymes and lactic acid bacteria present in yogurt (Alonso et al., 2009). According to Alonso et al. (2009) the sugars present in apple pomace could be readily converted to lactic acid with a product yield of 0.693g LA/g of dry AP obtained after 30 h of fermentation time. Klavins et al. (2018) also explored the valorization of blueberry pomace (BP) such that lipid extraction of mainly C18 unsaturated fatty acids of ~ 102 μg/g and extraction of phytosterols of ~ 86 μg/g, was achieved. The valorization of the BP was facilitated via the use of supercritical carbon dioxide extraction as a suitable "green" approach. The study by Klavins et al. (2018) demonstrated that further valorization of the, now defatted BP, in the presence of aqueous ethanol (40–70%) and the presence of formic acid, could also facilitate the recovery of polyphenolics (~2 wt.%). Similarly, the extraction of polyphenolics from grape pomace was also explored in the study by Boussetta et al. (2011). In the study by Boussetta et al. (2011) the extraction of polyphenolics from grape pomace was assessed using an optimized electrically assisted extraction process while using high voltage electrical discharges (HVED) for process intensification. The study was able to show that the most efficient extraction of polyphenols generated a polyphenolic yield of ~2.8% (gallic acid equivalent). The conditions of other extraction variables of liquid-to-solid ratio, solvent concentration, temperature, and time were determined to be 5, 30% ethanol in water, 60°C and 30 min respectively. The optimally generated polyphenolics were shown to have an anti-oxidant activity of 66.8 g (trolox equivalent anti-oxidant capacity) per kg dry pomace with a positive correlation between the polyphenolic extraction rate and temperature observed. Martinez et al. (2016) proposed the development of a biorefinery system that facilitated the valorization of red grape pomace. The proposed biorefinery was composed of integrated steps for the extraction of polyphenols and volatile fatty acids via supercritical CO_2 extraction and anaerobic acidogenic digestion respectively. The recovered volatile fatty acids (VFAs) were subsequently employed in the production of polyhydroxyalkanoates (PHAs) and biogas. The study was able to show that a total polyphenolic yield of ~2.7 wt.% was achievable from dry red grape pomace. Employing the recovered VFAs (20 g/L), fermentation volatile fatty acids under the action of *Cupriavidus*

necator strain facilitated the production of PHAs (yield 0.26 g/g-$_{VFAs}$) with anaerobic digestion of the residual VFAs leading to the production of 113 mL of bioCH4 per gram of fed volatile solids. Another study focused on the valorization of polyphenolics from black carrot pomace (Kumar et al., 2019). In the study by Kumar et al. (2019) the methods of microwave-assisted extraction, ultrasonic-assisted extraction, and conventional solvent extraction for the recovery of polyphenolic compounds from black carrot pomace were comparatively assessed via the Box-Behnken design method. According to Kumar et al. (2019), it is possible to facilitate the optimal recovery of ~ 0.265 g gallic acid equivalents per 100 mL of sample. This optimal yield of polyphenolics was possible when conditions of 348.07 W, 9.8 min 19.3 mL/g, and 19.8% for microwave power, extraction time, solvent–solid ratio, and ethanol concentration respectively were imposed. The study was able to demonstrate that microwave-assisted extraction constituted the preferred approach for polyphenol extraction from pomace, compared to other methods of ultrasonic-assisted extraction and conventional solvent extraction (Kumar et al., 2019). More recently, another study explored the scaled-up production of succinic acid from waste apple pomace which was achieved via the fermentative action of *Actinobacillus succinogenes* microbes (Okoro & Shavandi, 2021). In this study, two scenarios for large-scale succinic acid production were assessed, namely succinic acid coupled with electricity generation and succinic acid coupled with biogas generation. The study established the preference for the biogas co-production scenario with a succinic acid minimum selling price (MSP) of US$ 0.33 per kg compared to the MSP of US$ 0.73 per kg that characterized the electricity generation pathway(Okoro & Shavandi, 2021). The viability of extracting valuable products of pectin, chlorogenic acid, and caffeic acid has also been demonstrated in the work of Yates et al. (2017). Schievano et al. (2015) explored possible biorefinery strategies for value extraction from WP via the integration of supercritical treatments using solvents of carbon dioxide and polar ethanol and thermochemical treatments to extract value-added polyphenols and mono/poly-unsaturated fatty acids and energy, biofuels, and materials respectively. A similar biorefinery exploration of grape pomace was investigated by Jin et al. (2021). In the study, different configurations for the production of different combinations of grape seed oil, polyphenols, and biochar via the integration of seed grinding, solvent extraction, and pyrolysis technologies were assessed. The study was able to show that the valorization of grape pomace had the potential to present significant economic benefits with a scaled-up pomace valorization plant characterized by a net present value of US$ 111.7 $\times 10^6$. Other studies have investigated WP conversion to valuable chemicals such as Poly(3-Hydroxybutyrate-co-3-Hydroxyvalerate), xylitol, polyhydroxyalkanoates, levulinic acid, and n-Butyl levulinate (Antonetti et al.,

2020; Kovalcik et al., 2020; López-Linares et al., 2020; Martinez et al., 2016). Based on the studies presented above, the valorization of WP has so far focused on the optimized recovery of carbohydrate forms before their conversion to bioproducts (i.e. succinic acid, VFAs, PHAs, etc.) (**Figure 1**) or direct extraction of valuable extracts such pectic and polyphenols. Notably, the residual fraction of the waste pomace containing lignin is typically discarded, more so as it is considered as a low value fraction of biomass resources.

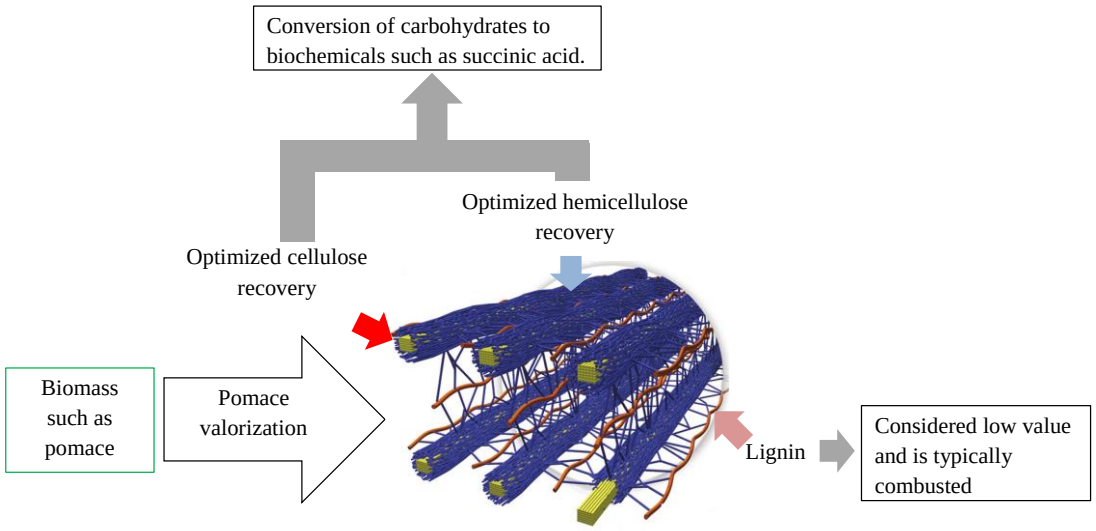

Figure 1: Current value extraction from biomass with emphasis on carbohydrate recovery. Adapted with permission from (Doherty et al., 2011). (Copyright © (2011) Elsevier B.V.).

Indeed, there is a historical misconception that lignin presents a subordinate opportunity for value extraction and is not the primary concern in valorization systems. This reduced exploration of value extraction opportunities from pomace sourced lignin is particularly noteworthy given that the WP is not only substantial but can contain as much as 69 wt. % lignin content (**Table 1**, cherry pomace), which constitutes a significant component of the WP that is currently not utilized. This poor valorization strategy for value extraction from lignin is largely due to the difficulty of executing lignin valorization, relative to the transformation of other pomace components of cellulose and hemicelluloses (Ayyachamy et al., 2013; Parsell et al., 2013). Further utilization of lignin is limited by the harsh operating conditions employed in biomass pretreatment steps that lead to modification of the lignin molecule, via its irreversible degradation and subsequent formation of recalcitrant condensed structures (Gillet et al., 2017; Renders et al., 2017). These recalcitrant structures are difficult to disassemble into chemicals. Due to the reduced value attributed to lignin, it is typically used as a solid fuel via combustion

for heat and electricity generation using combined heat and power systems (Amezcua-Allieri & Aburto, 2018; Petersen et al., 2021; Petersen et al., 2020). However, lignin could constitute a versatile and low-cost by-product capable of presenting a broad range of applications, from biofuels to biomedical materials in wound healing due to its bioactivity, or could serve as a feedstock for the production of aromatics, supramolecular materials, and phenolic compounds that may be used in the biomedical industry (Renders et al., 2017). Pomace-lignin could sustainably meet the demand for aromatic rings in the medical industry in drug manufacturing (Polêto et al., 2018) due to the abundance of the WP resource as earlier discussed. The next section, therefore, extensively discusses the recent trends in lignin research, chemistry and structure of lignin, and extraction opportunities for biomedical applications.

3 Pomace-Lignin as a 'futuristic' biopolymer

3.1 Recent trends in Lignin research as a resource

There is, an increasing acknowledgment of the potential of lignin as a useful biopolymer, leading to a significant increase in investigations into its valorization and the associated research publications as illustrated in **Figure 2.**

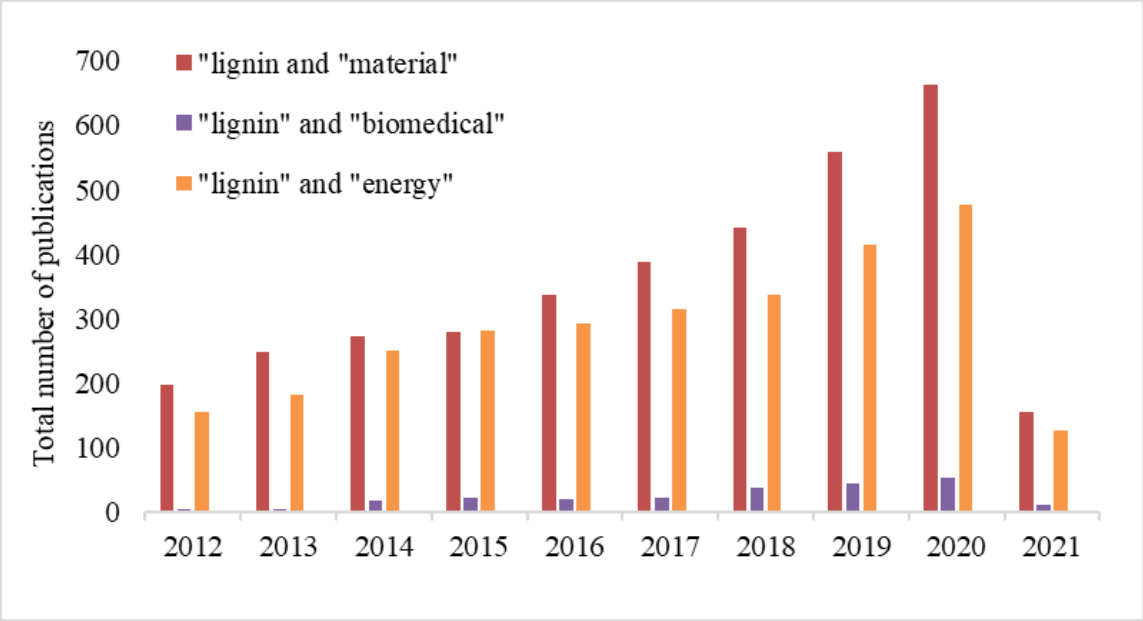

Figure 2: Lignin based research trends in the past ten years (PubMed, 2020).

The data presented in **Figure 2** have been sourced via a rigorous consideration of relevant journal papers and books available from the National Library of Medicine

(PubMed®) database (PubMed, 2020). Publications reported in the last ten years have been captured. **Figure 2** also shows that publications related to the application of lignin in the areas of material engineering, biomedical applications, and energy applications have increased by ~325%, ~70%, and 333%, respectively from the year 2012 to 2020. These numbers are substantial. **Figure 2** also shows that over 6,500 publications have been generated from 2012 to date (2021). The growing interest may be due to the enhancements in analytical methods that have revealed lignin as a natural source of high-value products (Anwunobi & Emeje, 2011; Castro et al., 2019). **Figure 2** shows that the investigations related to the biomedical applications of lignin present a growing research interest. Our interest in the WP-sourced lignin is further supported by its high productivity potential in most WP streams as shown in **Table 1**. Indeed, there are indications that lignin may be successfully employed in tissue engineering and drug delivery (Anwunobi & Emeje, 2011; Dai et al., 2017). In addition to enhancements in analytical methods, the increased interest in the exploration of lignin valorization is due to the development of multiple technologies for lignin extraction.

3.2 Chemistry of lignin

Lignin is composed of three 4-hydroxyphenylpropanoids of namely, p-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol with have their aromatic rings designated as p-hydroxyphenyl (H), guaiacyl (G), and syringyl (S) respectively(Boerjan et al., 2003; Pereira, 2007) (**Figure 3**).

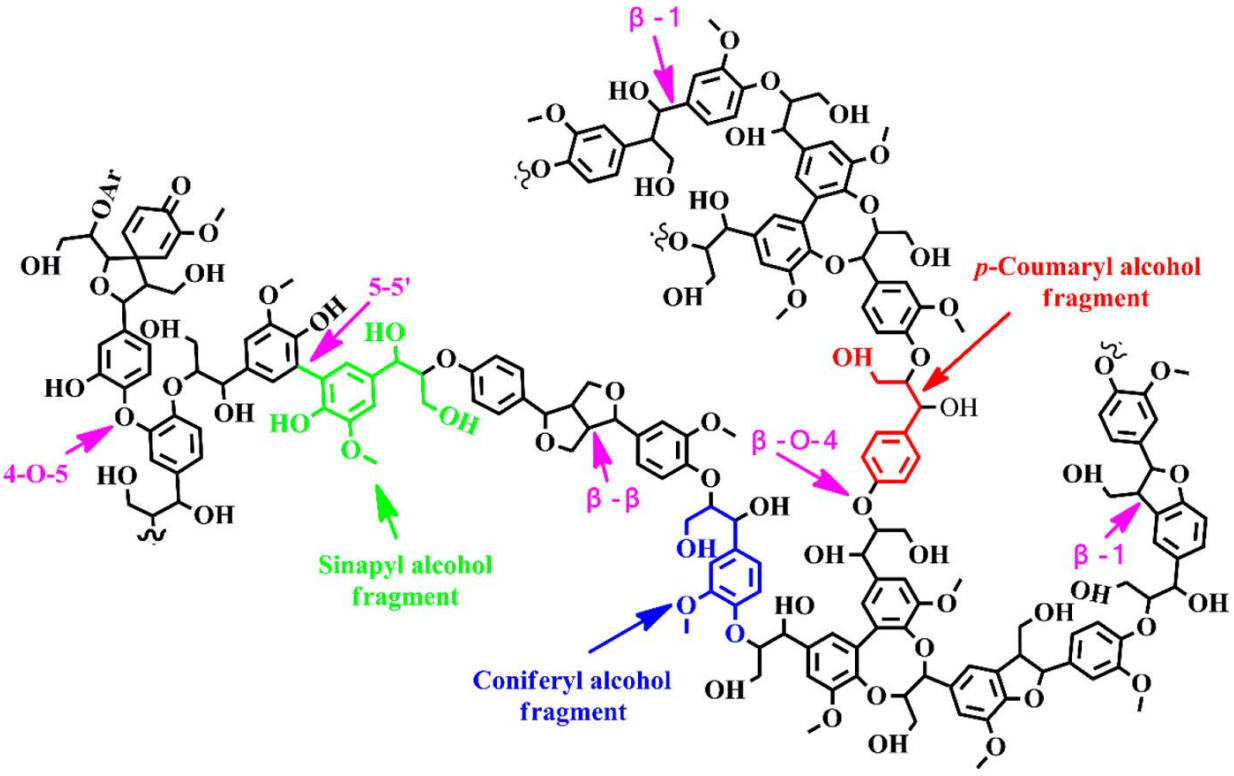

Figure 3: An illustration of the lignin structure. Adapted with permission from (Zakzeski et al., 2010). (Copyright © (2010) American Chemical Society).

The common linkages for lignin macromolecule are 4-O-5, ß-O-4, ß–ß, and 5–5′. The chemical structure of lignin varies based on the biomass source. For instance, a high amount of H units with a trace amount of G and S units have been identified in monocot grasses, while lignin in dicots contains a lower amount of H units in its structure (Vanholme et al., 2012). Also, lignin extracted from gymnosperm was composed of a very high level of G units when compared to other sources (Timell, 1986). The presence of OH functional groups in lignin structure (**Figure 3**) plays a major role in the lignin's reactivity, functionality, and hydrophilicity (Evstigneyev & Shevchenko, 2019; Ge & Li, 2018; Lu et al., 2017). The modification of polymeric material structure with bioengineering approaches is now widespread and well established within the tissue engineering and nanobiotechnology sciences (Kohane & Langer, 2008; Rinaldi et al., 2016).

3.2.1 Lignification: The formation of lignin

Lignin polymerization occurs as a result of monomer oxidization following their translocation into the plant cell wall (Boerjan et al., 2003), the development of inter-unit linkages, and the combinatorial radical coupling process. This process is mediated by a phenolic radical generation which produces a single-electron density

around the aromatic ring (del Río et al., 2020). The lignification includes the chemical bond between phenolic monolignol radicals, which results in ß-O-4, ß -5, and ß-ß dehydrodimers inter-unit linkages production. The most important chemical bond during lignification can be found at the lignin ß position of the 4-O-phenolic (Ralph et al., 2004). In addition, 5-5- and 4-O-5-type linkages can be developed between two oligomeric phenolic end units (Ralph et al., 2004).

3.2.2 Unconventional Monolignols

Lignin biosynthesis has been attracting a lot of interest and a considerable amount of literature has been published on lignin owing to its recalcitrance properties. Previous research comparing lignin structure in several plants has detected the presence of unconventional units such as monolignol acetate, p-hydroxybenzoate (pBA), p-coumarate (pCA), monolignol ferulate conjugates, tricin, caffeyl alcohol, and 5-hydroxyconiferyl alcohol, as well as the newly characterized benzoate (BA) in this biopolymer (Kim et al., 2020; Ralph et al., 2004). Hydroxycinnamyl acetate was reported as a main element of lignin in kenaf and palms (del Río et al., 2020). The acetylation degree is up to 80% in these plants in comparison to other sources (del Río et al., 2020). It was also reported that willows, poplars, palms, and aspens have a considerable amount of Hydroxycinnamyl pBAs, but hydroxycinnamyl pCAs are recognized in all species(Chan et al., 2020). Overall, there seems to be some evidence to indicate that the malleability of lignification provides an opportunity to modify the structures of lignins for biomedical application. To date, various methods have been developed and introduced to engineer the structure of lignin. Unconventional units are also recognized in transgenic or mutant plants to be the most important in the monolignol biosynthetic pathway (Boerjan et al., 2003; Ralph et al., 2019). Recent findings regarding the bioengineering of lignin have led to a revolution in many fields such as the biomedical industry (Eudes et al., 2014; Liu et al., 2020; Terzioğlu et al., 2020). For instance, zip-lignin is bio-engineered lignin-containing ester bonds in its structure (Wilkerson et al., 2014). Ester bonds enhance lignin mechanical properties and thus extend possible applications in 3D printing (Han et al., 2021; Shavandi et al., 2020).

3.3 Lignin recovery techniques

There have been many breakthrough technologies for the isolation of the aromatic biopolymer from the WP. These technologies may combine biological, chemical, or thermochemical conversion operations. **Table 2** summarizes the existing major approaches for lignin solubilization from biomass and the limitation associated with each technique. For instance, the Kraft and Sulphite processes are characterized by

the introduction of sulfur groups of sulfate and sulfite in the lignin structure, respectively. These groups may have some consequences on lignin properties such as enhanced solubility in aqueous solutions. The application of these techniques (i.e. Kraft and Sulphite) in the recovery of lignin from WP may lead to the generation of highly hydrophilic lignin that may not be suitable for some of the biomedical applications such as hydrophobic drug delivery and anti-microbial activity as discussed in section 4. The use of the alternative processes of organolsolv and alkaline also lead to low molecular masses of lignin products characterized by high levels of polydispersity, thus limiting biomedical applications such as in three-dimensional (3D) scaffold fabrication. This is because lower molecular masses may translate to poorer mechanical properties. Apart from these four commercially employed techniques, lignin may also be recovered from WP using the two-step sulfur acid hydrolysis approach (Kalson method), for the production of the acid-soluble and acid-insoluble lignin fractions (Sluiter et al., 2008). The use of these acids may, however, lead to similar issues associated with the introduction of sulfur to the lignin structure. Apart from the challenges highlighted in Table 2, the literature also indicates that the transformation of lignin obtained via Kraft, soda, and sulfite processes is at risk of undesirable char formation and low product yield (Rinaldi et al., 2019). The utilization of ionic liquid (IL) solvents has also been explored for lignin (Hasanov et al., 2020) extraction (Hossain & Aldous, 2012) (Yinghuai et al., 2013). ILs can facilitate the production of high yields of lignin at low temperatures (i.e. 30 ^{o}C) (George et al., 2015; Hasanov et al., 2020). For instance the work of Hart, et al., (Hart et al., 2015) demonstrated that it was possible to achieve complete lignin extraction when ILs of [EMIM][CH_3CO_2], [EMIM][$O_2P(OCH_2CH_3)_2$], [EMIM][CH_3SO_3], [EMIM][NCS], [EMIM][CF_3CO_2], [EMIM][CF_3SO_3], [EMIM][BF_4] and [EMIM][$(SO_2CF_3)_2N$] were employed. Applying ILs in lignin extraction may enhance thermal stability and high recycling capacities of the product compared to the chemical methods (Hart et al., 2015). Recently solvolysis and catalytic hydrogenolysis using ethanol and hydrogen have been employed to achieve pure lignin oil from biomass (Van den Bosch et al., 2015) with yields as high as > 80 wt.%. Notably, the use of ILs and the integrated solvolysis - hydrogenolysis processes may facilitate the production of purer lignin than that generated via processes highlighted in **Table 2**. More work is required to investigate the possible effects of these techniques on the major lignin properties such as molecular mass and structure. It should be stated that the yield and properties of isolated lignin depend on the method of extraction (Chung & Washburn, 2016; Sun, 2020) with slight variations in the biopolymer chemistry depending on the lignin source.

Table 2: Major lignin recovery technologies

Process	Some notes	References
Kraft process	In the Kraft process, lignin solubilization is achieved via biomass treatment in a solution containing sodium hydroxide and sodium sulfide. This approach attacks the ether bonds in the lignin molecule leading to its fragmentized low molecular weight ranging from 2000–3000 Da, with a polydispersity index ranging from 2-4. The lignin product is also characterized by a sulfur content ranging from 1-2.5 wt%. Apart from the issues associated with chemical cost, the Kraft process, there is an issue of unwanted gypsum formation when downstream neutralization reactions are undertaken.	(Chen, 2015; Gordobil et al., 2014; Windeisen & Wegener, 2012)
Alkaline Process	This strategy served to facilitate interaction primarily with lignin thus particularly useful for efficient lignin recovery. Alkaline pretreatment is mainly achieved using NaOH and KOH although chemical cost constitutes a limitation. The lignin generated from this technique is referred to as Soda lignin and is characterized by the presence of p-hydroxyl groups in its structure with a molar mass ranging from 5000–6000 Da. polydispersity index that ranges from 9-10.	(Goñi, 2018; Jong & Gosselink, 2014; Jönsson & Martín, 2016; Kim et al., 2016; Windeisen & Wegener, 2012)
Sulfite process	Lignin solubilization is achieved via biomass treatment in aqueous sulfur dioxide (SO_2) and a base (i.e. NaOH, $Ca(OH)_2$, etc). The solubilization of lignin involves the incorporation of sulfur into the lignin structure in form of sulfonate groups such that the recovered lignin are referred to as lignosulfonates with sulfur contents of up to 2.5 wt.%. These lignosulfonates have higher molar masses (20 000–50000 Da) than the lignin produced from the Kraft lignin. Polydispersity index ranges from 6-8.	(Gordobil et al., 2014; Windeisen & Wegener, 2012)
Organosolv	The organosolv pretreatment is considered quite promising for lignin recovery, due to its capability to facilitate efficient isolation of high-quality lignin while also reducing the possibility of water pollution. This is because the lignin recovered is sulfur-free unlike the sulfite process and is also easier to recover from the organic solvent since most solvents have low boiling temperatures. It is also hypothesized that the cleavage of ß-ether linkages is the most important step of lignin extraction. The sulfur-free lignin is characterized by molar masses ranging from 2000-5000 Da with a polydispersity index ranging from 2.4-6.4. Since the organosolv pretreatment may employ a variety of solvents such as methanol, ethanol, acetone, and triethylene glycol, this lignin solubilization strategy may be associated with higher operating costs.	(Acosta et al., 2014; Badiei et al., 2013; Salapa et al., 2017; Windeisen & Wegener, 2012)

4 Pomace-lignin and the biomedical industry

4.1 Direct uses of pomace-lignin in the biomedical industry

Until recently, the utilization of lignin in the biomedical industry has been relatively limited. However, because of the microbiological, properties, and bioactivity of lignin, it has recently been directly employed in several biomedical applications such as the development of hydrogels, nanomaterials, anti-oxidants, anti-microbials, tablets, 3D printed materials, ultra violet light (UV) blockers, etc.(Domínguez-Robles, Cárcamo-Martínez, Stewart, Donnelly, Larrañeta, Borrega, et al., 2020; Liu et al., 2020). Notably, lignin sourced from pomace may provide enhanced biomedical applications due to the reduced possibility of such 'food grade' pomace-lignin containing toxic components that may be harmful to tissues and cells. The possible biomedical applications are therefore discussed in the following subsections.

4.1.1 Development of hydrogels

Hydrogels are cross-linked polymers that mimic human tissues in their ability to absorb and retain large masses of biological fluids within their structure (Larrañeta et al., 2019). Due to the presence of a polymeric network, hydrogels can absorb fluids such as water to achieve a mass of approximately one thousand times their dry mass without dissolving (Thakur & Thakur, 2015). In recent times there has been an enhanced interest in the utilization of natural polymers rather than synthetic (fossil-based) ones for hydrogels production, due to the renewed drive to explore fossil alternatives (Deng et al., 2021; Safarzadeh Kozani et al., 2021; Samadian et al., 2020). In line with this interest, the potential of utilizing lignin as a sustainable feedstock in hydrogel development has been investigated (Fernandes et al., 2013).

Recognising the capability of lignin to potentially introduce favourable properties to hydrogels, several investigations have focused on the impact of lignin on the hydrophilicity, thermal stability, biodegradability, and biocompatibility of hydrogels (Bajwa et al., 2019; Feng et al., 2011; Meng et al., 2019; Witzler et al., 2018) (Al-Rudainy et al., 2019). Additionally, Lignin-based hydrogels have been shown to demonstrate self-healing (**Figure 4**) capabilities (Huang et al., 2019). In the study a lignin-based ink composed of lignin (0.5 wt%-3 wt%) as plasticizer, 1 wt% of hydroxyethyl cellulose, 0.8 % borax (cross-linker) and 3 % polyvinyl alcohol (framework) was developed. The study was able to show that positive correlations existed between increasing lignin contents and storage modulus and viscoelasticity

of the resulting lignin-based hydrogel. Higher lignin contents also translated to improved thermosensitivity. The lignin-based hydrogel also demonstrated ionic conductivity property (**Figure 4**). The possibility of employing lignin in producing self healing hydrogels reinforces its utility in biomedical applications. It can also be employed as a bioink for 3D printing via reversible sol-gel transitions and as a vehicle for drug or cell delivery (Liu & Hsu, 2018) .

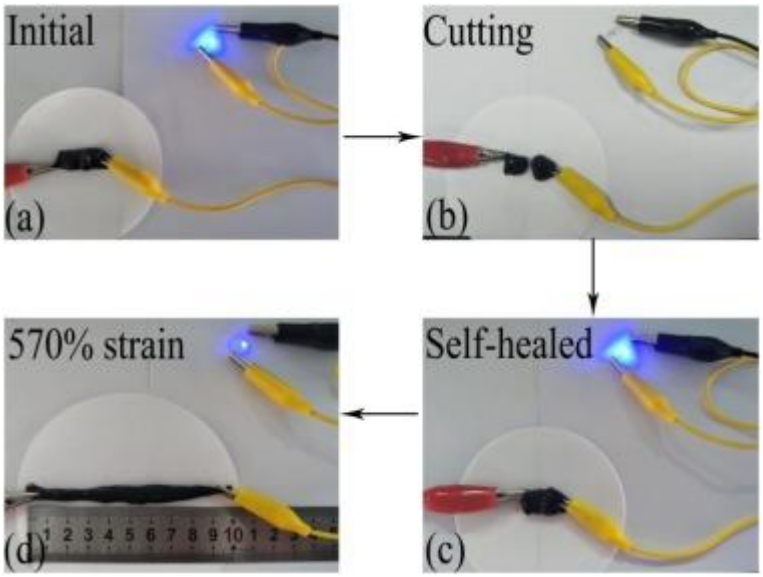

Figure 4: Highlighting the self-healing property of the lignin-based hydrogel. Adapted with permission from (Huang et al., 2019). (Copyright © (2019) Elsevier B.V.).

Larrañeta et al. (2018) developed lignin-based hydrogels that facilitated the controlled delivery of curcumin (hydrophobic) and recorded up to 4 days of delivery of this hydrophobic compound. Additionally, the produced hydrogel showed distinct anti-microbial activity against *Staphylococcus aureus* and *Proteus mirabilis*. Witzler et al. (2018) also reported that for the case of controlled drug release, the surface morphology, drug loading, and release were dependent on the type of lignin used in preparing the hydrogel. This observation reinforced our view that the properties of lignin were impacted by its source and origin. In another study Borisenkov et al. (2016) investigated the development of supramolecular hydrogel from lignin while also incorporating hemicellulose and pectin into the hydrogel structure. The authors demonstrated that the lignin-based hydrogel could facilitate the controlled release of estrogen and ß-glucuronidase. Furthermore, the

introduction of lignin to cellulose-based hydrogels improved the controlled release of lysozyme and metronidazole from the hydrogels (Dong et al., 2018). Zmejkoski et al. (2018) also showed that the incorporation of lignin enhanced the performance of hydrogel produced from bacteria cellulose for wound healing applications. The highest drug release was observed within the first 24 h while the wound healing ability of the hydrogel was linked to its improved swelling ability. Lignin-derived hydrogels have also been mentioned as possible 'vehicles' for human hepatocyte cell cultures. Indeed, it was shown that the porous nature of the hydrogel facilitated the adsorption of the cells to the pores which resulted in increased metabolic activity and cell proliferation (Zhao et al., 2017). Additional studies have also shown that for lignin-based hydrogel systems characterized by the immobilization of lipase, the presence of lignin enhances the activity and stability of the enzymes compared to systems without this biopolymer (Park, Kim, Kim, et al., 2015; Park, Kim, Won, et al., 2015). It was also established that the activity and stability of the enzyme were dependent on the lignin content. These observations were indicative of lignin's potential application in biocatalysis and biomedicine (Sun et al., 2016). Furthermore, the anti-microbial, anti-oxidant, and biocompatibility properties of lignin, may be combined with other polymers such as poly(vinyl alcohol), chitosan, xanthan, cellulose, and alginate to produce hydrogels for a variety of uses. For instance, Răschip et al. (2015) developed hydrogels from lignin and xanthan for the controlled release of bisoprolol. From the results obtained, between 14.4 % and 19.2% efficiency in drug delivery was recorded thus demonstrating a potential for pharmaceutical and medical applications. In another work, Shen et al. (2016) investigated the preparation of hydrogels from Kraft lignin and IL-produced lignin via chemical cross-linking. They found that hydrogels were only produced when epoxide-terminated polyethylene glycol was used as a cross linker. Properties of the prepared hydrogel such as anti-microbial and anti-oxidant activity as well as water vapor transmission suggested potential application as wound dressings. Ravishankar et al. (2019) also developed biocompatible hydrogels from Soda lignin and chitosan for wound healing purposes. It was found that the introduction of lignin improved the viscosity and shear strength of the chitosan and this was attributed to the electrostatic interactions that were presented between the ammonium ions in the chitosan and the phenolic units in the lignin. In another study, El-Zawawy (2005) produced renewable hydrogels from kraft and Soda lignin via graft copolymerization in the presence of acrylamide and poly(vinyl alcohol). The findings revealed that the hydrogel prepared from the Soda lignin performed better than that prepared from the Kraft lignin in terms of swelling ratio, water uptake, and de-swelling rate.

4.1.2 Lignin based 3D printed products

3D printing, otherwise known as additive manufacturing, involves the creation of 3D shapes and parts on a layer-by-layer basis using digital models (Han et al., 2021). In recent times, the combination of lignin with other polymeric materials to form composite products for 3D printing has been receiving a lot of attention (Domínguez-Robles, Martin, et al., 2019; Roman et al., 2020; Yang et al., 2020; Yu & Kim, 2020). The properties that qualify a material as an excellent candidate for 3D printing include extrudability, mechanical strength, and stability since these properties enable the resultant printed material to retain its shape and structure(Mirzaei et al., 2021; Yu & Kim, 2020). In this regard, pomace lignin may be given significant consideration as a material that may be employed in 3D printing as a result of its anticipated properties of non-cytotoxicity, biocompatibility, and biodegradability (Domínguez-Robles, Cárcamo-Martínez, Stewart, Donnelly, Larrañeta, & Borrega, 2020). In particular, the unique structural configuration and composition of lignin with its aliphatic ether and oxygenated aromatic groups make it an excellent candidate for 3D printing applications (Nguyen, Barnes, et al., 2018). Thus, there are many potential benefits to be gained by combining lignin with other polymers for use in 3D printing. This has raised the interest in using 3D printing technology in developing biomedical solutions within the past few years (Liu et al., 2019; Mimini et al., 2019; Sutton et al., 2018; Tanase-Opedal et al., 2019; Yang et al., 2020). For example, Jiang et al. (2020) demonstrated the possibility of employing lignin-based ink in fabricating 3D structures for biomedical applications. In the study a low temperature (25 ^{o}C) and low-cost direct ink printing strategy was employed with a soft triblock copolymer F127 used as the crosslinking agent. The study was able to demonstrate that the utilization of lignin-based ink facilitated the production of constructs with improved mechanical properties (i.e. tensile strength of ~30 MPa) compared to the mechanical properties of constructs based on another biopolymer of cellulose (i.e. tensile strength of ~30 MPa) (**Figure 5**). The lignin-based constructs were also shown to demonstrate high stability in water.

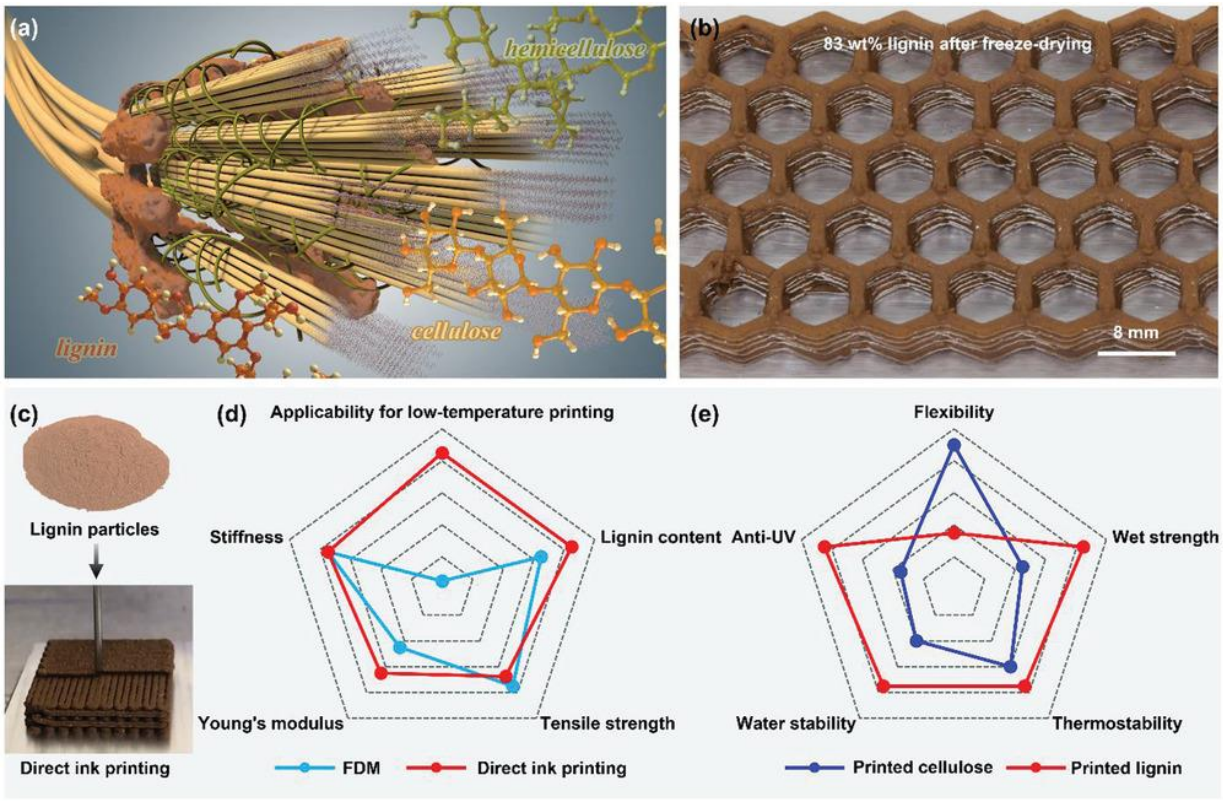

Figure 5: a) Illustrating biomass components of hemicellulose, cellulose, and lignin. b) 3D-structure developed using lignin-based ink c) Image showing the direct ink printing strategy using lignin particles in formulation. d) A chart highlighting the properties of 3D printed lignin-based structure printed by fused deposition modeling (FDM) and direct ink printing. e) A chart highlighting differences in properties of 3D constructs using lignin and cellulose inks. Adapted with permission from Jiang et al. (2020) (Copyright © (2020) John Wiley and Sons).

In another study the introduction of lignin (20 wt.%) improved the surface quality and shrinkage property during polyhydroxybutyrate (PHB) composite filament printing (Vaidya et al., 2019). Also, Nguyen, Barnes, et al. (2018) incorporated lignin into acrylonitrile butadiene styrene rubber to produce 3D products and reported that the presence of lignin enhanced the tensile strength of the resulting material due to cross-linking and enhanced hydrogen bond formation within the composite. In a further work by Nguyen, Bowland, et al. (2018) lignin obtained from organosolv hardwood was combined with nylon. The incorporation of lignin enhanced 3D printability as a result of reduced melt viscosity and increased stiffness of the thermoplastic structure. Although polylactic acid is one of the most commonly used base-polymeric materials for 3D printing because of its low melting

point, biodegradability, and biocompatibility (Liu et al., 2020), it is limited by its brittleness and propensity for degradation during processing. Several works have, therefore, focused on combining lignin with polylactic acid to enhance its printability. As an example Domínguez-Robles, Martin, et al. (2019) successfully printed meshes of different sizes for wound healing via fused deposition modeling of lignin-incorporated polylactic acid filament (**Figure 6**). Composites containing different concentrations of lignin content (0-3 wt.%) were investigated, with higher lignin contents shown to facilitate improved composite wettability and also enhance antioxidant capabilities of the composite.

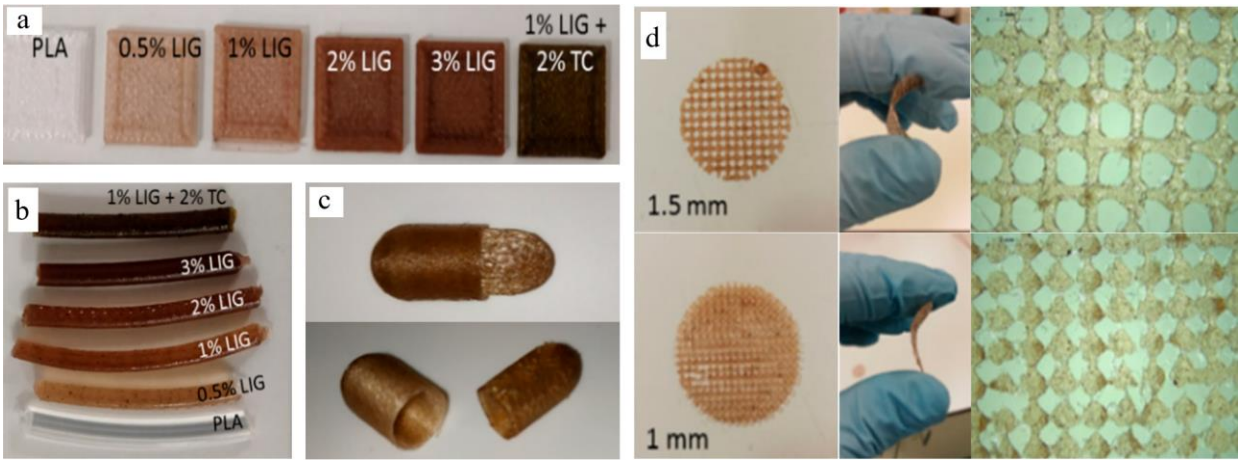

Figure 6. (a) Polylactic acid (PLA)/ lignin composites (1 cm × 1 cm) prepared using 3D printing for healthcare fused filament fabrication (FFF) applications, (b) Lignin and tetracycline containing PLA filaments, (c) capsule shape lignin and tetracycline containing PLA filaments prepared using 3D printing, and (d) 3D printed meshes made of PLA and 2% (*w*/*w*) lignin (Domínguez-Robles, Martin, et al., 2019). Open access

Tanase-Opedal et al. (2019) showed that polylactic acid filament containing between 20 to 40% lignin can be printed using fused deposition modeling. The researchers observed that the printed materials performed poorly in terms of interlayer adhesion due to the high lignin content. However, the poor performance was corrected by undertaking the printing at temperatures higher than 215 ^{o}C(Tanase-Opedal et al., 2019). Gkartzou et al. (2017) reported contrary observations to those of Tanase-Opedal et al. (2019). The study by Gkartzou et al. (2017) showed that printing at temperatures above 215 ^{o}C resulted in undesirable surface roughness which was attributed to the thermal degradation of lignin at that temperature. They also reported that the material printed at low temperatures was characterized by high viscosity, which caused lignin agglomeration and ultimately difficulty in

printing. Another study, however, reported that the thermal stability of polylactic acid-lignin composite for 3D printing was enhanced (Gordobil et al., 2014). Aside from the studies reported already, several other researchers have investigated the potential of combining lignin with other polymeric materials for 3D printing applications and they have all reported beneficial effects of lignin (Grigsby et al., 2020; Lee et al., 2021) (Spiridon & Tanase, 2018).

4.1.3 Lignin as a natural anti-oxidant

Lignin has strong anti-oxidant properties that are closely linked to the hydroxyl and methoxy functional groups in the lignin structure, which can scavenge free radicals (Ugartondo et al., 2008). According to Dizhbite et al. (2004), its structural constituents such as the hydroxyl and aromatic groups, and substituted side chains significantly determine the anti-oxidant properties of lignin. Again, extraction conditions such as temperature, reaction time, catalyst, extraction solvent influence the anti-oxidant properties of lignin. For example, higher temperatures, longer reaction residence times, high catalyst dosage, and dilute solvents enhance the anti-oxidant properties of lignin by increasing the number of phenolic groups while reducing the number of aliphatic hydroxyl groups, the molecular weight and the polydispersity (Pan et al., 2006). Lignin extracted using milder conditions (i.e. enzyme and microwave-facilitated lignin extraction) may present higher anti-oxidant activity thus enhancing their applicability in the biomedical sector (Li et al., 2018; Monteil-Rivera et al., 2012; Sun et al., 2019).

For instance, the work of Li et al. (2018) reported the enzymatic treatment of lignin using laccase in sodium acetate buffer under mild environmental conditions. The enzyme-treated lignin had low molecular weight and high phenol content due to the depolymerization and demethylation reactions. The high phenol content bequeathed the treated lignin with higher anti-oxidant properties. An et al., (An et al., 2017) were able to further improve the anti-oxidant properties of lignin by combining enzymatic treatment with fractionation via sequential extraction to reduce the polydispersity of lignin. According to Gong et al. (2016) taking lignin through post-extraction purification steps also enhances its anti-oxidant activity. In particular, they found that reducing the concentration of associated structural carbohydrates could significantly improve the anti-oxidant activity of lignin. Research has also shown that the addition of small amounts of lignin to biomedically formulated hydrogels improved the anti-oxidant and anti-microbial activities. For example, Yang et al. (2018) incorporated lignin (1-3 wt%) in chitosan/polyvinyl alcohol hydrogels and reported enhanced anti-oxidant and anti-microbial activities. The presence of lignin inhibits the oxidative degradation of oxygen-sensitive materials

for the production of hydrogen peroxide for use in biomedical applications (Domenek et al., 2013; Yang et al., 2020; Yang et al., 2016). Highly effective oxidation-stable biomaterials used for regenerative tissue engineering have been developed using lignin. These materials are very useful alternatives to polycaprolactone (PCL) and also reduce the unfavorable associated effects of PCL such as the introduction of oxidative stress in tissues (Mondal et al., 2016). In a similar effort, lignin copolymerized with polymers (poly (ε-caprolactone-co-lactide)) was found to have excellent anti-oxidant activities with 99 % inhibition of free radicals recorded (Kai et al., 2017).

4.1.4 Lignin as an anti-microbial agent

A significant characteristic of lignin that has attracted the interest of researchers in recent times is its anti-microbial activity which is linked to its phenolic content(Liao et al., 2020). Previous studies have established that lignin's ethylenic double bond and orthomethoxy groups also contribute to its anti-microbial activity (Aadil et al., 2016; Espinoza-Acosta et al., 2016; Kai et al., 2016). According to Yun et al. (2021) the anti-microbial activity of lignin is mainly due to its anti-oxidation properties which arise due to the hydroxyl groups in lignin. These hydroxyl groups facilitate lignin's capacity to scavenge reactive oxygen species and free radicals under oxidative stress. The anti-microbial activity of lignin was demonstrated by via *in vivo* studies using mice models (**Figure 7a**). The study showed that the ingestion of lignin by mice was able to ameliorate E. coli diarrhea issues of intestinal swelling and hyperemia (**Figure 7b**) associated with *E. coli*-induced diarrhea. Further investigations via histopathological analyses (**Figure 7c**) showed that lignin ingestion had the capability to reduce pathological inflammations associated with *E. coli* compared to the diarrhea group.

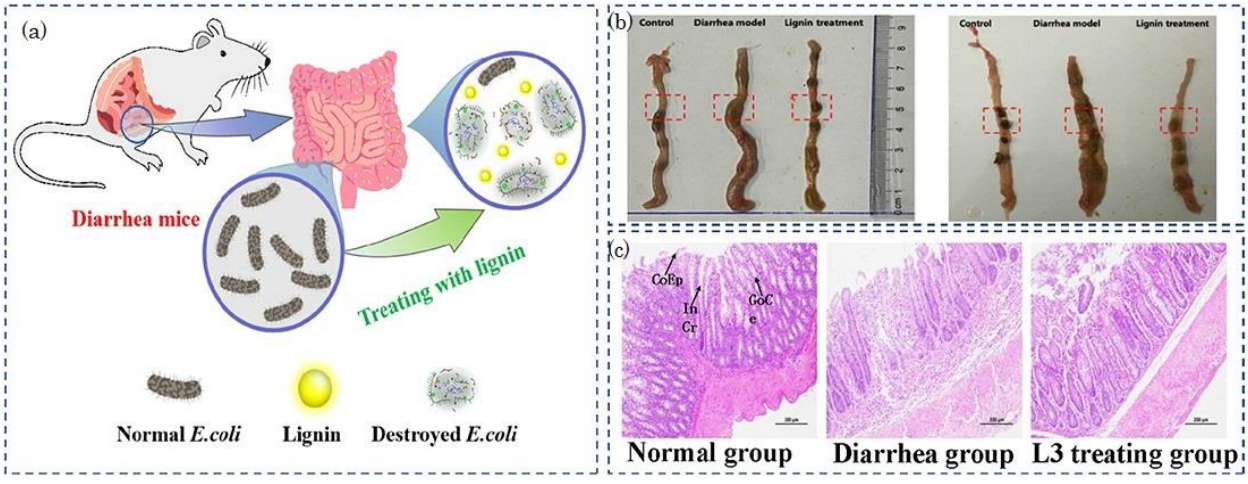

Figure 7: (a) denotes the infection of the mice model treated and the treatment with lignin, (b) denotes the pictorial illustration of the intestinal contents of the mice model, (c) denotes the histopathological colons of the mice models. CoEp, InCr, and GoCe denote the columnar epithelium, intestinal crypt and goblet cell respectively (Yun et al., 2021). Open access

Additionally, the lignin extraction conditions (biomass source, solvent-solid ratio, solvent polarity, etc), post-extraction processes, and type of microorganism have also been reported to influence the anti-microbial activity of the biopolymer (Dong et al., 2011; Ndaba et al., 2020). For example, Kai et al. (2016) showed that Kraft lignin was able to inhibit the growth of *Erwinia carotovora* and *Xanthomonas vesicatoria* although it was ineffective against *Pseudomonas syringae*. Also, Nada et al. (1989) observed that lignin extracted from cotton stalks and bagasse showed anti-microbial activity against gram-positive bacteria *(Bacillus mycoids* and *Bacillus subtilis), but not* against gram-negative bacteria (*e.g Escherichia coli)* or the fungus (*Aspergillus niger).* They also found that the biocidal efficacy of lignin was strongly temperature-dependent, and decreased to zero at temperatures greater than 160 ^{o}C. A lot of research interest has been recently focused on combining lignin with other polymer materials to enhance the anti-microbial property of the resulting composite material. For example, Liu et al. (2019) developed a novel hydrogel with unique anti-microbial activity by blending lignin, poly(vinyl alcohol), and silver nanoparticles. The hydrogel showed good potential for biomedical applications. Sunthornvarabhas et al. (2017) also used lignin from food-grade biomass to produce fabric with an anti-microbial activity which was subsequently used to produce face masks. Their findings revealed that the lignin coating on the fabric posed resistance to the growth of *Staphylococcus epidermidis* for 24 h. Alzagameem et al. (2019) developed a cellulose and lignin-based film that exhibitted anti-microbial activity against *Staphylococcus aureus, Listeria monocytogenes, Bacillus thermosphacta*, and *Pseudomonas fluorescens.* The biocidal properties were attributed to the aliphatic hydroxyl groups in lignin. The effect of lignin type on anti-microbial activity was ranked in the order softwood lignin>kraft softwood lignin>grass lignin. In another work, Rai et al. (2017) also developed a film by blending lignin with chitosan. The resulting film showed anti-microbial activity against gram-positive bacteria like *Bacillus subtilis* and gram-negative bacteria like *Pseudomonas aeruginosa*, thus reinforcing its applicability in biomedical applications. Similarly, Soda lignin was used to prepare alginate films with improved mechanical, anti-microbial, cytotoxicity, and drug release properties (Aadil et al., 2016). produced nontoxic alginate hydrogel from a lignin-polymer blend for wound healing purposes. The material showed very fast epithelial

regeneration indicating huge potential for wound treatment therapy. Some studies have also reported that the anti-microbial and anti-oxidant properties of lignin are linked. In a study by Sunthornvarabhas et al. (2020) it was observed that the relative ratio of the syringyl and the 4-hydroxyl phenyl units played an important role in the anti-microbial activity of lignin when used on *Staphylococcus aureus* and *Staphylococcus epidermidis* (gram positive bacteria) as well as *Escherichia coli* and *Pseudomonas aeruginosa* (gram negative bacteria).

4.1.5 Development of nanomaterials

Lignin has also been applied in the preparation of nanomaterials. Nano-sized lignin, although not chemically different from macromolecular equivalent, exhibits some unique properties due to its higher surface area per volume (Beisl et al., 2017). Recently, lignin nanomaterials have been receiving attention in terms of wide usage for producing biomaterials for drug delivery solutions, anti-oxidant and anti-microbial agents, UV blocking, nanocomposites, etc. Figueiredo et al. (2017) investigated different formulations of lignin nanoparticles for use in controlled drug release. They found that the formulations improved the drug release profile and also inhibited proliferation when compared to the pure drug agent. Alqahtani et al. (2019) reported significantly improved bioavailability of the low water-soluble drug curcumin when delivered using lignin nanoparticles. Additionally Dai et al. (2017) demonstrated the possibility of employing nanoparticles based on lignin in drug delivery of the bioactive molecule, resveratrol, when mice models were employed (**Figure 8**). The study showed that nanoparticles based on lignin, resveratrol and Fe_3O_4 (AL/RSV/Fe_3O_4) could lead to improvements in the in vitro release of resveratrol for tumor reduction compared to other anti-cancer agents (i.e. phosphate-buffered saline (PBS), resveratrol, lignin nanoparticles, RSV-loaded lignin nanoparticles, and magnetic RSV-loaded lignin nanoparticles). AL/RSV/Fe_3O_4 was also shown to promote drug stability and drug accumulation.

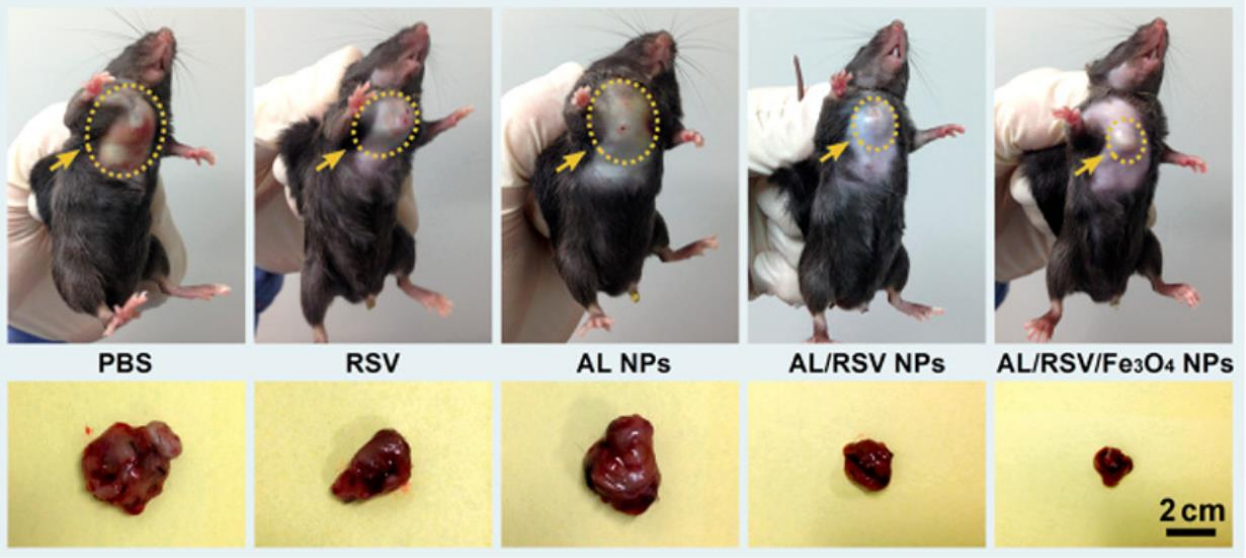

Figure 8: Tumor of mice treated with phosphate-buffered saline (PBS) (control), resveratrol (RSV), lignin nanoparticles (AL NPs), RSV-loaded lignin nanoparticles, and magnetic RSV-loaded lignin nanoparticles. Adapted with permission from Dai et al. (2017). Copyright © (2017) American Chemical Society.

Zhang et al. (2019) showed that lignin nanoparticles possessed better UV blocking and anti-oxidant properties compared with macromolecular lignin. The anti-microbial activity of lignin was utilized in the formulation of composite chitosan-lignosulphonate nanoparticles by Kim et al. (2013). The composite material developed showed better anti-microbial properties compared to standalone chitosan nanoparticles. In another study, Lee et al. (2018) prepared lignin-coated thin multi-walled carbon nanotubes to produce mechanically stable anti-microbial poly(vinyl alcohol) nanofibers. The performance of the formulation was linked to the enhanced dispersion of the poly (vinyl alcohol) matrix.

Nanoparticles of lignin have also been shown to have applications in peripheral nerve treatment (Amini et al., 2020). In the study by Amini et al. (2020), lignin nanoparticles were fabricated with polycaprolactone (PCL) fibers using the electrospinning method. The study was able to demonstrate the favorable effect of lignin nanoparticles on nerve regeneration via in vivo studies (**Figure 9**). The study was able to show that neurite length extension, cell viability, and cell differentiation increased with lignin content. Indeed the study demonstrated that the introduction of ~15 wt% lignin nanoparticles led to good nerve regeneration.

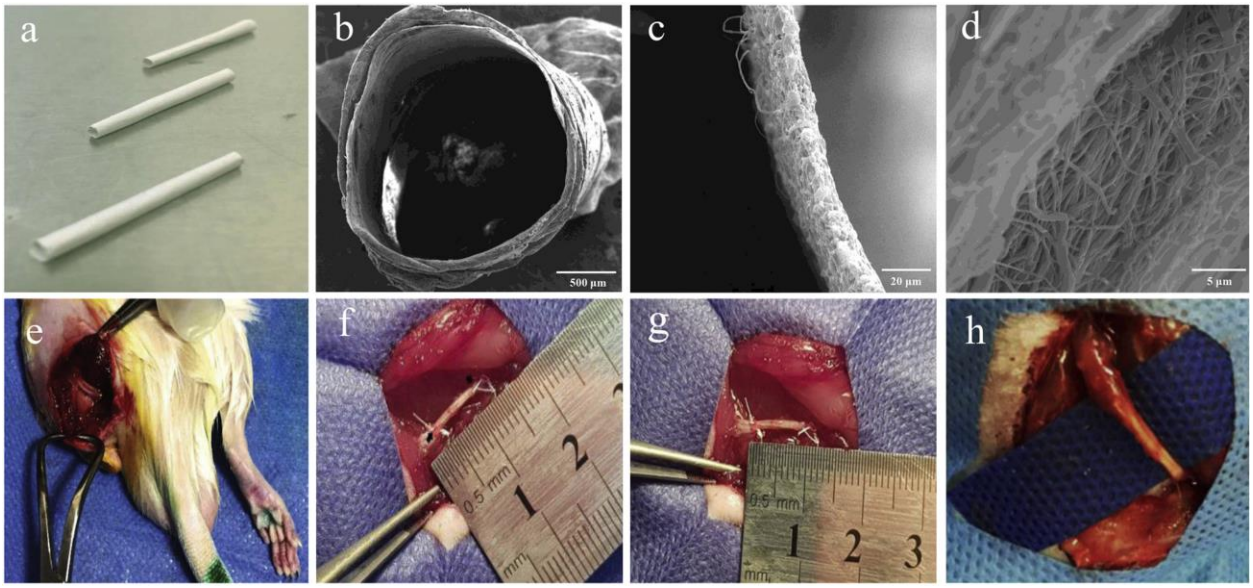

Figure 9: (a-d) Polycaprolactone (PCL)-lignin nanocomposite fiber-based nerve conduit in microscopic and macroscopic view, (e) intraoperative image of nerve conduit in the left sciatic nerve, implantation of (f) PCL fibers containing 10% lignin nanoparticle and (g) PCL fibers containing 15% lignin nanoparticle conduits in a 10 mm rat sciatic nerve gap, and (h) 3 months after surgery. Adapted with permission from Amini et al. (2020). (Copyright © 2020 Elsevier).

Hydroxyapatite coating for titanium material with enhanced anti-microbial activity against *Staphylococcus aureus* was produced from organosolv lignin (Erakovic et al., 2014). Lu et al. (2012) produced lignin nanoparticles via supercritical carbon dioxide and acetone. The produced nanoparticles displayed enhanced anti-oxidant activity and this was attributed to the increased water solubility. In a different study, Yang et al. (2016) also prepared lignin nanoparticles via acid precipitation into a blend of chitosan and poly(vinyl alcohol). The results showed that the nanoparticles produced displayed enhanced anti-oxidant capabilities that were linked to the improved synergy between the lignin and chitosan. Several studies have also reported improved performances of lignin-based composites compared to the natural macromolecular lignin in drug delivery (Chen et al., 2018; Mishra & Wimmer, 2017), UV blocking (Ju et al., 2019; Wang et al., 2019), anti-oxidants, and anti-microbials (Ge et al., 2014; He et al., 2019; Yearla & Padmasree, 2016) .

4.1.6 Lignin application in pills and tablets

Tablets have emerged as the most common solid dosage form for drugs. Pharmaceutical excipients play a significant role in the final form of a drug. Some examples of pharmaceutical excipients commonly used include starch,

microcrystalline cellulose, natural cellulose, xylitol, etc. All of these are necessary for the production of tablets and disintegration in the gastrointestinal tract and improving drug bioavailability (Gil-Chávez et al., 2021). Some researchers have explored the use of lignin as a pharmaceutical excipient to enhance drug bioavailability. For instance, Pishnamazi, Hafizi, et al. (2019) combined Alcell lignin with other pharmaceutical excipients (microcrystalline cellulose and lactose monohydrate) to assess the impact on the release rate of aspirin from tablets. They found that the incorporation of lignin in the formulation increased the aspirin release rate and reduced the disintegration time of the tablets. These favorable properties were attributed to the amorphous nature of lignin and the synergistic interaction between lignin and aspirin (Pishnamazi, Hafizi, et al., 2019). Domínguez-Robles, Stewart, et al. (2019) showed in their work that the introduction of low levels of lignin to the excipient formulation modified the drug dissolution pattern. In addition, they reported that the excellent anti-oxidant properties of lignin could help prevent oxidation of the active pharmaceutical ingredients in the drug. (Pishnamazi, Iqbal, et al., 2019) reported that including carboxylated lignin in the excipient formulation resulted in reduced drug hardness and thus, enabled faster disintegration of paracetamol tables. The performance of this formulation was explained by the fact that the release of hydrogen ions from the carboxylic group caused a reduction in the interaction between paracetamol and lignin. The reports presented thus have shown the important application of lignin as an excellent ingredient in excipient formulation for solid oral drug delivery.

4.1.7 Ultra violet (UV) absorbing agent

Lignin can absorb UV radiation because of the chromophore functional groups it contains like methoxy substituted groups and quinones which can have the capability to conjugate with carbonyl groups, aromatic rings, and double bonds (Lou et al., 2013). These UV-absorbing groups give lignin its distinct brownish to black color when exposed to UV radiation. Even though this is an undesirable property for mechanical pulps, it has a desirable use in terms of its application as a UV blocker due to this property, lignin can be used in the production of sun blockers or sunscreens. These sun blockers can shield the skin from the deleterious effect of UV radiation. Introducing lignin into commercially available sunscreens creams and lotions could potentially enhance the performance of these creams and lotions (Lee et al., 2019). For instance, Qian et al. (2015) incorporated lignin into commercially available sunscreen products and reported enhancement of the UV absorption performance. Specifically, the addition of 2 wt. % of lignin doubled the sun protection factor of the sunscreen from 15 to 30 while the sun protection factor was increased to 50 with the addition of 10 wt% lignin. Notably, the alternative

use of lignin is particularly welcome due to the adverse effects of inorganic agents such as titanium dioxide and zinc oxide which are currently used as UV absorbing agents in sunscreen lotions (Qian, Qiu, Zhu, et al., 2016).

In the work of Qian, Qiu and Zhu (2016), both low Kraft lignin and Soda lignin were incorporated into a commercially procured sunscreen lotion and hand cream. Their findings showed that the addition of lignin enhanced their capability to perform as a sunscreen. Kaur et al. (2020) also assessed the potential of using a combination of alkaline and Kraft lignin and several zinc compounds as a UV screen in a hand lotion cream. Their findings showed that hand cream containing ~20 wt. % was able to facilitate ~ 93% blocking of UV compared to ~75-90% UV blocking recorded when only the zinc compounds were used. The study further showed that combining the zinc compounds with lignin resulted in 100% UV blocking due to the synergy between the lignin and the zinc compounds. Significant increase in the sun protection factor of pure hand cream was recorded when it was blended with 5 wt.% lignin particles. The UV blocking performance of this blend was attributed to the excellent anti-oxidant properties of the lignin particles (Li et al., 2019). Yu et al. (2018) also explored the use of lignin-coated titanium dioxide as an inorganic sunscreen. They reported improved dispensability of the titanium dioxide particles because of the esterification reaction between the titanium dioxide hydroxyl groups and the lignin carboxylic acid groups. Their study also demonstrated a direct correlation between the UV blocking ability of the sunscreen and the lignin concentration of the sunscreen. Furthermore, enhanced UV blocking performance of sunscreen lotions have also been reported for the case of lignin-nano zinc oxide blend (Gutiérrez-Hernández et al., 2016), kraft lignin (Wu et al., 2019), and rice husk lignin (Lee et al., 2020).

4.2 Potential of pomace-lignin in the production of biomedical derivatives

It has been established that lignin constitutes the only natural polymeric source of aromatic compounds which are used in drug manufacturing (Li et al., 2015b). However, the conversion of lignin to aromatic compounds is not a straightforward process because of the complex nature of lignin, which significantly limits the efficiency of the conversion process. Several approaches have however been explored for the conversion of lignin to high-value products such as phenolic, lignan, neolignans, and aliphatic hydroxyl compounds which have notable biomedical applications (Liu et al., 2020). Four different approaches for the conversion of lignin to valuable precursors for biomedical applications namely depolymerization, creation of new chemically active sites, modification of the hydroxyl groups, and

grafting with other polymers (Figueiredo et al., 2017) have been reported in the literature and are discussed in the subsequent sections.

4.2.1 Thermal depolymerization of lignin

One of the most commonly deployed strategies for the depolymerization of lignin is thermal depolymerization via pyrolysis. Pyrolysis of lignin facilitates lignin depolymerization in an oxygen-deprived environment (Okoro et al., 2017b). The products obtained from this process are mostly gases and liquids with the liquid containing significant masses of simple aromatic compounds which can then be converted to other value-added products (Chio et al., 2019). The depolymerization of lignin begins with the cleavage of the weaker bonds (ether linkages) at lower temperatures and this process progresses to the much stronger bonds at the high temperature of ~450 ^{o}C (**Figure 10**). The products from this process include syringol, 4-methylguaiacol, coniferyl alcohol, isoeugenol, and vanillin which are useful in biomedical applications (Gerbin et al., 2020; Kawamoto, 2017; Lee et al., 2012; Siva et al., 2019).

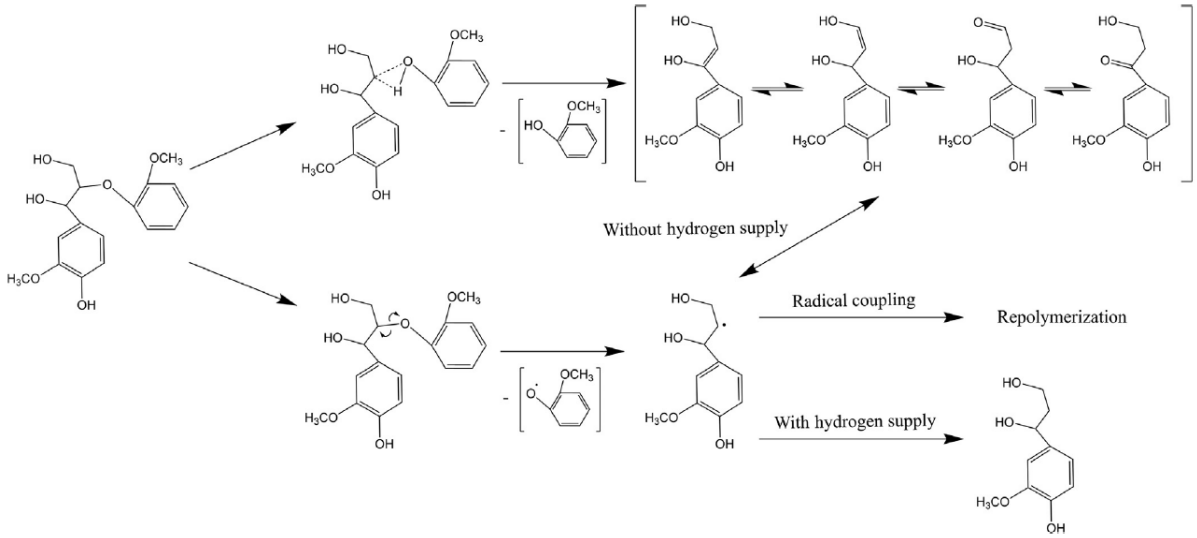

Figure 10: Mechanism for the cleavage of the ether bonds. Adapted with permission from (Chio et al., 2019). Copyright © (2021) Elsevier B.V.

At higher temperatures ranging from ~800 ^{o}C most linkages in lignin are cleaved. In particular, the methoxyl, hydroxyl, and methylated groups attached to the aromatic units are cleaved. Furthermore, initial products like syringol which are obtained when the temperature is ~ 450 ^{o}C are also further depolymerized to generate products such as guaiacol, o-quinone methide, and o-vanillin (Chio et al., 2019). Recently, catalytic pyrolysis has been investigated for improving the yield of

pyrolysis products. According to Mullen and Boateng (2010) the introduction of catalysts has the potential of improving the yield of pyrolysis products through the production of proton donors or oxidants that facilitate the demethoxylation reactions. A common catalyst used for lignin pyrolysis is zeolite and it has been shown to produce an increased yield of aromatic monomers by facilitating the depolymerization process (Gundekari & Kumar Karmee, 2021; Rezaei et al., 2016). Zeolites are also able to enhance the conversion of phenolic compounds derived from lignin to simpler aromatic compounds for use specifically in the biomedical industry (Junior et al., 2018).

4.2.2 Chemical depolymerization of lignin

Chemical depolymerization of lignin is reportedly the most effective of all depolymerization strategies for recovering phenol monomeric aromatics from lignin. These phenol monomers can be used in the production of compounds such as (Qiu et al., 2019) aniline which is used in the production of paracetamol (Thomas Paisley & Serpell, 2020). Specifically, catalytic depolymerization has numerous advantages such as high product selectivity and efficiency, easy reaction control, and moderate reaction conditions (Xu et al., 2014) . Wang et al. (2013) classified the chemical depolymerization of lignin based on the catalysts used. They include acid-, base-, metal-, ionic liquid- and supercritical fluids-catalyzed depolymerization. These catalysts can be used individually or in combination to improve process efficiency and selectivity for desired products. Acid-catalyzed depolymerization of lignin involves the use of acids either as standalone solvents or in combination with alcohols. The process has been in existence for almost eight decades and the mechanism involves the cleavage of the ether linkages as presented in **Figure 11.** Forchheim et al. (2012) combined formic acid (10 wt. %) and ethanol (77 wt. %) for the acid-catalyzed depolymerization of lignin from a wheat straw while in a similar study, Forchheim et al. (2012) used formic acid and ethanol in proportions of 10 wt. % and 81 wt. % respectively. In both cases, the reaction occurred in the temperature range of 360-400 ^{o}C and the major products were phenol, catechol, and methoxyphenol, which also have biomedical applications. Although acid-catalyzed depolymerization of lignin is commonly adopted, depolymerization is limited by several problems such as the requirement for severe reaction conditions such as corrosive solvent, high pressure, temperature, and long reaction times. Furthermore, the waste products from the process are usually categorized as toxic to the environment. There are also reported cases of repolymerization occurring where the simple monomeric compounds bind together to form macromolecules, a situation that reduces the yield of the desired product (Güvenatam et al., 2016).

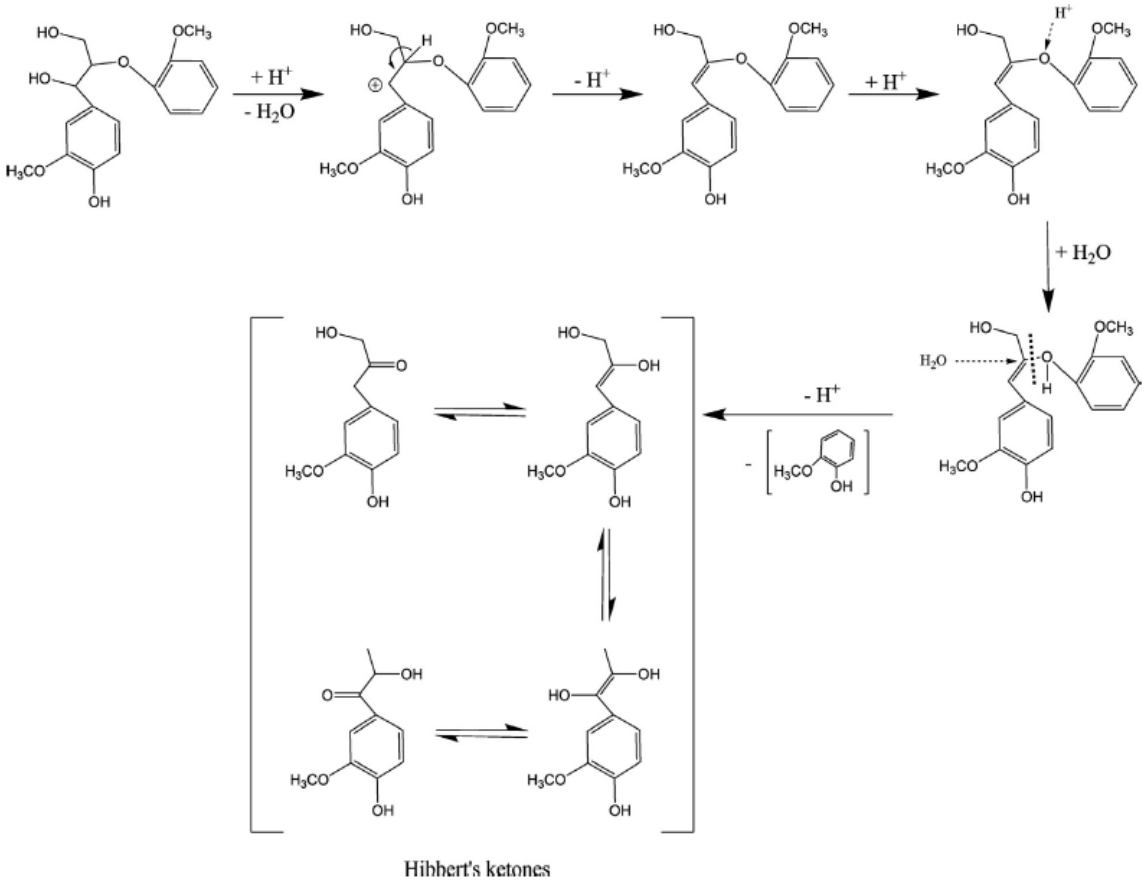

Figure 11: Mechanism for the cleavage of the ether bonds in lignin using acid catalyst. Adapted with permission from (Jia et al., 2010) Copyright © (2010) John Wiley and Sons.

Base(or alkaline)-catalyzed depolymerization of lignin involves the use of suitable alkalis to deconstruct lignin leading to the generation of low molecular weight products. Sodium hydroxide is the most commonly used base because of its low cost. The mechanism for lignin depolymerisation is presented in **Figure 12.**

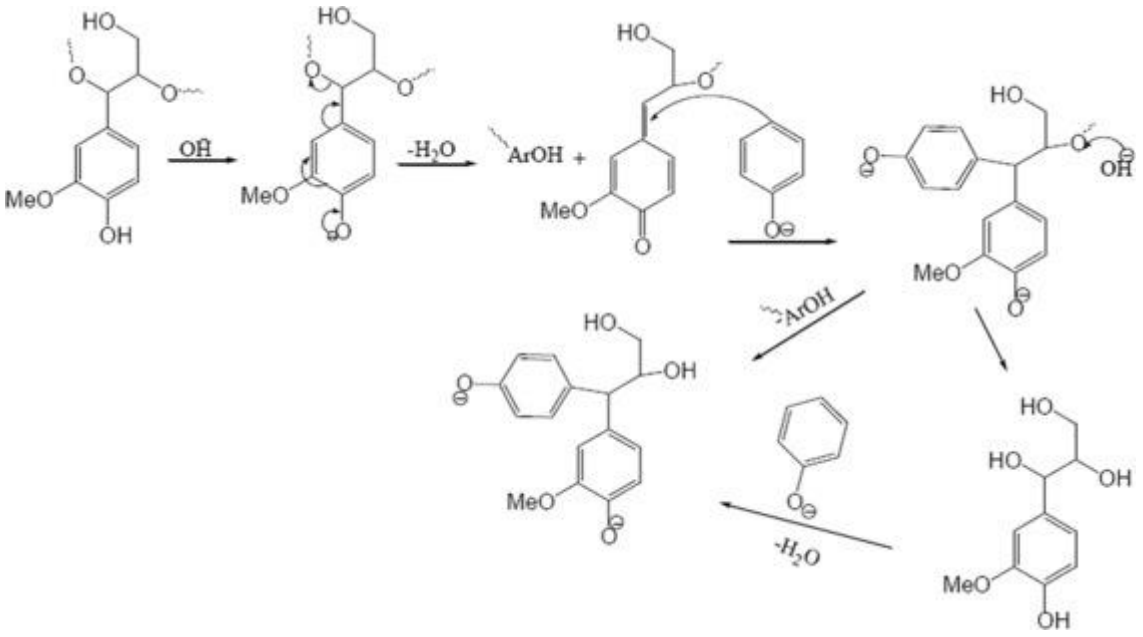

Figure 12: Depolymerisation of lignin using base (or alkaline) catalyst. Adapted with permission from Mahmood et al. (2016) Copyright © (2016) Elsevier.

Lavoie et al. (2011) applied sequential steam explosion and treatment with 5 wt.% NaOH for lignin obtained from softwood and hemp using a temperature range of 300-330 °C. They identified 26 compounds at the end of the process with the most abundant of them being catechol, guaiacol, and vanillin. In a similar work, organosolv lignin was subjected to base-catalyzed depolymerization at a temperature and pressure of 300 °C and 25 MPa respectively. The major products obtained were catechol, syringol, and hydroxyacetophenone (Roberts et al., 2011). Other researchers (Long et al., 2015; Roberts et al., 2011; Toledano et al., 2012; Toledano et al., 2014) reported the positive impact of base catalysis on lignin depolymerization. Although other bases like calcium hydroxide, potassium hydroxide, and cesium hydroxide can be used, Evans et al. (1999) however suggested that stronger bases like sodium hydroxide and potassium hydroxide are preferred as they result in stronger hydrolysis and production of depolymerized products. Metals have also been investigated as potential catalysts for lignin depolymerization. Metals are specifically used to overcome the limitations of acid- and base-catalyzed lignin depolymerization. For instance, Song et al. (2012) reported the potential of nickel to successfully catalyze lignin depolymerization to produce phenolic compounds. Some other reports have shown that nickel can be combined with other metals in the form of a bimetal alloy to yield positive outcomes (Molinari et al., 2014; Zhai et al., 2017; Zhang et al., 2016). Ionic liquids (Das et al., 2017; Dutta et al., 2017) and supercritical fluids (Gosselink et al., 2012; Hidajat et

al., 2017; Pérez et al., 2018) have also been investigated for lignin depolymerization. Ionic liquids are usually utilized as solvents and establish a synergistic effect with other catalysts during lignin depolymerization and this gives it the ability to facilitate the oxidation level. Yang et al. (2017) reported that 1-octyl-3-methylimidazolium acetate successfully catalyzed the conversion of over 96% of lignin macromolecules to simple phenolic compounds under moderate reaction conditions. Supercritical fluids are usually employed because of their excellent solubility properties (Rad et al., 2019). Sasaki and Goto (2008) undertook the treatment of alkaline lignin with supercritical water at a temperature of 300 ^{o}C within a pressure range of 25 to 40 MPa. They identified major products which included phenol, catechol, and cresol. Takami et al. (2012) also used supercritical water treatment for organosolv lignin. Despite the positive attributes of supercritical fluids, their use in lignin depolymerization is limited by high cost and harsh reaction conditions.

4.2.3 Biological depolymerization of lignin

The use of biological catalysts for lignin depolymerization has been touted as a sustainable alternative to chemically catalyzed depolymerization. The advantage of this option is the environmental friendliness and the specificity with which the biocatalysts catalyze the reactions which help to improve the selectivity of the desired products (Chio et al., 2019). In addition, the reactions are carried out under mild conditions. *Rhodococcus jostii* RHA1 is one of the most commonly used microorganisms for lignin conversion to other compounds. It was reported by Sainsbury et al. (2015) that *Rhodococcus jostii* RHA1 can cleave the ether bonds with the help of dye-decolorizing peroxidase to produce vanillin. Apart from *Rhodococcus jostii* RHA1, the bacteria species *Pseudomonas putida* KT2440 has been reported to be very efficient in degrading lignin and researchers have established the fact that *Pseudomonas putida* KT2440 can degrade lignin to low molecular weight compounds. It can also produce polyhydroxyalkanoates which is an important precursor for producing bioplastics (Xu et al., 2018). Despite the potential usefulness of different bacteria strains for lignin conversion, fungi perform better than the bacteria comparatively and as such, white-rot fungi have been the favored fungi for lignin depolymerization because of their excellent ability to deconstruct lignin (Salvachúa et al., 2015). The performance of white-rot fungi is closely linked to their ability to extracellularly produce different oxidases like laccases, phenol oxidase, etc. Koncsag et al. (2012) reported that *Pleurotus ostreatus* was able to successfully depolymerize lignin with the corresponding production of useful chemicals such as syringyl alcohol and ferulic acid. Baltierra-Trejo et al. (2015) used *Aspergillus fumigatus* to ferment lignin extracted from

wheat straw and detected the production of several useful chemicals like vanillic acid, syringic acid, butyric acid, and acetic acid.

4.3 Derivatives of lignin depolymerization

Derivatives of lignin depolymerization such as vanillin, catechol, phenol, guaiacol, cresol, syringol, *p*-coumarate, eugenol, benzene, etc. are very essential precursor materials in the biomedical industry (Li et al., 2015a). In terms of valorization and economic potential, lignin-derived aromatic compounds offer the most promise in terms of further value-chain gains. Thus, there is a lot of focus on phenolics and phenol aldehydes derived from lignin depolymerization. In particular, phenolic aldehydes such as syringaldehyde, vanillin, and 4-hydroxybenzaldehyde can be obtained via oxidative depolymerization and are useful in the biomedical industry (Banerjee & Chattopadhyay, 2019). For instance, syringaldehyde has excellent bioactivity which makes it very useful in the manufacture of pharmaceuticals (Ibrahim et al., 2012). On the other hand, vanillin can be employed as a masking agent in pharmaceutical formulations (Banerjee & Chattopadhyay, 2019; Ibrahim et al., 2012). Furthermore, guaiacol has anti-microbial activity, which has seen it used in the production of disinfectants. It also has anti-oxidant activity giving it the capacity to scavenge for reactive oxygen radicals in living systems. Catechol may be used as a precursor material in the pharmaceutical industry for the production of drugs. Some recent research has also seen catechol being combined with polymers to prepare other useful products for biomedical applications (Kim et al., 2021; Ryu et al., 2015; Zhang et al., 2018; Zhang et al., 2020). Eugenol is a very important chemical in dental hygiene formulations (Mohammadi Nejad et al., 2017). It can also be used as a sensitizing and anesthetic agent (Chung & Oh, 2013; Raja et al., 2015). Beyond that, it also has anti-oxidant, anti-inflammatory, antiviral, and antibacterial activity (Pavithra & Research, 2014). Syringol is useful in the pharmaceutical industry as an anti-dermatophyte and for platelet aggregation (Murwanashyaka et al., 2001).

5 Current challenges for the exploration of pomace-lignin and its aromatic derivatives in the medical industry

Initial consideration of the WP as a sustainable source of lignin for biomedical applications suggests that the high moisture content of up to 80 wt. % (Okoro & Shavandi, 2021), which characterizes typical pomaces may present some associated problems. This is because the high moisture content of pomace may translate to higher transportation costs and pomace acquisition costs (Woo et al., 2018). These transportation costs may be quite substantial. Initial logistic issues from the

microbial decomposition of the pomace may lead to handling difficulties, thus limiting the viability of exploring pomace-lignin utilization opportunities. Furthermore, the risk of rapid deterioration of the WP during storage may also limit enthusiasm for its valorization for enhanced lignin extraction and may introduce some health and safety concerns from microbial effects and exposure. Notably, there may be a need to explore energy-intensive and costly drying operations before lignin recovery from the pomace, thus further limiting the technical feasibility of large-scale lignin extractions. At this juncture, it should be stated that not 'all lignin are equal' since the source of the lignin influences not only the yield of the lignin but also influences properties of the lignin. Indeed, the study presented by Watkins et al. (2015) showed that lignin sourced from food-grade wheat presented the highest thermal stability relative to the thermal stabilities of flax fiber, alfalfa, and pine straw. According to Watkins et al. (2015) the higher thermal stability suggests that the lignin sourced from food-grade wheat could serve as a partial replacement of phenolics, in resin systems. Similarly, given the 'food origin' of the lignin similar improved properties are anticipated. Crucially, however, there is a possibility that the pomace-lignin may present a complex and disordered structure, leading to difficulties in executing the appropriate production craft approach and control of process parameters for nanofiber formation. Such complex and disordered structures characterize lignin from all sources and negatively affect its mechanical properties, thus increasing the risk of defective fabrications. The direct application of pomace-lignin application may also be limited by its thermal behavior. This is because the literature suggests that its melt-spinning and softening temperature characteristics provide only a narrow window for the formation of the nanofibers. Additionally, its thermal properties may lead to the formation of unwanted cross-linking during melt-spinning (Fang et al., 2017). Furthermore, although matrices in lignin can be used for the controlled release of bioactivities in biomedical applications, the utilization of lignin used in this manner is limited by variabilities in water uptake and swelling capacity of lignin due to its inherent structural heterogeneity (Klugman, 2015). According to Terzioğlu et al. (2020) the abundance of biomass such as waste pomace suggests that lignin-based applications may lead to improved economic outcomes compared to when synthetic polymer materials are used in biomedical applications. Notably, however, existing technologies are limited with respect to the use of lignin in 3D printing, melt-electrospinning, lithography, 3D braiding, etc. (Terzioğlu et al., 2020). Furthermore, although the medical benefits of lignin, have been established in the literature, work is required to demonstrate the efficacy and long-term effects of such lignin-derived drugs. Indeed, possible issues associated with the accumulation and biodegradation of lignin and lignin-derived products as well as

possible long-term effects on the retention of lignin and lignin-derived are yet to be extensively explored (Liu et al., 2020) . For instance, it may be suggested that the application of lignin in the manufacture of pharmaceutical drugs may lead to unwanted effects on humans via the translation of some unwanted effects of lignin extracted to lignin-derived pharmaceuticals. For instance, previous work has demonstrated the polydispersity of lignin leads to unfavorable adsorption effects on cholesterols and the unfavorable digestion effects in the human small intestine (Iravani & Varma, 2020). Additional issues that may limit the applicability of pomace-lignin in the biomedical industry may be due to concerns associated with the translation of bench-scale experimental outcomes to practical large-scale operations. This is because the heterogeneity and non-ordered structure of lignin is indicative of its complexity and varying molecular weight distributions making standardization and large-scale production difficult for lignin-derived products difficult (Ralph et al., 2008; Terzioğlu et al., 2020; Zhang et al., 2006). This limitation significantly hinders the feasibility of designing novel lignin-based products such as composites that are characterized by distinct properties (Terzioğlu et al., 2020). Furthermore, given that lignin modification processes typically require the utilization of significant masses of hydrogen as a reactant to facilitate lignin transformation (i.e. processes such as hydrocracking, hydrodealkylation and hydrodeoxygenation) (Strassberger et al., 2014), concerns related to the overall renewability of the lignin transformation processes may be raised. This is because since most hydrogen employed is currently sourced from fossil sources (i.e. natural gas) (EERE, 2021), associated unwanted GHG and natural resource depletion effects are unavoidable. In addition to the limitations associated use of lignin and its transformation to biomedical products, the lignin extraction process from pomace may also lead to associated unfavorable economic and environmental effects. For instance, the major approaches currently employed in large-scale lignin extraction of namely, the sulfite, Soda, kraft, and organosolv based processes (Carvajal et al., 2016) are characterized by several concerns as highlighted in **Table 2.** These concerns may limit the applicability of the lignin extracted in biomedical applications. Specifically, lignin extracted via the Kraft process is usually contaminated with polysaccharides. The Kraft lignin may also undergo several chemical changes due to the formation of covalent bonds sulfur in form of thiols, leading to the conversion of Kraft lignin into lower molecular weight fragments of thiolignin (Fernández-Rodríguez et al., 2019). The sulfite process also leads to alterations in lignin chemistry via the introduction of an aliphatic sulfonic acid function to the lignin backbone (Lora & Glasser, 2002). Similarly, the Soda pulping and the organosolv approaches may induce hydrolytic cleavage of native lignin into smaller fragments and structural changes in lignin (Windeisen &

Wegener, 2012). Therefore, existing conventional lignin extraction approaches lead to structural changes in the native lignin structure which also lead to alterations in the lignin properties, such as solubility, thermal stability, thermoplastic properties, and chemical reactivity (Windeisen & Wegener, 2012). These changes in lignin chemistry and structure, however, may subsequently limit the safety and applicability of lignin in biomedical applications. In an attempt to reduce possible toxicity issues associated when lignin extraction is effected using mature technologies, some recent works have demonstrated the possibility of pure lignin recovery via new technologies such as the reductive lignocellulose fractionation, for a so-called lignin-first process that involves solvolytic lignin extraction, depolymerization and catalytic stabilization steps (Abu-Omar et al., 2021; Chen et al., 2021; Renders et al., 2019; Van den Bosch et al., 2015). Other lignin-first processes include hydrothermal treatments (Lourencon et al., 2020) and the use of ionic liquids (ILs) (Xu et al., 2020) to enable purer lignin recovery. These technologies are however characterized by a low technology readiness level, with their applicability at the industrial scale, being currently unclear. More work is therefore required in this area.

6 Prospects for the utilization of pomace-lignin and its aromatic derivatives in the biomedical industry

The authors predict that over time, the interest in biopolymers such as pomace-lignin will increase geometrically due to lignin's biocompatibility, biodegradability, low toxicity, and low reactogenicity as well as their wide range of applications (Bernardini et al., 2018; Guo, 2017; Newman & Cragg, 2020) in the biomedical industry. This projection is based on the increasing demand for biomedical and pharmaceutical products. As an illustration, consider that in 2015 and 2016, the global market for cancer immunotherapy and wound care drugs was US$ 45.5 billion (Mikulic, 2018) and US$ 24.5 billion (Stewart, 2018). Notably, the market for cancer immunotherapy and wound care drugs is projected to reach US$ 117.1 billion (Mikulic, 2018) and US$ 40 billion (Stewart, 2018) by the years 2021 and 2022, respectively. There is also an increase in the demand for controlled-release drug formulations to extend the drug's effective duration, enhance stability and bioavailability and minimize the negative effects related to spikes in drug concentrations (Dabholkar et al., 2021; Davoodi et al., 2018). Apart from the enhanced demand for pharmaceutical drugs, the demand for naturally sourced materials in the production of 3D printing for scaffold fabrication is also expected to increase. This is because it is estimated that by 2050, approximately two billion people will require the use of assistive technology devices (WHO, 2018) with the global scaffold technology market projected to increase due to the escalating

demand for regenerative treatments (Gurtner & Chapman, 2016) and medical reconstruction procedures (Brydone et al., 2010). Although synthetic-based prosthetics, orthotics, and scaffolds are well-known, there is a need to improve the properties of these materials by eliminating the possible unwanted effects of using synthetic fibers, plastics, ceramic materials, and metals which are sometimes incompatible in human cells and tissues (Evans et al., 1974; Shahar et al., 2021; Vallittu, 2018). Additionally, some of these synthetic prosthetics and orthotics implants and scaffolds are not biostable leading to the need for secondary surgeries over time (Doppalapudi et al., 2014). The use of biopolymers such as lignin, to facilitate the complete or partial replacement of these synthetics will eliminate or reduce these highlighted concerns due to its undisputed biocompatibility. Furthermore, concerns associated with the non-biodegradability and non-renewability characteristics of the synthetics used in regenerative treatments can also be resolved using lignin as an alternative biopolymer. Pomace-lignin, therefore, presents an opportunity for the sustainable production of lignin, moreso since waste pomace constitutes an abundant waste stream that must be managed, sustainably. The use of this abundant waste stream will enable the resolution of the aforementioned demand issues since the large masses of the biomass waste will serve as an invaluable resource for lignin extraction. This lignin resource will provide benefits of enhanced immunomodulatory, anti-inflammatory, anti-oxidative and anti-bacterial effects, and may be employed in the fabrication of scaffolds, and wound dressings. It is acknowledged that economic considerations constitute a significant consideration in determining the viability of resources sourced from biomass, with the feedstock cost typically constituting the major determinant of the economics of valorization processes (Korányi et al., 2020; Okoro et al., 2017a; Zetterholm et al., 2020). The authors, however, anticipate that the availability of large masses freely available pomace (biomass), will translate to favorable lignin recovery, which may be transformed for biomedical applications, thus presenting the possibility of reducing costs the derived biomedical products. Future investigation must therefore explore strategies for enhanced recovery of lignin from large waste resources such as waste pomace for its use as low cost biomaterials and its subsequent conversion to aromatic derivatives for manufacture of pharmaceutical products (Mikulic, 2018). Looking ahead, biomedical products based on or containing lignin and/or its aromatic derivatives may be available in the market in no time.

7 Conclusions

This review has highlighted the waste management issues associated with fruit pomace while also elucidating the current management and valorization

approaches. The current challenges of the underutilization of pomace-lignin were discussed with the associated inadequacies of the existing waste pomace valorization frameworks, highlighted. The potential of pomace-lignin use via direct utilization in biomedical applications such as 3D printing and wound healing as well as indirect utilization via its depolymerization for the production of pharmaceutical drugs, was extensively discussed. Issues due to lignin chemistry such as heterogeneity, and the high moisture content of pomace, which lead to associated logistical concerns, that are capable of constraining the future use of pomace-lignin, were also highlighted.

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